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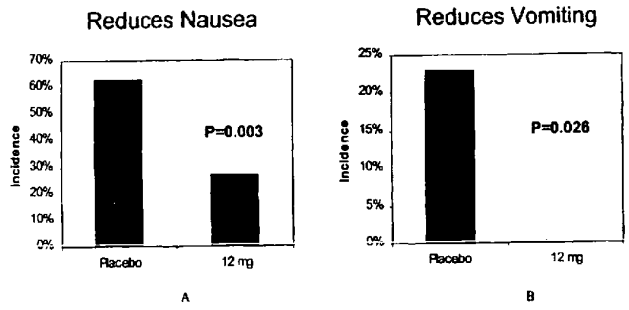
(54) Title: NOVEL METHODS AND COMPOSITIONS INVOLVING OPIOIDS AND ANTAGONISTS THEREOF



(57) Abstract: Novel methods and compositions comprising opioids and opioid antagonists. In preferred embodiments, the methods and compositions comprise opioids and peripheral mu opioid antagonist compounds. The methods and compositions are particularly suitable for treating and/or preventing side effects associated with opioids including, for example, constipation, vomiting and/or nausea. Figures 2A aand 2B are graphical representations of studies on the inhibition of nausea and vomiting employing methods according to an embodiment of the present invention.

WO 01/37785 A3

NOVEL METHODS AND COMPOSITIONS INVOLVING OPIOIDS AND ANTAGONISTS THEREOF

Field of the Invention

The present invention relates to novel methods and compositions comprising opioids and opioid antagonists. More particularly, the present invention relates to novel methods and compositions comprising opioids and peripheral mu opioid antagonist compounds.

Background of the Invention

It is well known that opioid drugs target three types of endogenous opioid receptors (*i.e.*, mu, delta and kappa receptors) in biological systems. Most opioids, such as morphine, are mu opioid agonists that are often used as analgesics for the treatment of severe pain due to their activation of mu opioid receptors in the brain and central nervous system (CNS). Opioid receptors are, however, not limited to the CNS, and may be found in other tissues throughout the body. A number of side effects of opioid drugs may be caused by activation of these peripheral receptors. Administration of mu opioid agonists often results in intestinal dysfunction due to the large number of receptors in the wall of the gut (Wittert, G., Hope, P. and Pyle, D., *Biochemical and Biophysical Research Communications* **1996**, 218, 877-881; Bagnol, D., Mansour, A., Akil, A. and Watson, S.J., *Neuroscience* **1997**, 81, 579-591). Specifically, opioids are generally known to cause nausea and vomiting as well as inhibition of normal propulsive gastrointestinal function in animals and man (Reisine, T., and Pasternak, G., *Goodman & Gilman's The Pharmacological Basis of Therapeutics Ninth Edition* **1996**, 521-555) resulting in side effects such as, for example, constipation. It has been reported that acute nausea or vomiting may occur in up to about 33% of patients who receive oral narcotic analgesics and in up to about 80% of patients who receive injectable narcotics following surgery or trauma. This is due, at least in part, to direct effects of narcotics on the gastrointestinal (GI) tract.

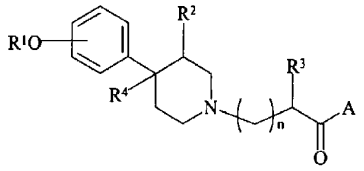
Opioid-induced side effects, such as nausea, vomiting, and inhibited gastrointestinal propulsive activity remain serious problems for patients being

administered opioid analgesics for both short term and long term pain management. Opioid antagonist compounds that do not readily cross the blood-brain barrier (peripherally acting drugs) have been tested for use in curbing opioid-induced side effects. For instance, the peripheral mu opioid antagonist compound methylnaltrexone and related compounds have been suggested for use in curbing opioid-induced side effects in patients. U.S. Patent Nos. 5,972,954, 5,102,887, 4,861,781, and 4,719,215 disclose the use of methylnaltrexone and related compounds in controlling opioid-induced pruritus, nausea, and/or vomiting. Additionally, methylnaltrexone has been shown to effectively reduce the incidence of opioid-induced nausea and pruritus as disclosed by Yuan, C.-S. et al. *Drug and Alcohol Dependence* **1998**, *52*, 161. Similarly, U.S. Patent Nos. 5,250,542, 5,434,171, 5,159,081, and 5,270,328, disclose peripherally selective piperidine-N-alkylcarboxylate opioid antagonists as being useful for the treatment of the opioid side effects constipation, nausea or vomiting, as well as irritable bowel syndrome and idiopathic constipation.

It is frequently the case that drugs have undesirable side effects, and patients taking such drugs are often prescribed additional drugs for countering these side effects. Thus, patients may be required to take multiple doses of different drugs, causing inconvenience and possible administration of incorrect doses. It may therefore be desirable for multiple drugs to be combined as one dose in a fixed ratio for ease of administration. Given that nausea, vomiting, and inhibited gastrointestinal propulsive activity are common side effects of opioid analgesics that contribute to the discomfort of a patient receiving such therapy, a need for a specific and effective side effect-relieving remedy is present. As it is not readily evident to combine two or more drugs for simultaneous administration, due to the complex nature of drug interactions which are often undesirable and even fatal to the patient, it is desirable to identify drug formulations that contain compounds when taken simultaneously in pre-measured, fixed-dose forms, resulting in safe alternative means for administering multiple drugs. In the present invention, it has been found that opioid analgesics, with their common undesirable side effects, are optimal candidates for such formulations in combination with peripheral mu opioid antagonist compounds. The methods and formulations of the present invention are directed toward these, as well as other, important ends.

Summary of the Invention

Accordingly, the present invention is directed, in part, to novel methods and compositions for treating and/or preventing side effects that may be associated, for example, with the administration of opioids. Specifically, in one embodiment, there are provided methods of preventing or treating a side effect associated with an opioid comprising administering to a patient, in combination with an effective amount of an opioid, an effective amount of a compound of the following formula (I):



I

wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

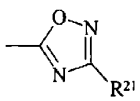
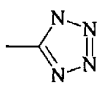
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substitued B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

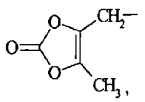
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

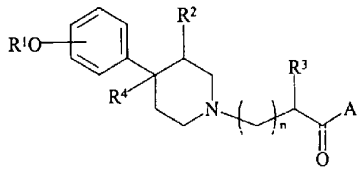
R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

Another embodiment of the invention relates to methods of preventing or treating a side effect associated with an opioid comprising administering to a patient an effective amount of an opioid in combination with an effective amount of a peripheral mu opioid antagonist compound.

Still another embodiment of the invention relates to methods of treating or preventing pain comprising administering to a patient an effective amount of an opioid, in combination with an effective amount of a compound of the following formula (I):



I

wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

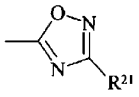
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substitued B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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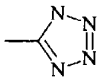
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C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

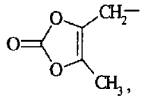
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

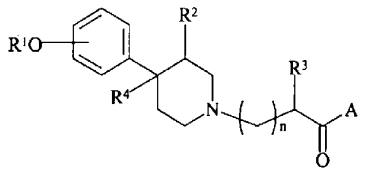
R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

Yet another embodiment of the invention relates to methods of treating or preventing pain comprising administering to a patient an effective amount of an opioid in combination with an effective amount of a peripheral mu opioid antagonist compound.

In another embodiment of the invention, there are provided pharmaceutical compositions comprising an effective amount of an opioid and an effective amount of a compound of the following formula (I):



I

wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substitued B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

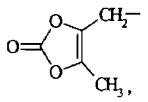
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

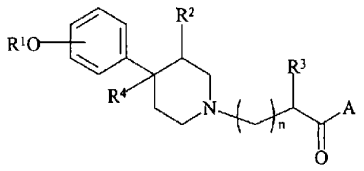
R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

Still another embodiment of the invention relates to pharmaceutical compositions comprising an effective amount of an opioid, an effective amount of a peripheral mu opioid antagonist, and a pharmaceutically acceptable carrier.

Yet another embodiment of the invention relates to pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising an effective amount of an opioid and an effective amount of a compound of the following formula (I):



I

wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

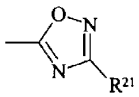
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substitued B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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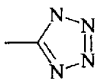

,

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

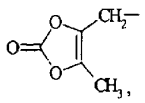
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

Still another embodiment of the invention relates to pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising an effective amount of an opioid and an effective amount of a peripheral mu opioid antagonist.

These and other aspects of the invention will become more apparent from the following detailed description.

Brief Description of the Drawing

Figure 1 is a graphical representation of studies on the inhibition of the slowing of gut motility employing compositions and methods according to an embodiment of the present invention.

Figures 2A and 2B are graphical representations of studies on the inhibition of nausea and vomiting employing methods according to an embodiment of the present invention.

Detailed Description of the Invention

As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Alkyl" 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. "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. In certain preferred embodiments, the alkyl group is a C_1-C_5 alkyl group, *i.e.*, a branched or linear alkyl group having from 1 to about 5 carbons. In other preferred embodiments, the alkyl group is a C_1-C_3 alkyl group, *i.e.*, a branched or linear alkyl group having from 1 to about 3 carbons. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl. "Lower alkyl" refers to an alkyl group having 1 to about 6 carbon atoms. Preferred alkyl groups include the lower alkyl groups of 1 to about 3 carbons.

"Alkenyl" refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to about 10 carbon atoms in the chain, and all combinations and subcombinations of ranges therein. In certain preferred embodiments, the alkenyl group is a C_2-C_{10} alkyl group, *i.e.*, a branched or linear alkenyl group having from 2 to about 10 carbons. In other preferred embodiments, the alkenyl group is a C_2-C_6 alkenyl group, *i.e.*, a branched or linear alkenyl group having from 2 to about 6 carbons. In still other preferred embodiments, the alkenyl group is a C_3-C_{10} alkenyl group, *i.e.*, a branched or linear alkenyl group having from about 3 to about 10 carbons. In yet other preferred embodiments, the alkenyl group is a C_2-C_5 alkenyl group, *i.e.*, a branched or linear alkenyl group having from 2 to about 5 carbons. Exemplary alkenyl groups include,

for example, vinyl, propenyl, butenyl, pentenyl hexenyl, heptenyl, octenyl, nonenyl and decenyl groups.

"Alkylene" refers to a straight or branched bivalent aliphatic hydrocarbon group having from 1 to about 6 carbon atoms, and all combinations and subcombinations of ranges therein. The alkylene group may be straight, branched or cyclic. Exemplary alkylene groups include, for example, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) and propylene ($-(CH_2)_3-$). There may be optionally inserted along the alkylene group one or more oxygen, sulphur or optionally substituted nitrogen atoms, wherein the nitrogen substituent is alkyl as described previously. Preferred alkylene groups have from about 1 to about 4 carbons.

"Alkenylene" refers to an alkylene group containing at least one carbon-carbon double bond. Exemplary alkenylene groups include, for example, ethenylene ($-CH=CH-$) and propenylene ($-CH=CHCH_2-$). Preferred alkenylene groups have from 2 to about 4 carbons.

"Cycloalkyl" refers to any stable monocyclic or bicyclic ring having from about 3 to about 10 carbons, and all combinations and subcombinations of ranges therein. In preferred embodiments, the cycloalkyl group is a C_3-C_8 cycloalkyl group, *i.e.*, a cycloalkyl group having from about 3 to about 8 carbons, with C_3-C_6 cycloalkyl groups, *i.e.*, cycloalkyl groups having from about 3 to about 6 carbons being more preferred. The cycloalkyl group may be optionally substituted with one or more cycloalkyl group substituents. Preferred cycloalkyl group substituents include alkyl, prefcrably C_1-C_3 alkyl, alkoxy, preferably C_1-C_3 alkoxy, or halo. Exemplary cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

"Cycloalkyl-substituted alkyl" refers to a linear alkyl group, preferably a lower alkyl group, substituted at a terminal carbon with a cycloalkyl group, preferably a C_3-C_8 cycloalkyl group. Typical cycloalkyl-substituted alkyl groups include cyclohexylmethyl, cyclohexylethyl, cyclopentylethyl, cyclopentylpropyl, cyclopropylmethyl and the like.

"Cycloalkenyl" refers to an olefinically unsaturated cycloalkyl group having from about 4 to about 10 carbons, and all combinations and subcombinations of

ranges therein. In preferred embodiments, the cycloalkenyl group is a C_5-C_8 cycloalkenyl group, *i.e.*, a cycloalkenyl group having from about 5 to about 8 carbons.

"Alkoxy" refers to an alkyl-O- group where alkyl is as previously described. Exemplary alkoxy groups include, for example, methoxy, ethoxy, propoxy, butoxy and heptoxy.

"Alkoxy-alkyl" refers to an alkyl-O-alkyl group where alkyl is as previously described.

"Acyl" means an alkyl-CO- group wherein alkyl is as previously described. Preferred acyl groups comprise lower alkyl groups, such as alkyl of about 1 to about 3 carbons. Exemplary acyl groups include acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aryl" refers to an aromatic carbocyclic radical containing from about 6 to about 10 carbons, and all combinations and subcombinations of ranges therein. The phenyl group may be optionally substituted with one or two or more aryl group substituents. Preferred aryl group substituents include alkyl groups, preferably C_1-C_2 alkyl groups. Exemplary aryl groups include phenyl and naphthyl.

"Aryl-substituted alkyl" refers to an linear alkyl group, preferably a lower alkyl group, substituted at a terminal 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.

"Heterocyclic" refers to a monocyclic or multicylic ring system carbocyclic radical containing from about 4 to about 10 members, and all combinations and subcombinations of ranges therein, wherein one or more of the members is an element other than carbon, for example, nitrogen, oxygen or sulfur. The heterocyclic group may be aromatic or nonaromatic. Exemplary heterocyclic groups include, for example, pyrrole and piperidine groups.

"Halo" refers to fluoro, chloro or bromo.

"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 benefitted by its administration. In the

case, for example, of opioids, the term "side effect" may preferably refer to such conditions as, for example, constipation, nausea and/or vomiting.

"Effective amount" refers to an amount of a compound as described herein that may be therapeutically effective to inhibit, prevent or treat the symptoms of particular disease, disorder or side effect. Such diseases, disorders and side effects include, but are not limited to, those pathological conditions associated with the administration of opioids (for example, in connection with the treatment and/or prevention of pain), wherein the treatment or prevention comprises, for example, inhibiting the activity thereof by contacting cells, tissues or receptors with compounds of the present invention. Thus, for example, the term "effective amount", when used in connection with opioids, for example, for the treatment of pain, refers to the treatment and/or prevention of the painful condition. The term "effective amount", when used in connection with peripheral mu opioid antagonist compounds, refers to the treatment and/or prevention of side effects typically associated with opioids including, for example, such side effects as constipation, nausea and/or vomiting.

"In combination with", "combination therapy" and "combination products" refer, in certain embodiments, to the concurrent administration to a patient of opioids and peripheral mu opioid antagonists, including, for example, the compounds of formula (I). When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

"Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit may contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention may be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

"Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which 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.

"Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. 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.

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.

"Patient" refers to animals, including mammals, preferably humans.

The present invention is directed to methods and pharmaceutical compositions involving opioid compounds. As discussed above, such opioid compounds may be useful, for example, in the treatment and/or prevention of pain. However, as also discussed above, undesirable side effects including, for example, constipation, nausea and vomiting, as well as other side effects, may frequently occur in patients receiving opioid compounds. By virtue of the methods and compositions of the present invention, effective and desirable inhibition of undesirable side effects that may be associated with opioid compounds may be advantageously achieved. Accordingly, combination methods and compositions, where opioids are combined or co-administered with suitable peripheral mu opioid antagonist compounds, may afford an efficacy advantage over the compounds and agents alone.

In this connection, as discussed above, patients are often administered opioids for the treatment, for example, of painful conditions. However, as noted above, undesirable side effects such as, for example, constipation, nausea and/or vomiting, may result from opioid administration. These undesirable side effects may act as a limiting factor in connection with the amount of opioid that may be administered to the patient. That is, the amount of opioid capable of being administered to the patient may be limited due to the undesired occurrence of the aforementioned side effects. The limited amounts of opioid that may be administered to a patient may, in turn, result in a disadvantageously diminished degree of pain alleviation. The present combination methods and compositions may be used to advantageously increase the amount of opioid administered to a patient, thereby obtaining enhanced pain alleviation, while reducing, minimizing and/or avoiding undesirable side effects that may be associated with the opioid. The peripheral mu opioid antagonists employed in the methods and compositions of the present invention preferably have substantially no central nervous system activity and, accordingly, desirably do not affect the pain killing efficacy of the opioid.

While not intending to be bound by any theory or theories of operation, it is contemplated that opioid side effects, such as constipation, vomiting and nausea, may result from undesirable interaction of the opioid with peripheral mu receptors. Administration of a mu opioid antagonist according to the methods of the present invention may block interaction of the opioid compounds with the mu receptors, thereby preventing and/or inhibiting the side effects.

In accordance with the present invention, there are provided methods which comprise administering to a patient, *inter alia*, an opioid compound. A wide variety of opioids are available which may be suitable for use in the present methods and compositions. Generally speaking, it is only necessary that the opioid provide the desired effect (for example, pain alleviation), and be capable of being incorporated into the present combination products and methods (discussed in detail below). In preferred embodiments, the present methods and compositions may involve an opioid which is selected from alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil

and/or tramadol. More preferably, the opioid is selected from morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and/or tramadol.

The opioid component of the present compositions may further include one or more other active ingredients that may be conventionally employed in analgesic and/or cough-cold-antitussive combination products. Such conventional ingredients include, for example, aspirin, acetaminophen, phenylpropanolamine, phenylephrine, chlorpheniramine, caffeine, and/or guaifenesin. Typical or conventional ingredients that may be included in the opioid component are described, for example, in the *Physicians' Desk Reference*, 1999, the disclosures of which are hereby incorporated herein by reference, in their entirety.

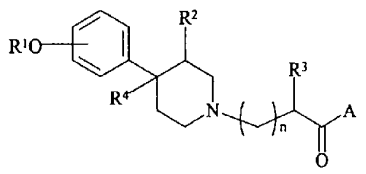
In addition, the opioid component may further include one or more compounds that may be designed to enhance the analgesic potency of the opioid and/or to reduce analgesic tolerance development. Such compounds include, for example, dextromethorphan or other NMDA antagonists (Mao, M. J. et al., *Pain* **1996**, *67*, 361), L-364,718 and other CCK antagonists (Dourish, C.T. et al., *Eur J Pharmacol* **1988**, *147*, 469), NOS inhibitors (Bhargava, H.N. et al., *Neuropeptides* **1996**, *30*, 219), PKC inhibitors (Bilsky, E.J. et al., *J Pharmacol Exp Ther* **1996**, *277*, 484), and dynorphin antagonists or antisera (Nichols, M.L. et al., *Pain* **1997**, *69*, 317). The disclosures of each of the foregoing documents are hereby incorporated herein by reference, in their entireties.

Other opioids, optional conventional opioid components, and optional compounds for enhancing the analgesic potency of the opioid and/or for reducing analgesic tolerance development, that may be employed in the methods and compositions of the present invention, in addition to those exemplified above, would be readily apparent to one of ordinary skill in the art, once armed with the teachings of the present disclosure.

In preferred form, the methods of the present invention may further involve administering to a patient a compound which is a mu peripheral opioid antagonist compound. The term peripheral designates that the compound acts primarily on physiological systems and components external to the central nervous system, *i.e.*, the compound preferably does not readily cross the blood-brain barrier. In preferred form, the peripheral mu opioid antagonist compounds employed in the methods of the present invention exhibit high levels of activity with respect to gastrointestinal tissue, while

exhibiting reduced, and preferably substantially no, central nervous system (CNS) activity. The term "substantially no CNS activity", as used herein, means that less than about 20% of the pharmacological activity of the peripheral mu opioid antagonist compounds employed in the present methods is exhibited in the CNS. In preferred embodiments, the peripheral mu opioid antagonist compounds employed in the present methods exhibit less than about 15% of their pharmacological activity in the CNS, with less than about 10% being more preferred. In even more preferred embodiments, the peripheral mu opioid antagonist compounds employed in the present methods exhibit less than about 5% of their pharmacological activity in the CNS, with about 0% (*i.e.*, no CNS activity) being still more preferred.

In more preferred embodiments, the present methods involve the administration to a patient of a mu peripheral opioid antagonist compound that is a piperidine-N-alkylcarboxylate compound. Preferred piperidine-N-alkylcarboxylate opioid antagonist compounds include, for example, the compounds disclosed in U.S. Patent Nos. 5,250,542; 5,159,081; 5,270,328; and 5,434,171, the disclosures of which are hereby incorporated herein by reference, in their entireties. A particularly preferred class of piperidine-N-alkylcarboxylate opioid antagonist compounds include those having the following formula (I):



I

wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

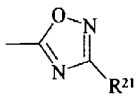
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substitued B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is



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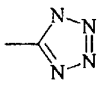

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C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

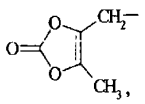
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



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alkylene substituted (C=O)D, or -R^{13}OC(=O)R^{14};

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to about 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

In the above formula (I), R^1 is hydrogen or alkyl. In preferred embodiments, R^1 is hydrogen or C_1-C_3alkyl. In even more preferred embodiments, R^1 is hydrogen.

In the above formula (I), R^2 is hydrogen, alkyl or alkenyl. In preferred embodiments, R^2 is hydrogen, C_1-C_3alkyl or C_2-C_6alkenyl. Also in preferred embodiments, R^2 is alkyl, with C_1-C_3alkyl being more preferred.

In the above formula (I), R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl. In preferred embodiments, R^3 is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, phenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkyl-substituted C_1-C_3alkyl or phenyl-substituted C_1-C_3 alkyl. In more preferred embodiments, R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

In the above formula (I), R^4 is hydrogen, alkyl or alkenyl. In preferred embodiments, R^4 is hydrogen, C_1-C_5alkyl or C_2-C_6alkenyl. In more preferred embodiments, R^4 is C_1-C_3alkyl, with methyl being even more preferred.

In the above formula (I), A is OR^5 or NR^6R^7.

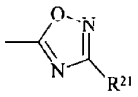
In the above formula (I), R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl. In preferred embodiments, R^5 is hydrogen, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substitutedC_1-C_3 alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, or phenyl-substituted C_1-C_3alkyl. Also in preferred embodiments, R^5 is hydrogen or alkyl, with C_1-C_3alkyl being more preferred.

In the above formula (I), R^6 is hydrogen or alkyl. Preferably, R^6 is hydrogen or C_1-C_3alkyl. Even more preferably, R^6 is hydrogen.

In the above formula (I), R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl or alkylene substituted B. In preferred embodiments, R^7 is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, phenyl, cycloalkyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, phenyl-substituted C_1-C_3alkyl or $(CH_2)_q$-B. In more preferred embodiments, R^7 is $(CH_2)_q$-B.

In certain alternative embodiments, in the above formula (I), R^6 and R^7 form, together with the nitrogen atom to which they are attached, a heterocyclic ring.

The group B in the definition of R^7 is



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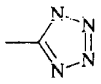


,

C(=O)W or NR^8R^9. In preferred embodiments, B is C(=O)W.

The group R^8 in the definition of B is hydrogen or alkyl. In preferred embodiments, R^8 is hydrogen or C_1-C_3alkyl.

The group R^9 in the definition of B is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl. In preferred embodiments, R^9 is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, cycloalkyl-substituted C_1-C_3alkyl, cycloalkyl, C_5-C_8cycloalkenyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, phenyl or phenyl-substituted C_1-C_3alkyl.

In certain alternative embodiments, in the definition of B, R^8 and R^9 form, together with the nitrogen atom to which they are attached, a heterocyclic ring.

The group W in the definition of B is OR^{10}, $NR^{11}R^{12}$ or OE.

The group R^{10} in the definition of W is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl. In preferred embodiments, R^{10} is hydrogen, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, or phenyl-substituted C_1-C_3alkyl. Also in preferred embodiments, R^{10} is hydrogen, alkyl, preferably C_1-C_5alkyl, phenyl-substituted alkyl, preferably phenyl-substituted C_1-C_2alkyl, cycloalkyl or cycloalkyl-substituted alkyl, preferably C_5-C_6cycloalkyl-substituted C_1-C_3alkyl.

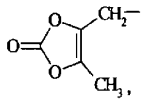
The group R^{11} in the definition of W is hydrogen or alkyl. In preferred embodiments, R^{11} is hydrogen or C_1-C_3alkyl.

The group R^{12} in the definition of W is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene-substituted C(=O)Y. In preferred embodiments, R^{12} is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, phenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, phenyl-substituted C_1-C_3alkyl, or alkylene-substituted C(=O)Y. Also in preferred embodiments, R^{12} is hydrogen, alkyl, preferably C_1-C_3alkyl or $(CH_2)_mC(O)Y$, where m is 1 to 4.

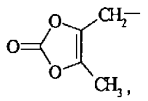
The group Y in the definition of R^{12} is OR^{18} or $NR^{19}R^{20}$.

In certain alternative embodiments, in the definition of W, R^{12} and R^{13} form, together with the nitrogen atom to which they are attached, a heterocyclic ring.

The group E in the definition of W is



alkylene substituted (C=O)D, or -R^{13}OC(=O)R^{14}. In preferred embodiments, E is



$(CH_2)_m$(C=O)D (where m is as defined above), or -R^{13}OC(=O)R^{14}.

The group R^{13} in the definition of E is alkyl substituted alkylene. In preferred embodiments, R^{13} is C_1-C_3alkyl substituted methylene. In more preferred embodiments, R^{13} is -CH(CH_3)- or -CH(CH_2CH_3)-.

The group R^{14} in the definition of E is alkyl. In preferred embodiments, R^{14} is C_1-C_{10}alkyl.

The group D in the definition of E is D is OR^{15} or $NR^{16}R^{17}$.

The group R^{15} in the definition of D is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl. In preferred embodiments, R^{15} is hydrogen, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, or phenyl-substituted C_1-C_3alkyl. Also in preferred embodiments, R^{15} is hydrogen or alkyl, with C_1-C_3alkyl being more preferred.

The group R^{16} in the definition of D is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl. In preferred embodiments, R^{16} is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, phenyl, phenyl-substituted C_1-C_3alkyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl. In even more preferred embodiments, R^{16} is methyl or benzyl.

The group R^{17} in the definition of D is hydrogen or alkyl. In preferred embodiments, R^{17} is hydrogen or C_1-C_3 alkyl. In even more preferred embodiments, R^{17} is hydrogen.

In certain alternative embodiments, in the definition of D, R^{16} and R^{17} form, together with the nitrogen atom to which they are attached, a heterocyclic ring.

The group R^{18} in the definition of Y is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl. In preferred embodiments, R^{18} is hydrogen, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, or phenyl-substituted C_1-C_3alkyl. In more preferred embodiments, R^{18} is hydrogen or C_1-C_3alkyl.

The group R^{19} in the definition of Y is hydrogen or alkyl. In preferred embodiments, R^{19} is hydrogen or C_1-C_3alkyl.

The group R^{20} in the definition of Y is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl. In preferred embodiments, R^{20} is hydrogen, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, phenyl, cycloalkyl, C_5-C_8cycloalkenyl, cycloalkyl-substituted C_1-C_3alkyl, C_5-C_8cycloalkenyl-substituted C_1-C_3alkyl, or phenyl-substituted C_1-C_3alkyl. In more preferred embodiments, R^{20} is hydrogen or C_1-C_3alkyl.

In certain alternative embodiments, in the definition of Y, R^{19} and R^{20} form, together with the nitrogen atom to which they are attached, a heterocyclic ring.

The group R^{21} in the definition of B is hydrogen or alkyl. Preferably, R^{21} is hydrogen or C_1-C_3alkyl. Even more preferably, R^{21} is hydrogen.

In the above formula (I), n is 0 to about 4. In preferred embodiments, n is about 1 or 2.

In the above definition of R^7, q is about 1 to about 4. In preferred embodiments, q is about 1 to about 3.

In the above definition of E, m is about 1 to about 4. In preferred embodiments, m is about 1 to about 3.

The compounds of formula (I) can occur as the trans and cis stereochemical isomers by virtue of the substituents at the 3- and 4-positions of the piperidine ring, and such stereochemical isomers are within the scope of the claims. The term "trans", as used herein, refers to R^2 in position 3 being on the opposite side from the methyl group in position 4, whereas in the "cis" isomer R^2 and the 4-methyl are on the same side of the

ring. In the methods of the present invention, the compounds employed may be the individual stereoisomers, as well as mixtures of stereoisomers. In the most preferred embodiments, the methods of the present invention involve compounds of formula (I) wherein the group R^2 at the 3-position is situated on the opposite side of the ring, *i.e.*, trans to the methyl group in the 4-position and on the same side of the ring. These trans isomers can exist as the 3R,4R-isomer, or the 3S,4S-isomer.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" refers to "right" and refers 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 is based upon their 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.

Preferred piperidine-N-alkylcarboxylate compounds for use in the methods of the present invention are those of formula (I) in which the configuration of substituents on the piperidine ring is 3R and 4R.

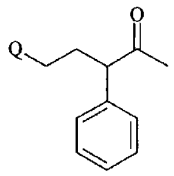
When R^3 is not hydrogen, the carbon atom to which R^3 is attached is asymmetric. As such, this class of compounds can further exist as the individual R or S stereoisomers at this chiral center, or as mixtures of stereoisomers, and all are contemplated within the scope of the present invention. Preferably, a substantially pure stereoisomer of the compounds of this invention is used, *i.e.*, an isomer in which the configuration at the chiral center to which R^3 is attached is R or S, *i.e.*, those compounds in which the configuration at the three chiral centers is preferably 3R, 4R, S or 3R, 4R, R.

Furthermore, other asymmetric carbons can be introduced into the molecule depending on the structure of A. As such, these classes of compounds can exist as the individual R or S stereoisomers at these chiral centers, or as mixtures of stereoisomers, and all are contemplated as being within the scope of methods of the present invention.

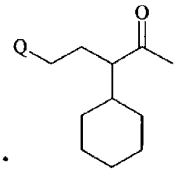
Preferred piperidine-N-alkylcarboxylate compounds for use in the methods of the present invention include the following:

U-OCH_2CH_3; U-OH; G-OH; U-$NHCH_2C(O)NHCH_3$; U-$NHCH_2C(O)NH_2$; G-$NHCH_2C(O)NHCH_3$; U-$NHCH_2C(O)NHCH_2CH_3$; G-$NH(CH_2)_3C(O)OCH_2CH_3$; G-$NHCH_2C(O)OH$; M-$NHCH_2C(O)NH_2$; M-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$; X-$OCH_2CH_3$; X-OH; X-$NH(CH_2)_2CH_3$; Z-$NH(CH_2)_3C(O)OCH_2CH_3$; X-$NHCH_2C(O)OH$; Z-$NH(CH_2)_2N(CH_3)_2$; Z-$NH(CH_2)_2C(O)NHCH_2CH_3$; X-$OCH_2(C_6H_5)$; X-$N(CH_3)_2$; Z-$NH(CH_2)_3C(O)NHCH_3$; Z-$NH(CH_2)_3C(O)NH_2$; Z-$NH(CH_2)_3C(O)NHCH_2CH_3$; X-$OCH_2C(O)OCH_3$; X-$OCH_2C(O)NHCH_3$; and X-$N(CH_3)CH_2C(O)CH_2CH_3$; in which:

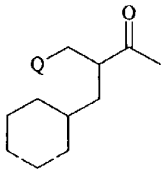
U represents



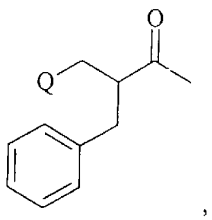
G represents



M represents

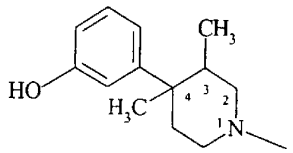


Z represents



X represents -ZNHCH$_2$C(=O)-;

wherein Q represents

trans-3,4-dimethyl 

Particularly preferred piperidine-N-alkylcarboxylate compounds for use in the methods of the present invention include the following:

Z-OH; Z-NH(CH$_2$)$_2$C(O)OH; G-NH(CH$_2$)$_2$C(O)NH$_2$; G-NH(CH$_2$)$_2$C(O)NHCH$_3$; G-NHCH$_2$C(O)NH$_2$; G-NHCH$_2$C(O)NHCH$_2$CH$_3$; G-NH(CH$_2$)$_3$C(O)NHCH$_3$; G-NH(CH$_2$)$_2$C(O)OH; G-NH(CH$_2$)$_3$C(O)OH; X-NH$_2$; X-NHCH(CH$_3$)$_2$; X-OCH$_2$CH(CH$_3$)$_2$; X-OCH$_2$C$_6$H$_5$; X-OH; X-O(CH$_2$)$_4$CH$_3$; X-O-(4-methoxycyclohexyl); X-OCH(CH$_3$)OC(O)CH$_3$; X-OCH$_2$C(O)NHCH$_2$(C$_6$H$_5$); M-NHCH$_2$C(O)OH; M-NH(CH$_2$)$_2$C(O)OH; M-NH(CH$_2$)$_2$C(O)NH$_2$; U-NHCH$_2$C(O)OCH$_2$CH$_3$; and U-NHCH$_2$C(O)OH;

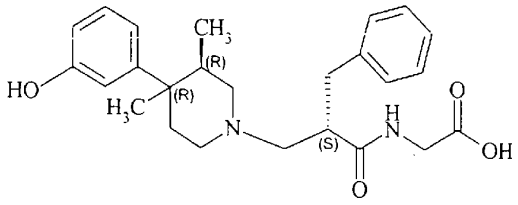
wherein Z, G, X, M and U are as defined above.

Stated another way, in accordance with preferred embodiments of the invention, the compound of formula (I) has the formula Q-CH$_2$CH(CH$_2$(C$_6$H$_5$))C(O)OH, Q-CH$_2$CH$_2$CH(C$_6$H$_5$)C(O)NHCH$_2$C(O)OCH$_2$CH$_3$, Q-CH$_2$CH$_2$CH(C$_6$H$_5$)C(O)NHCH$_2$C(O)OH, Q-CH$_2$CH$_2$CH(C$_6$H$_5$)C(O)NHCH$_2$C(O)NHCH$_3$, Q-CH$_2$CH$_2$CH(C$_6$H$_5$)C(O)NHCH$_2$C(O)NHCH$_2$CH$_3$, G-NH(CH$_2$)$_2$C(O)NH$_2$, G-NH(CH$_2$)$_2$C(O)NHCH$_3$, G-NHCH$_2$C(O)NH$_2$, G-NHCH$_2$C(O)NHCH$_3$, G-NHCH$_2$C(O)NHCH$_2$CH$_3$, G-NH(CH$_2$)$_3$C(O)OCH$_2$CH$_3$, G-NH(CH$_2$)$_3$C(O)NHCH$_3$,

G-$NH(CH_2)_2C(O)OH$, G-$NH(CH_2)_3C(O)OH$,
Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NHCH_2C(O)OH$,
Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)OH$,
Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$,
Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$,
Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$,
Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-$NH(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$,
Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$,
Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2C(O)O(CH_2)_4CH_3$,
Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl),
Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$ or Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$;
wherein Q, G and Z are as defined above.

In even more preferred embodiments, the compound of formula (I) has the formula (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)-Z-$NHCH_2C(O)OH$, (-)-Z-$NHCH_2C(O)OH$, (3R,4R,R)-Z-$NHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-Z-$NHCH_2C(O)NHCH_2(C_6H_5)$ or (3R,4R)-G-$NH(CH_2)_3C(O)OH$, where Z and G are as defined above. In still more preferred embodiments, the compound of formula (I) has the formula (+)-Z-$NHCH_2C(O)OH$ or (-)-Z-$NHCH_2C(O)OH$ where Z is as defined above.

Compounds of formula (I) that act locally on the gut, have high potency, and are orally active are most preferred. A particularly preferred embodiment of the present invention is the compound (+)-Z-$NHCH_2C(O)OH$, *i.e.*, the compound of the following formula (II).



II

The compound of formula (II) has low solubility in water except at low or high pH conditions. Zwitterionic character may be inherent to the compound, and may impart desirable properties such as poor systemic absorption and sustained local affect on the gut following oral administration.

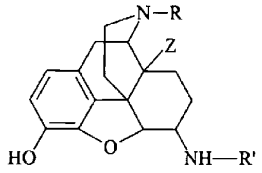
In an alternate embodiment, the methods of the present invention may involve administering to a patient a peripheral mu opioid antagonist compound that is a quaternary morphinan compound. Examples of quaternary morphinan compounds that may be suitable for use in the methods of the present invention include, for example, quaternary salts of N-methylnaltrexone, N-methylnaloxone, N-methylnalorphine, N-diallylnormorphine, N-allyllevallorphan and N-methylnalmefene.

In yet another alternate embodiment, the methods of the present invention may involve administering to a patient a peripheral mu opioid antagonist compound in the form of an opium alkaloid derivative. The term "opium alkaloid derivative", as used herein, refers to peripheral mu opioid antagonist compounds that are synthetic or semi-synthetic derivatives or analogs of opium alkaloids. In preferred form, the opium alkaloid derivatives employed in the methods of the present invention exhibit high levels of morphine antagonism, while exhibiting reduced, and preferably substantially no, agonist activity. The term "substantially no agonist activity", as used herein in connection with the opium alkaloid derivatives, means that the maximal response with respect to electrically stimulated guinea pig ileum, at a concentration of 1 μM, is about 60% or less relative to morphine. In preferred embodiments, the opium alkaloid derivatives employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1 μM, of about 50% or less relative to morphine, with a maximal response of about 40% or less being more preferred. In even more preferred embodiments, the opium alkaloid derivatives employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1 μM, of about 30% or less relative to morphine, with a maximal response of about 20% or less being more preferred. In still more preferred embodiments, the opium alkaloid derivatives employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1 μM, of about 10% or less relative to morphine. In certain particularly preferred

embodiments, the opium alkaloid derivatives have a maximal response with respect to guinea pig ileum, at a concentration of 1 μM, of about 0% (*i.e.*, no response).

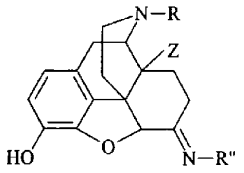
Suitable methods for determining maximal response of opium alkaloid derivatives with respect to electrically stimulated guinea pig ileum are described, for example, in U.S. Patent Nos. 4,730,048 and 4,806,556, the disclosures of which are hereby incorporated herein by reference, in their entireties.

In preferred form, the opium alkaloid derivatives employed in the methods of the present invention have the following formulas (III) or (IV):



III

or



IV

wherein:

R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl;

Z is hydrogen or OH;

R' is X'-J(L)(T), wherein:

J is alkylene or alkenylene;

L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl; and

T is CO_2H, SO_3H, amino or guanidino;

X' is a direct bond or C(=O); and

R" is NH-J(L)(T) or guanidino;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

In the compounds of formulas (III) and (IV) above, R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl. In preferred embodiments, R is C_1-C_5alkyl, C_3-C_6cycloakyl-substituted alkyl, aryl, arylalkyl or trans-C_2-C_5alkenyl. In more preferred embodiments, R is C_1-C_3alkyl, allyl or cyclopropylmethyl, with cyclopropylmethyl being even more preferred.

In the compounds of formulas (III) and (IV) above, Z is hydrogen or OH. In preferred embodiments, Z is OH.

In the compounds of formulas (III) and (IV), R' is X-J(L)(T) and R" is NH-J(L)(T) or guanidino.

In the definitions of R' and R", G is alkylene or alkenylene. In preferred embodiments, J is C_1-C_5alkylene, C_2-C_6alkylene interrupted by an oxygen atom, or C_2-C_5alkenylene.

In the definitions of R' and R", L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl. In preferred embodiments, L is hydrogen, amino, or C_1-C_5alkyl optionally substituted with CO_2H, OH or phenyl. In more preferred embodiments, L is hydrogen or amino.

In the definitions of R' and R", T is CO_2H, SO_3H, amino or guanidino. In preferred embodiments, T is CO_2H or guanidino.

In the definition of R', X is a direct bond or C(=O).

Preferred opioid alkaloid derivatives that may be employed in the methods of the present invention include compounds of formula (III) wherein R is cyclopropylmethyl, Z is OH, and R' is selected from $C(=O)(CH_2)_2CO_2H$, $C(=O)(CH_2)_3CO_2H$, $C(=O)CH=CHCO_2H$, $C(=O)CH_2OCH_2CO_2H$, $C(=O)CH(NH_2)(CH_2)_3NHC(=NH)NH_2$ or $C(=O)CH(NH_2)CH_2CO_2H$. Also preferred are

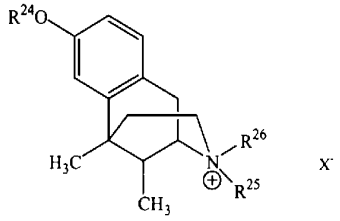
opioid alkaloid derivatives of formula (III) wherein R is cyclopropylmethyl, Z is OH, and R'isCH2CO2H. In other preferred embodiments, the opioid alkaloid derivatives that may be employed in the methods of the present invention include compounds of formula (IV) wherein R is cyclopropylmethyl, Z is OH, and R"isNHCH2CO2H.

Other opioid alkaloid derivatives that may be employed in the methods of the present invention are described, for example, in U. S. Patent Nos. 4, 730, 048 and 4, 806, 556, the disclosures of which are hereby incorporated herein by reference, in their entireties.

In still another alternate embodiment, the methods of the present invention may involve administering to a patient a peripheral mu opioid antagonist compound in the form of a quaternary benzomorphan compound. In preferred form, the quaternary benzomorphan compounds employed in the methods of the present invention exhibit high levels of morphine antagonism, while exhibiting reduced, and preferably substantially no, agonist activity. The term"substantially no agonist activity", as used herein in connection with the quaternary benzomorphan compounds, means that the maximal response with respect to electrically stimulated guinea pig ileum, at a concentration of 1iM, is about 60% or less relative to morphine. In preferred embodiments, the quaternary benzomorphan compounds employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1pM, of about 50% or less relative to morphine, with a maximal response of about 40% or less being more preferred. In even more preferred embodiments, the quaternary benzomorphan compounds employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1uM, of about 30% or less relative to morphine, with a maximal response of about 20% or less being more preferred. In still more preferred embodiments,

the quaternary benzomorphan compounds employed in the present methods have a maximal response with respect to guinea pig ileum, at a concentration of 1pM, of about 10% or less relative to morphine. In certain particularly preferred embodiments, the quaternary benzomorphan compounds have a maximal response with respect to guinea pig ileum, at a concentration of 1pM, of about 0% (i. e., no response).

In preferred form, the quaternary benzomorphan compounds employed in the methods of the present invention have the following formula (V):



V

where:

R^{24} is hydrogen or acyl;

R^{25} is alkyl or alkenyl;

R^{26} is alkyl or alkenyl; and

X^- is a counter ion;

or a stereoisomer, prodrug, or pharmaceutically acceptable hydrate or N-oxide thereof.

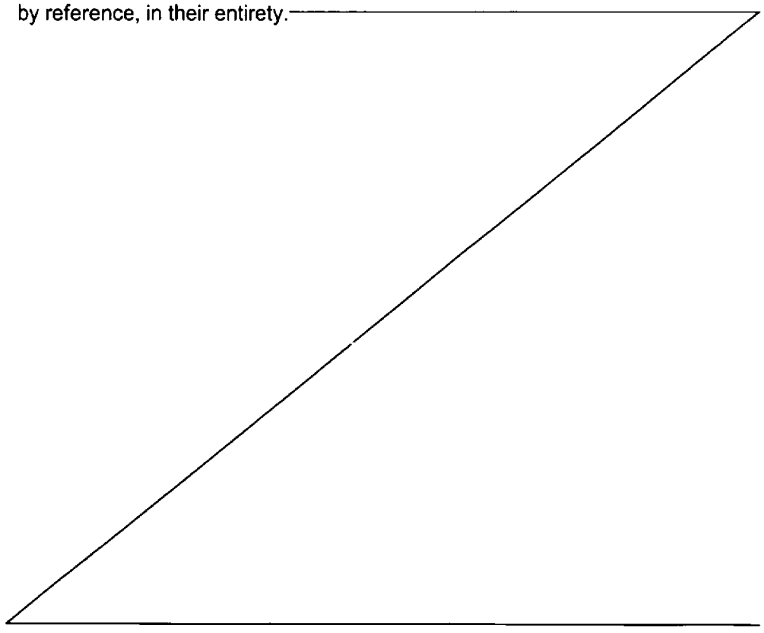
In the above formula (V), R^{24} is hydrogen or acyl. In preferred embodiments, R^{24} is hydrogen or C_1-C_6 acyl. In more preferred embodiments, R^{24} is hydrogen or C_1-C_2 acyl. In even more preferred embodiments, R^{24} is hydrogen or acetoxy, with hydrogen being still more preferred.

In the above formula (V), R^{25} and R^{26} are independently alkyl or alkenyl. In preferred embodiments, R^{25} and R^{26} are C_1-C_6 alkyl or C_2-C_6

alkenyl. In even more preferred embodiments, R^{25} and R^{26} are C_1-C_3 alkyl or C_2-C_3 alkenyl. In still more preferred embodiments, R^{25} is propyl or allyl and R^{26} is propyl or methyl.

Preferred quaternary benzomorphan compounds that may be employed in the methods of the present invention include the following compounds of formula (V): 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide; 2'-hydroxy-5,9-dimethyl-2,2-di-n-propyl-6,7-benzomorphanium bromide; 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide; 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide; and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

Other quaternary benzomorphan compounds that may be employed in the methods of the present invention are described, for example, in U. S. PatentNo. 3, 723, 440, the disclosures of which are hereby incorporated herein by reference, in their entirety.



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Other mu opioid antagonist compounds which may be employed in the methods and compositions of the present invention, in addition to those exemplified above, would be readily apparent to one of ordinary skill in the art, once armed with the teachings of the present disclosure.

The compounds employed in the methods of the present invention may exist in prodrug form. As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug, for example, as according to formulas (I) or (II) or other formulas or compounds employed in the methods of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, etc.) the compounds employed in the present methods may, if desired, be delivered in prodrug form. Thus, the present invention contemplates methods of delivering prodrugs. Prodrugs of the compounds employed in the present invention, for example formula (I), 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.

Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

The compounds employed in the methods of the present invention may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by the methods described below, or variations thereon as appreciated by the skilled artisan. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

As discussed in detail above, compounds employed in the present methods may contain one or more asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. Thus, all chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. It is well known in the art how to prepare and isolate such optically active forms. For example, mixtures of stereoisomers may be separated by standard techniques including, but not limited to, resolution of racemic forms, normal, reverse-phase, and chiral chromatography, preferential salt formation, recrystallization, and the like, or by chiral synthesis either from chiral starting materials or by deliberate synthesis of target chiral centers.

As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Preferred protecting groups include the benzyloxycarbonyl group and the tert-butyloxycarbonyl group. Other preferred protecting groups that may be employed in accordance with the present invention may be described in Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2d. Ed., Wiley & Sons, 1991.

Piperidine-N-alkylcarboxylate compounds according to the present invention may be synthesized employing methods taught, for example, in U.S. Patent Nos. 5,250,542, 5,434,171, 5,159,081, and 5,270,328, the disclosures of which are hereby incorporated herein by reference in their entireties. For example, the 3-substituted-4-methyl-4-(3-hydroxy- or alkanoyloxyphenyl)piperidine derivatives employed as starting materials in the synthesis of the present compounds may be prepared by the general procedure taught in U.S. Patent No. 4,115,400 and U.S. Patent No. 4,891,379, the disclosures of which are hereby incorporated herein by reference in their entireties. The starting material for the synthesis of compounds described herein, (3R,4R)-4-(3-hydroxypheny)-3,4-dimethylpiperidine, may be prepared by the procedures described in U.S. Patent No. 4,581,456, the disclosures of which are hereby incorporated herein by

reference, in their entirety, but adjusted as described such that the β-stereochemistry is preferred.

The first step of the process may involves the formation of the 3-alkoxyphenyllithium reagent by reacting 3-alkoxybromobenzene with an alkyllithium reagent. This reaction may be performed under inert conditions and in the presence of a suitable non-reactive solvent such as dry diethyl ether or preferably dry tetrahydrofuran. Preferred alkyllithium reagents used in this process are n-butyllithium, and especially sec-butyllithium. Generally, approximately an equimolar to slight excess of alkyllithium reagent may be added to the reaction mixture. The reaction may be conducted at a temperature of from about -20°C and about -100°C, more preferably from about -50°C to about -55°C.

Once the 3-alkoxyphenyllithium reagent has formed, approximately an equimolar quantity of a 1-alkyl-4-piperidone may be added to the mixture while maintaining the temperature between -20°C and -100°C. The reaction is typically complete after about 1 to 24 hours. At this point, the reaction mixture may be allowed to gradually warm to room temperature. The product may be isolated by the addition to the reaction mixture of a saturated sodium chloride solution to quench any residual lithium reagent. The organic layer may be separated and further purified if desired to provide the appropriate 1-alkyl-4-(3-alkoxyphenyl)piperidinol derivative.

The dehydration of the 4-phenylpiperidinol prepared above may be accomplished with a strong acid according to well known procedures. While dehydration occurs in various amounts with any one of several strong acids such as hydrochloric acid, hydrobromic acid, and the like, dehydration is preferably conducted with phosphoric acid, or especially p-toluenesulfonic acid in toluene or benzene. This reaction may be typically conducted under reflux conditions, more generally from about 50°C and 150°C. The product thus formed may be isolated by basifying an acidic aqueous solution of the salt form of the product and extracting the aqueous solution with a suitable water immiscible solvent. The resulting residue following evaporation can then be further purified if desired.

The 1-alkyl-4-methyl-4-(3-alkoxyphenyl)tetrahydropyridine derivatives may be prepared by a metalloenamine alkylation. This reaction is preferably conducted

with n-butyllithium in tetrahydrofuran (THF) under an inert atmosphere, such as nitrogen or argon. Generally, a slight excess of n-butyllithium may be added to a stirring solution of the 1-alkyl-4-(3-alkoxyphenyl)-tetrahydropyridine in THF cooled to a temperature in the range of from about -50°C to about 0°C, more preferably from about -20°C to -10°C. This mixture may be stirred for approximately 10 to 30 minutes followed by the addition of approximately from 1.0 to 1.5 equivalents of methyl halide to the solution while maintaining the temperature of the reaction mixture below 0°C. After about 5 to 60 minutes, water may be added to the reaction mixture and the organic phase may be collected. The product can be purified according to standard procedures, but the crude product is preferably purified by either distilling it under vacuum or slurrying it in a mixture of hexane:ethyl acetate (65:35, v:v) and silica gel for about two hours. According to the latter procedure, the product may be then isolated by filtration followed by evaporating the filtrate under reduced pressure.

The next step in the process may involve the application of the Mannich reaction of aminomethylation to non-conjugated, endocyclic enamines. This reaction is preferably carried out by combining from about 1.2 to 2.0 equivalents of aqueous formaldehyde and about 1.3 to 2.0 equivalents of a suitable secondary amine in a suitable solvent. While water may be the preferred solvent, other non-nucleophilic solvents, such as acetone and acetonitrile can also be employed in this reaction. The pH of this solution may be adjusted to approximately 3.0 to 4.0 with an acid that provides a non-nucleophilic anion. Examples of such acids include sulfuric acid, the sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, phosphoric acid, and tetrafluoroboric acid, with sulfuric acid being preferred. To this solution may be added one equivalent of a 1-alkyl-4-methyl-4-(3-alkoxyphenyl)tetrahydropyridine, typically dissolved in aqueous sulfuric acid, and the pH of the solution may be readjusted with the non-nucleophilic acid or a suitable secondary amine. The pH is preferably maintained in the range of from about 1.0 to 5.0, with a pH of about 3.0 to 3.5 being more preferred during the reaction. The reaction is substantially complete after about 1 to 4 hours, more typically about 2 hours, when conducted at a temperature in the range of from about 50°C to about 80°C, more preferably about 70°C. The reaction may then be cooled to approximately 30°C, and added to a sodium hydroxide solution. This solution may then be extracted with a water

immiscible organic solvent, such as hexane or ethyl acetate, and the organic phase, following thorough washing with water to remove any residual formaldehyde, may be evaporated to dryness under reduced pressure.

The next step of the process may involve the catalytic hydrogenation of the prepared 1-alkyl-4-methyl-4-(3-alkoxyphenyl)-3-tetrahydropyridinemethanamine to the corresponding trans-1-alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)piperidine. This reaction actually occurs in two steps. The first step is the hydrogenolysis reaction wherein the exo C-N bond is reductively cleaved to generate the 3-methyltetrahydropyridine. In the second step, the 2,3-double bond in the tetrahydropyridine ring is reduced to afford the desired piperidine ring.

Reduction of the enamine double bond introduced the crucial relative stereochemistry at the 3 and 4 carbon atoms of the piperidine ring. The reduction generally does not occur with complete stereoselectivity. The catalysts employed in the process may be chosen from among the various palladium and preferably platinum catalysts.

The catalytic hydrogenation step of the process is preferably conducted in an acidic reaction medium. Suitable solvents for use in the process include the alcohols, such as methanol or ethanol, as well as ethyl acetate, tetrahydrofuran, toluene, hexane, and the like.

Proper stereochemical outcome may be dependent on the quantity of catalyst employed. The quantity of catalyst required to produce the desired stereochemical result may be dependent upon the purity of the starting materials in regard to the presence or absence of various catalyst poisons.

The hydrogen pressure in the reaction vessel may not be critical but can be in the range of from about 5 to 200 psi. Concentration of the starting material by volume is preferably around 20 mL of liquid per gram of starting material, although an increased or decreased concentration of the starting material can also be employed. Under the conditions specified herein, the length of time for the catalytic hydrogenation may not be critical because of the inability for over-reduction of the molecule. While the reaction can continue for up to 24 hours or longer, it may not be necessary to continue the reduction conditions after the uptake of the theoretical two moles of hydrogen. The product may

then be isolated by filtering the reaction mixture for example through infusorial earth, and evaporating the filtrate to dryness under reduced pressure. Further purification of the product thus isolated may not be necessary and preferably the diastereomeric mixture may be carried directly on to the following reaction.

The alkyl substituent may be removed from the 1-position of the piperidine ring by standard dealkylation procedures. Preferably, a chloroformate derivative, especially the vinyl or phenyl derivatives, may be employed and removed with acid. Next, the prepared alkoxy compound may be dealkylated to the corresponding phenol. This reaction may be generally carried out by reacting the compound in a 48% aqueous hydrobromic acid solution. This reaction may be substantially complete after about 30 minutes to 24 hours when conducted at a temperature of from about 50°C to about 150°C, more preferably at the reflux temperature of the reaction mixture. The mixture may then be worked up by cooling the solution, followed by neutralization with base to an approximate pH of 8. This aqueous solution may be extracted with a water immiscible organic solvent. The residue following evaporation of the organic phase may then be used directly in the following step.

The compounds employed as starting materials to the compounds of the invention can also be prepared by brominating the 1-alkyl-4-methyl-4-(3-alkoxyphenyl)-3-tetrahydropyridinemethanamine at the 3-position, lithiating the bromo compound thus prepared, and reacting the lithiated intermediate with a methylhalide, such as methyl bromide to provide the corresponding 1-alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)tetrahydropyridinemethanamine. This compound may then be reduced and converted to the starting material as indicated above.

As noted above, the compounds of the present invention can exist as the individual stereoisomers. Preferably reaction conditions are adjusted as disclosed in U.S. Patent No. 4,581,456 or as set forth in Example 1 of U.S. Patent No. 5,250,542 to be substantially stereoselective and provide a racemic mixture of essentially two enantiomers. These enantiomers may then be resolved. A procedure which may be employed to prepare the resolved starting materials used in the synthesis of these compounds includes treating a racemic mixture of alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)piperidine with either (+)- or (-)-ditoluoyl tartaric acid to provide the resolved intermediate. This compound may then be

dealkylated at the 1-position with vinyl chloroformate and finally converted to the desired 4-(3-hydroxyphenyl)piperidine isomer.

As will be understood by those skilled in the art, the individual enantiomers of the invention can also be isolated with either (+) or (-) dibenzoyl tartaric acid, as desired, from the corresponding racemic mixture of the compounds of the invention. Preferably the (+)-trans enantiomer is obtained.

Although the (+)trans-3,4 stereoisomer is preferred, all of the possible stereoiosmers of the compounds described herein are within the contemplated scope of the present invention. Racemic mixtures of the stereoisomers as well as the substantially pure stereoisomers are within the scope of the invention. The term "substantially pure", as used herein, refers to at least about 90 mole percent, more preferably at least about 95 mole percent and most preferably at least about 98 mole percent of the desired stereoisomer is present relative to other possible stereoisomers.

Intermediates can be prepared by reacting a 3,4-alkyl-substituted-4-(3-hydroxyphenyl)piperidine with a compound of the formula $LCH_2(CH_2)_{n-1}CHR^3C(O)E$ where L is a leaving group such as chlorine, bromine or iodine, E is a carboxylic acid, ester or amide, and R^3 and n are as defined hereinabove. Preferably L may be chlorine and the reaction is carried out in the presence of a base to alkylate the piperidine nitrogen. For example 4-chloro-2-cyclohexylbutanoic acid, ethyl ester can be contacted with (3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidine to provide 4-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]butanoic acid, ethyl ester. Although the ester of the carboxylic acid may be preferred, the free acid itself or an amide of the carboxylic acid may be used.

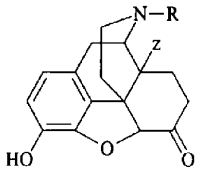
In alternative synthesis, the substituted piperidine can be contacted with a methylene alkyl ester to alkylate the piperidine nitrogen. For example, 2-methylene-3-phenylproponic acid, ethyl ester can be contacted with a desired piperidine to provide 2-benzyl-3-piperidinepropanoic acid ethyl ester.

Another synthetic route can involve the reaction of a substituted piperidine with a haloalkylnitrile. The nitrile group of the resulting piperidine alkylnitrile can be hydrolyzed to the corresponding carboxylic acid.

With each of the synthetic routes, the resulting ester or carboxylic acid can be reacted with an amine or alcohol to provide modified chemical structures. In the

preparation of amides, the piperidine-carboxylic acid or -carboxylic acid ester may be reacted with an amine in the presence of a coupling agent such as dicyclohexylcarbodiimide, boric acid, borane-trimethylamine, and the like. Esters can be prepared by contacting the piperidine-carboxylic acid with the appropriate alcohol in the presence of a coupling agent such as p-toluenesulfonic acid, boron trifluoride etherate or N,N'-carbonyldiimidazole. Alternatively, the piperidine-carboxylic acid chloride can be prepared using a reagent such as thionyl chloride, phosphorus trichloride, phosphorus pentachloride and the like. This acyl chloride can be reacted with the appropriate amine or alcohol to provide the corresponding amide or ester.

Opium alkaloid derivatives according to the present invention may be synthesized employing methods taught, for example, in U.S. Patent Nos. 4,730,048 and 4,806,556, the disclosures of which are hereby incorporated herein by reference in their entireties. For example, opium alkaloid derivatives of formula (III) may be prepared by attaching hydrophilic, ionizable moieties R' and R" to the 6-amino group of naltrexamine (formula (III) where R is (cyclopropyl)methyl, Z is OH and R' is H) or oxymorphamine (formula (III) where R is CH_3, Z is OH and R' is H). The opium alkaloid derivatives of formula IV may be prepared by converting the 6-keto-group of oxymorphone (formula (VI) where R is CH_3 and Z is OH) or naltrexone (formula (VI) where R is (cyclopropyl)methyl and Z is OH) to the ionizable, hydrophilic group (R"N=) by a Schiff base reaction with a suitable amino-compound.



VI

In a similar fashion, deoxy-opiates of formulae (III) and (IV) wherein Z is hydrogen may be prepared from readily available starting materials.

The compounds of formula (V) may be synthesized employing methods taught, for example, in U.S. Patent No. 3,723,440, the disclosures of which are hereby incorporated herein by reference in their entirety.

The compounds employed in the methods of the present invention including, for example, opioid and peripheral mu opioid antagonist compounds, may be administered by any means that results in the contact of the active agents with the agents' site or site(s)of action in the body of a patient. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. For example, they may be administered as the sole active agents in a pharmaceutical composition, or they can be used in combination with other therapeutically active ingredients.

The compounds are preferably combined with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980), the disclosures of which are hereby incorporated herein by reference, in their entirety.

Compounds of the present invention can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, *e.g.*, orally or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation, aerosol and rectal systemic.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The amount of active compound(s) in such therapeutically useful compositions is preferably such that a suitable dosage will be obtained. Preferred compositions or preparations according to the

present invention may be prepared so that an oral dosage unit form contains from about 0.1 to about 1000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder, such as gum tragacanth, acacia, corn starch or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent, such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form is preferably pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compounds as free bases or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form is preferably sterile and fluid to provide easy syringability. It is preferably stable under the conditions of manufacture and storage and is preferably preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures

thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of a dispersion, and by the use of surfactants. The prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions may be achieved by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions may be prepared by incorporating the active compounds in the required amounts, in the appropriate solvent, with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions may be prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation may include vacuum drying and the freeze drying technique which yield a powder of the active ingredient, plus any additional desired ingredient from the previously sterile-filtered solution thereof.

The therapeutic compounds of this invention may be administered to a patient alone or in combination with a pharmaceutically acceptable carrier. As noted above, the relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

The dosage of the compounds of the present invention that will be most suitable for prophylaxis or treatment will vary with the form of administration, the particular compound chosen and the physiological characteristics of the particular patient under treatment. Generally, small dosages may be used initially and, if necessary, increased by small increments until the desired effect under the circumstances is reached. Generally speaking, oral administration may require higher dosages.

The combination products of this invention, such as pharmaceutical compositions comprising opioids in combination with a peripheral mu opioid antagonist compound, such as the compounds of formula (I), may be in any dosage form, such as

those described herein, and can also be administered in various ways, as described herein. In a preferred embodiment, the combination products of the invention are formulated together, in a single dosage form (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the combination products are not formulated together in a single dosage form, the opioid compounds and the peripheral mu opioid antagonist compounds may be administered at the same time (that is, together), or in any order. When not administered at the same time, preferably the administration of an opioid and a peripheral mu opioid antagonist occurs less than about one hour apart, more preferably less than about 30 minutes apart, even more preferably less than about 15 minutes apart, and still more preferably less than about 5 minutes apart. Preferably, administration of the combination products of the invention is oral, although other routes of administration, as described above, are contemplated to be within the scope of the present invention. Although it is preferable that the opioids and peripheral mu opioid antagonists are both administered in the same fashion (that is, for example, both orally), if desired, they may each be administered in different fashions (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously). The dosage of the combination products of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired.

Although the proper dosage of the combination products of this invention will be readily ascertainable by one skilled in the art, once armed with the present disclosure, by way of general guidance, where an opioid compounds is combined with a peripheral mu opioid antagonist, for example, typically a daily dosage may range from about 0.01 to about 100 milligrams of the opioid (and all combinations and subcombinations of ranges therein) and about 0.001 to about 100 milligrams of the peripheral mu opioid antagonist (and all combinations and subcombinations of ranges therein), per kilogram of patient body weight. Preferably, the a daily dosage may be about 0.1 to about 10 milligrams of the opioid and about 0.01 to about 10 milligrams of the peripheral mu opioid antagonist per kilogram of patient body weight. Even more

preferably, the daily dosage may be about 1.0 milligrams of the opioid and about 0.1 milligrams of the peripheral mu opioid antagonist per kilogram of patient body weight. With regard to a typical dosage form of this type of combination product, such as a tablet, the opioid compounds (*e.g.*, morphine) generally may be present in an amount of about 15 to about 200 milligrams, and the peripheral mu opioid antagonists in an amount of about 0.1 to about 4 milligrams.

Particularly when provided as a single dosage form, the potential exists for a chemical interaction between the combined active ingredients (for example, an opioid and a peripheral mu opioid antagonist compound). For this reason, the preferred dosage forms of the combination products of this invention are formulated such that although the active ingredients are combined in a single dosage form, the physical contact between the active ingredients is minimized (that is, reduced).

In order to minimize contact, one embodiment of this invention where the product is orally administered provides for a combination product wherein one active ingredient is enteric coated. By enteric coating one or more of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Pharmaceutical kits useful in, for example, the treatment of pain, which comprise a therapeutically effective amount of an opioid along with a therapeutically effective amount of a peripheral mu opioid antagonist compound, in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as exemplified by the UNIVIAL™ two-part container (available from Abbott Labs, Chicago, Illinois), as desired. The opioid compound and the peripheral mu opioid antagonist compound may be separate, or combined into a single dosage form as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for

administration, and/or guidelines for mixing the components, may also be included in the kit.

Compounds for use in the methods of the present invention, including piperidine-N-alkylcarboxylate compounds of formula (I), have been characterized in opioid receptor binding assays showing preferential binding to mu opioid receptors. Studies in isolated tissues (guinea pig and mouse vas deferens) have shown that these compounds may act as antagonists with no measurable agonist activity. Studies in animals have demonstrated that the present compounds may reverse constipation in morphine-dependent mice when administered orally or parenterally at very low doses, and do not block the analgesic actions of morphine unless given in hundred-fold or higher doses. Collectively, the data indicate that the compounds described herein may have a very high degree of peripheral selectivity.

EXAMPLES

The invention is further demonstrated in the following examples. All of the examples are actual examples. The examples are for purposes of illustration and are not intended to limit the scope of the present invention.

Example 1

This example is directed to *in vivo* experiments in mice which demonstrate the effectiveness of the combination methods and products of the present invention.

In a mouse model of opioid-induced constipation (measured by the charcoal meal transit time), the compound of formula (II), orally administered, prevented acute morphine-induced constipation. A 3 mg/kg oral dose had a duration of action between 8 and 24 hours. Additional studies showed that the compound of formula (II) was even more potent in reversing morphine-induced constipation in chronic morphine treated mice. This establishes that the compound of formula (II) is a gut-selective and peripherally-selective mu antagonist compound. In addition, it is orally effective in preventing or reversing morphine-induced constipation in mice.

The following examples are directed to *in vivo* experiments in humans which demonstrates the effectiveness of the combination methods and products of the present invention.

Example 2

A clinical study in man was an 8 subject multiple crossover study of the effects of oral pre-treatment with placebo, 2.4 mg or 24 mg t.i.d. of the compound of formula (II) on slowing of gut motility induced with 8 mg of b.i.d. of oral loperamide (a peripheral mu opioid agonist). Both doses of the compound of formula (II) prevented loperamide-induced slowing of gut motility as shown in the graph illustrated in Figure 1. The graph presents the effects of 2.4 or 24 mg of the compound of formula (II) on colonic transit time (in hours) following administration of loperamide. The loperamide dose was constant in the three treatment groups. Since both doses of the compound of formula (II) completely prevented loperamide-induced increased colonic transit time, the effective dose range of the compound of formula (II) may be well below the lowest dose (2.4 mg t.i.d.) evaluated in the study.

Example 3

A Phase I study in 20 healthy volunteers demonstrated that a 4 mg oral dose of the compound of formula (II) blocked the effect of intravenous morphine sulfate on upper gastrointestinal motility ($P<0.01$). The compound of formula (II) also showed a trend toward antagonizing morphine-induced nausea ($P=0.07$) indicating that the compound of formula (II) may provide additional benefits to patients experiencing common adverse side effects from morphine or other opioids.

Example 4

A Phase I study in 11 volunteers demonstrated that a 3 mg oral dose of the compound of formula (II) administered three times daily for 4 days blocked the inhibition of gastrointestinal transit produced by oral sustained-release morphin (MS Contin®, 30 mg twice daily) without antagonizing MS Contin® effects on pupil size. Pupil size was used as a surrogate measure of the morphine's analgesic activity.

Example 5

A double-blind Phase II clinical study in 24 young healthy patients undergoing third molar extraction dental surgery showed that the compound of formula (II) (4 mg total oral dose) did not antagonize analgesia or pupil constriction produced by intravenous morphine sulfate. No patients were withdrawn for adverse effects.

Example 6

A 78 patient Phase II clinical study was conducted which compared two doses (2 mg and 12 mg) of the compound of formula (II) versus placebo in patients undergoing partial colectomy or simple or radical hysterectomy surgical procedures. All patients in this clinical study received morphine or meperidine infusions to treat postoperative pain. Oral doses of compound (II) or placebo were administered to block postsurgical opioid effects, including postoperative nausea and vomiting. Results of this study comparing patients receiving 12 mg of compound (II) and placebo are depicted graphically in Figures 2A and 2B.

The intensity of nausea was evaluated by patients on a 100-point visual analog scale (VAS) with VAS=0 being no nausea and VAS=100 being the worst nausea that a patient could imagine. The highest VAS nausea score (worst nausea) recorded for each patient was computed and the distributions of these maximum values were compared among the treatment groups. Nearly 40% of the patients receiving 12 mg per day of the compound of formula (II) exhibited no nausea (highest VAS score = 0), compared to approximately 25% of the 2 mg per day group and just over 10% of the placebo group. The overall treatment differences in the distributions were significant when compared using a Kruskal-Wallis test (P=0.0184). The improved outcomes observed in the 12 mg per day dose group are evident in the pairwise comparisons based on the Wilcoxon rank sum tests. The 12 mg per day dose group had results that were statistically significantly improved compared to the placebo dose (P=0.0072). These results are further supported by noting that only 27% of the 12 mg per day dose group reported VAS scores over 20, compared to 63% of the placebo group and 67% of the 2 mg dose group (P=0.003 using the Mantel-Haenszel test for linear trend). No patients experienced serious adverse side effects in this trial that were judged by the clinical investigator to be related to the activity

of the compound of formula (II). None of the patients receiving the compound of formula (II) experienced a reduction in postoperative pain control, indicating the selectivity of the compound of formula (II) for blocking opioid nausea and vomiting without blocking analgesia.

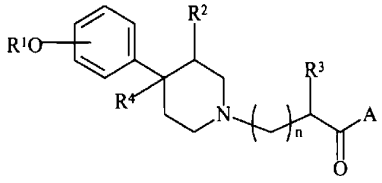
These results demonstrate that the compound of formula (II) blocked the adverse gastrointestinal effects of morphine or other narcotic analgesics that were used for post-surgical pain relief.

The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Various modification of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system comprising administering to a patient from about 0.1 mg/day to about 1000 mg/day of an opioid in combination with from about 0.1 mg/day to about 1000 mg/day of a compound of the following formula (I):



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

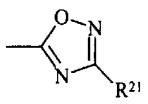
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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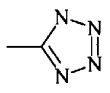
,

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

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R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

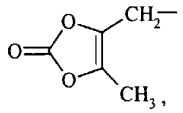
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or,

together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

2. A method according to Claim 1 wherein the compound of formula (I) is a trans 3,4-isomer.

3. A method according to Claim 1 wherein R^1 is hydrogen; R^2 is alkyl; n is 1 or 2; R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl; and R^4 is alkyl.

4. A method according to Claim 3 wherein A is OR^5 in which R^5 is hydrogen or alkyl.

5. A method according to Claim 3 wherein A is NR^6R^7 in which R^6 is hydrogen and R^7 is alkylene substituted B wherein B is C(O)W.

6. A method according to Claim 5 wherein R^7 is $(CH_2)_q$-B in which q is about 1 to about 3; and W is OR^{10} in which R^{10} is hydrogen, alkyl, phenyl-substituted alkyl, cycloalkyl or cycloalkyl-substituted alkyl.

7. A method according to Claim 5 wherein W is $NR^{11}R^{12}$ in which R^{11} is hydrogen or alkyl, and R^{12} is hydrogen, alkyl or alkylene substituted C(=O)Y.

8. A method according to Claim 7 wherein R^{12} is $(CH_2)_mC(O)Y$ in which m is 1 to 3 and Y is OR^{18} or $NR^{19}R^{20}$ wherein R^{18}, R^{19} and R^{20} are independently hydrogen or alkyl.

9. A method according to Claim 5 wherein W is OE in which E is $CH_2C(=O)D$ wherein D is OR^{15} or $NR^{16}R^{17}$ in which R^{15} is hydrogen or alkyl, R^{16} is methyl or benzyl and R^{17} is hydrogen.

10. A method according to Claim 5 wherein W is OE in which E is $R^{13}OC(=O)R^{14}$, wherein R^{13} is $-CH(CH_3)-$ or $-CH(CH_2CH_3)-$ and R^{14} is alkyl.

11. A method according to Claim 1 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

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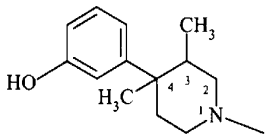
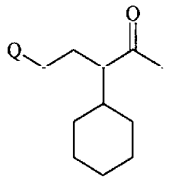
12. A method according to Claim 1 wherein said compound is selected from the group consisting of Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OCH_2CH_2$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)OH$, G-$NH(CH_2)_3C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NHCH_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-$NH(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$ or Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$; wherein:

Q represents

trans-3,4-dimethyl  ;

G represents

 ;

and Z represents

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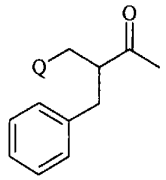

13. A method according to Claim 12 wherein said compound is selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)-Z-$NHCH_2C(O)OH$, (-)-Z-$NHCH_2C(O)OH$, (3R,4R,R)-Z-$NHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-Z-$NHCH_2C(O)NHCH_2(C_6H_5)$ or (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

14. A method according to Claim 13 wherein said compound is selected from the group consisting of (+)-Z-$NHCH_2C(O)OH$ and (-)-Z-$NHCH_2C(O)OH$.

15. A method according to Claim 14 wherein said compound is (+)-Z-$NHCH_2C(O)OH$.

16. A method according to Claim 1 wherein said compound is a substantially pure stereoisomer.

17. A method according to Claim 1 wherein said compound is a peripheral mu opioid antagonist.

18. A method according to Claim 1 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

19. A method according to Claim 18 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

20. A method according to Claim 1 wherein said side effect is selected from the group consisting of constipation, nausea and vomiting.

21. A method according to Claim 20 wherein said side effect is constipation.

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22. A method according to Claim 20 wherein said side effect is nausea.

23. A method according to Claim 20 wherein said side effect is vomiting.

24. A method according to Claim 1 wherein said opioid and said compound of formula (I) are in a single dosage unit form.

25. A method according to Claim 1 wherein said compound of formula (I) is administered in an amount of from about 2 mg/day to about 1000 mg/day.

26. A method according to Claim 25 wherein said compound of formula (I) is administered in an amount of from about 4 mg/day to about 1000 mg/day.

27. A method according to Claim 25 wherein said compound of formula (I) is administered in an amount of from about 12 mg/day to about 1000 mg/day.

28. A method according to Claim 1 wherein said opioid is administered in an amount of from about 15 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.1 mg/day to about 4 mg/day.

29. A method of preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system comprising administering to a patient from about 0.1 mg/day to about 1000 mg/day of an opioid in combination with from about 0.1 mg/day to about 1000 mg/day of a peripheral mu opioid antagonist compound, wherein said peripheral mu opioid antagonist compound is selected from the group consisting of a piperidine-N-alkylcarboxylate, an opium alkaloid derivative, a quaternary benzomorphan compound, and a quaternary salt of N-methylnalorphine, N-diallylnormorphine or N-methylnalmefene.

30. A method according to Claim 29 wherein said peripheral mu opioid antagonist compound is a piperidine-N-alkylcarboxylate compound.

31. A method according to Claim 30 wherein said piperidine-N-alkylcarboxylate compound has the following formula (I):

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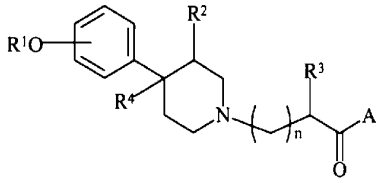


wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

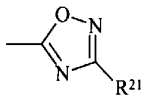
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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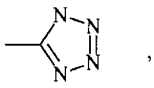

,

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

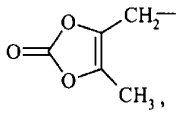
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

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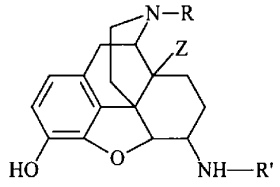
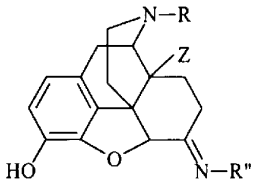
32. A method according to Claim 29 wherein said peripheral mu opioid antagonist compound is an opium alkaloid derivative.

33. A method according to Claim 32 wherein said opium alkaloid derivative has the following formula (III) or (IV):



III

or



IV

wherein:

R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl;

Z is hydrogen or OH;

R' is X'-J(L)(T), wherein:

J is alkylene or alkenylene;

L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl; and

T is CO_2H, SO_3H, amino or guanidino;

X' is a direct bond or C(=O); and

R" is NH-J(L)(T) or guanidino;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

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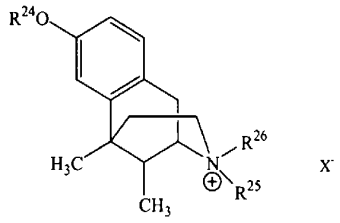
34. A method according to Claim 33 wherein R is C_1-C_3alkyl, allyl or cyclopropylmethyl; Z is OH; J is C_1-C_5alkylene, C_2-C_6alkylene interrupted by an oxygen atom, or C_2-C_5alkenylene; L is hydrogen or amino; and T is CO_2H or guanidino.

35. A method according to Claim 34 wherein R is cyclopropylmethyl, R' is $C(=O)(CH_2)_2CO_2H$, $C(=O)(CH_2)_3CO_2H$, $C(=O)CH=CHCO_2H$, $C(=O)CH_2OCH_2CO_2H$, $C(=O)CH(NH_2)(CH_2)_3NHC(=NH)NH_2$, $C(=O)CH(NH_2)CH_2CO_2H$ or CH_2CO_2H and R" is $NHCH_2CO_2H$.

36. A method according to Claim 29 wherein said peripheral mu opioid antagonist compound is a quaternary benzomorphan compound.

37. A method according to Claim 36 wherein said quaternary benzomorphan compound has the following formula (V):



V

wherein:

R^{24} is hydrogen or acyl;

R^{25} is alkyl or alkenyl;

R^{26} is alkyl or alkenyl; and

X^- is a counter ion;

or a stereoisomer, prodrug, or pharmaceutically acceptable hydrate or N-oxide thereof.

38. A method according to Claim 37 wherein R^{24} is hydrogen or C_1-C_2 acyl and R^{25} and R^{26} are independently C_1-C_3 alkyl or C_2-C_3 alkenyl.

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39. A method according to Claim 38 wherein R^{24} is hydrogen or acetoxy, R^{25} is propyl or allyl and R^{26} is propyl or methyl.

40. A method according to Claim 37 wherein the quaternary benzomorphan compound is selected from the group consisting of 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2,2-di-n-propyl-6,7-benzomorphanium bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

41. A method according to Claim 29 wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

42. A method according to Claim 29 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

43. A method according to Claim 42 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

44. A method according to Claim 29 wherein said side effect is selected from the group consisting of constipation, nausea and vomiting.

45. A method according to Claim 44 wherein said side effect is constipation.

46. A method according to Claim 44 wherein said side effect is nausea.

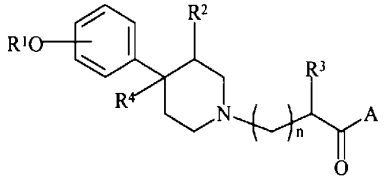
47. A method according to Claim 44 wherein said side effect is vomiting.

48. A method according to Claim 29 wherein said opioid and said peripheral mu opioid antagonist are in a single dosage unit form.

49. A method according to Claim 29 wherein said opioid is administered in an amount of from about 15 mg/day to about 200 mg/day and said peripheral

mu opioid antagonist compound is administered in an amount of from about 0.1 mg/day to about 4 mg/day.

50. A method of treating or preventing pain comprising administering to a patient from about 0.1 mg/day to about 1000 mg/day of an opioid in combination with from about 0.1 mg/day to about 1000 mg/day of a compound of the following formula (I):



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

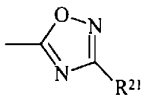
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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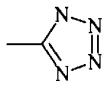
,

C(=O)W or NR^8R^9; wherein;

R^8 is hydrogen or alkyl;

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R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

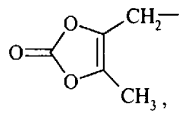
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or,

together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

51. A method according to Claim 50 wherein the compound of formula (I) is a trans 3,4-isomer.

52. A method according to Claim 50 wherein R^1 is hydrogen; R^2 is alkyl; n is 1 or 2; R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl; and R^4 is alkyl.

53. A method according to Claim 52 wherein A is OR^5 in which R^5 is hydrogen or alkyl.

54. A method according to Claim 53 wherein A is NR^6R^7 in which R^6 is hydrogen and R^7 is alkylene substituted B wherein B is C(O)W.

55. A method according to Claim 54 wherein R^7 is $(CH_2)_q$-B in which q is about 1 to about 3; and W is OR^{10} in which R^{10} is hydrogen, alkyl, phenyl-substituted alkyl, cycloalkyl or cycloalkyl-substituted alkyl.

56. A method according to Claim 54 wherein W is $NR^{11}R^{12}$ in which R^{11} is hydrogen or alkyl, and R^{12} is hydrogen, alkyl or alkylene substituted C(=O)Y.

57. A method according to Claim 56 wherein R^{12} is $(CH_2)_mC(O)Y$ in which m is 1 to 3 and Y is OR^{18} or $NR^{19}R^{20}$ wherein R^{18}, R^{19} and R^{20} are independently hydrogen or alkyl.

58. A method according to Claim 54 wherein W is OE in which E is $CH_2C(=O)D$ wherein D is OR^{15} or $NR^{16}R^{17}$ in which R^{15} is hydrogen or alkyl, R^{16} is methyl or benzyl and R^{17} is hydrogen.

59. A method according to Claim 54 wherein W is OE in which E is $R^{13}OC(=O)R^{14}$, wherein R^{13} is $-CH(CH_3)-$ or $-CH(CH_2CH_3)-$ and R^{14} is alkyl.

60. A method according to Claim 50 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

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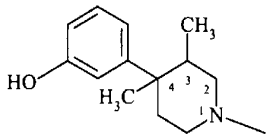
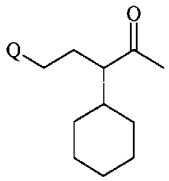
61. A method according to Claim 50 wherein said compound is selected from the group consisting of Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OCH_2CH_2$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)OH$, G-$NH(CH_2)_3C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NHCH_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-$NH(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$ or Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$; wherein:

Q represents

trans-3,4-dimethyl  ;

G represents

 ;

and Z represents

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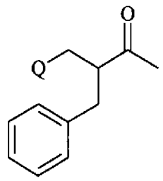

62. A method according to Claim 61 wherein said compound is selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)-Z-$NHCH_2C(O)OH$, (-)-Z-$NHCH_2C(O)OH$, (3R,4R,R)-Z-$NHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-Z-$NHCH_2C(O)NHCH_2(C_6H_5)$ or (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

63. A method according to Claim 62 wherein said compound is selected from the group consisting of (+)-Z-$NHCH_2C(O)OH$ and (-)-Z-$NHCH_2C(O)OH$.

64. A method according to Claim 63 wherein said compound is (+)-Z-$NHCH_2C(O)OH$.

65. A method according to Claim 50 wherein said compound is a substantially pure stereoisomer.

66. A method according to Claim 50 wherein said compound is a peripheral mu opioid antagonist.

67. A method according to Claim 50 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

68. A method according to Claim 67 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

69. A method according to Claim 50 wherein said opioid and said compound of formula (I) are in a single dosage unit form.

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70. A method according to Claim 50 wherein said compound of formula (I) is administered in an amount of from about 2 mg/day to about 1000 mg/day.

71. A method according to Claim 70 wherein said compound of formula (I) is administered in an amount of from about 4 mg/day to about 1000 mg/day.

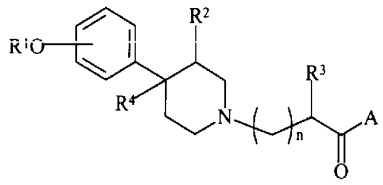
72. A method according to Claim 70 wherein said compound of formula (I) is administered in an amount of from about 12 mg/day to about 1000 mg/day.

73. A method according to Claim 50 wherein said opioid is administered in an amount of from about 15 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.1 mg/day to about 4 mg/day.

74. A method of treating or preventing pain comprising administering to a patient from about 0.1 mg/day to about 1000 mg/day of an opioid in combination with from about 0.1 mg/day to about 1000 mg/day of a peripheral mu opioid antagonist compound, wherein said peripheral mu opioid antagonist compound is selected from the group consisting of a piperidine-N-alkylcarboxylate, an opium alkaloid derivative, a quaternary benzomorphan compound, and a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

75. A method according to Claim 74 wherein said peripheral mu opioid antagonist compound is a piperidine-N-alkylcarboxylate compound.

76. A method according to Claim 75 wherein said piperidine-N-alkylcarboxylate compound has the following formula (I):



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

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R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

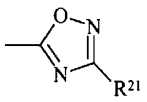
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is



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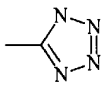


,

C(=O)W or NR^8R^9;

wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

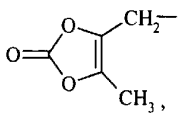
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



,

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alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

77. A method according to Claim 74 wherein said peripheral mu opioid antagonist compound is an opium alkaloid derivative.

78. A method according to Claim 77 wherein said opium alkaloid derivative has the following formula (III) or (IV)

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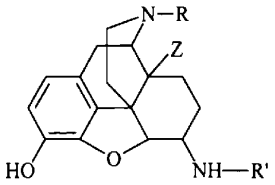
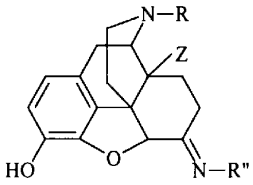


III

or



IV

wherein:

R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl;

Z is hydrogen or OH;

R' is X'-J(L)(T), wherein:

J is alkylene or alkenylene;

L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl; and

T is CO_2H, SO_3H, amino or guanidino;

X' is a direct bond or C(=O): and

R" is NH-J(L)(T) or guanidino;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

79. A method according to Claim 78 wherein R is C_1-C_3alkyl, allyl or cyclopropylmethyl; Z is OH; J is C_1-C_5alkylene, C_2-C_6alkylene interrupted by an oxygen atom, or C_2-C_5alkenylene; L is hydrogen or amino; and T is CO_2H or guanidino.

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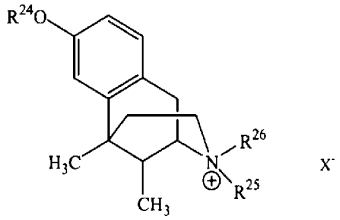
80. A method according to Claim 79 wherein R is cyclopropylmethyl, R' is $C(=O)(CH_2)_2CO_2H$, $C(=O)(CH_2)_3CO_2H$, $C(=O)CH=CHCO_2H$, $C(=O)CH_2OCH_2CO_2H$, $C(=O)CH(NH_2)(CH_2)_3NHC(=NH)NH_2$, $C(=O)CH(NH_2)CH_2CO_2H$ or CH_2CO_2H and R" is $NHCH_2CO_2H$.

81. A method according to Claim 74 wherein said peripheral mu opioid antagonist compound is a quaternary benzomorphan compound.

82. A method according to Claim 81 wherein said quaternary benzomorphan compound has the following formula (V):



V

where:

R^{24} is hydrogen or acyl;

R^{25} is alkyl or alkenyl;

R^{26} is alkyl or alkenyl; and

X^- is a counter ion;

or a stereoisomer, prodrug, or pharmaceutically acceptable hydrate orN-oxide thereof.

83. A method according to Claim 82 wherein R^{24} is hydrogen or C_1-C_2 acyl and R^{25} and R^{26} are independently C_1-C_3 alkyl or C_2-C_3 alkenyl.

84. A method according to Claim 82 wherein R^{24} is hydrogen or acetoxy, R^{25} is propyl or allyl and R^{26} is propyl or methyl.

85. A method according to Claim 74 wherein the quaternary benzomorphan compound is selected from the group consisting of 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2,2-di-n-propyl-6,7-benzomorphanium bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-

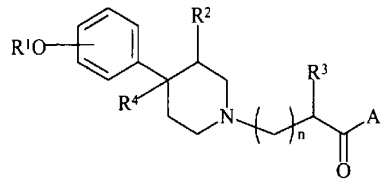
benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

86. A method according to Claim 74 wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

87. A method according to Claim 74 wherein said opioid and said peripheral mu opioid antagonist compound are in a single dosage unit form.

88. A method according to Claim 74 wherein said opioid is administered in an amount of from about 15 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered in an amount of from about 0.1 mg/day to about 4 mg/day.

89. A pharmaceutical composition comprising an opioid and a compound of formula (I) wherein, in use, said opioid is administered to a patient in an amount of from about 0.1 mg/day to about 1000 mg/day and said compound of formula (I) is administered to the patient in an amount of from about 0.1 mg/day to about 1000 mg/day:



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

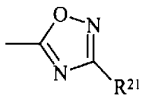
A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is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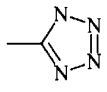

,

C(=O)W or NR^8R^9;

wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

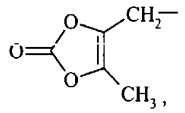
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

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wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

90. A composition according to Claim 89 wherein the compound of formula (I) is a trans 3,4-isomer.

91. A composition according to Claim 89 wherein R^1 is hydrogen; R^2 is alkyl; n is 1 or 2; R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl; and R^4 is alkyl.

92. A composition according to Claim 91 wherein A is OR^5 in which R^5 is hydrogen or alkyl.

93. A composition according to Claim 91 wherein A is NR^6R^7 in which R^6 is hydrogen and R^7 is alkylene substituted B wherein B is C(O)W.

94. A composition according to Claim 93 wherein R^7 is $(CH_2)_q$-B in which q is about 1 to about 3; and W is OR^{10} in which R^{10} is hydrogen, alkyl, phenyl-substituted alkyl, cycloalkyl or cycloalkyl-substituted alkyl.

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95. A composition according to Claim 93 wherein W is $NR^{11}R^{12}$ in which R^{11} is hydrogen or alkyl, and R^{12} is hydrogen, alkyl or alkylene substituted C(=O)Y.

96. A composition according to Claim 95 wherein R^{12} is $(CH_2)_mC(O)Y$ in which m is 1 to 3 and Y is OR^{18} or $NR^{19}R^{20}$ wherein R^{18}, R^{19} and R^{20} are independently hydrogen or alkyl.

97. A composition according to Claim 93 wherein W is OE in which E is $CH_2C(=O)D$ wherein D is OR^{15} or $NR^{16}R^{17}$ in which R^{15} is hydrogen or alkyl, R^{16} is methyl or benzyl and R^{17} is hydrogen.

98. A composition according to Claim 93 wherein W is OE in which E is $R^{13}OC(=O)R^{14}$, wherein R^{13} is $-CH(CH_3)-$ or $-CH(CH_2CH_3)-$ and R^{14} is alkyl.

99. A composition according to Claim 89 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

100. A composition according to Claim 89 wherein said compound is selected from the group consisting of Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OCH_2CH_2$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)OH$, G-$NH(CH_2)_3C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NHCH_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-$NH(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$ or Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$; wherein:

Q represents

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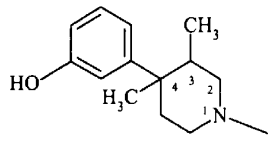
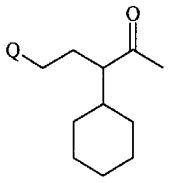
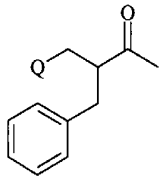
trans-3,4-dimethyl  ;

G represents

 ;

and Z represents

 .

101. A composition according to Claim 100 wherein said compound is selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)-Z-$NHCH_2C(O)OH$, (-)-Z-$NHCH_2C(O)OH$, (3R,4R,R)-Z-$NHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-Z-$NHCH_2C(O)NHCH_2(C_6H_5)$ or (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

102. A composition according to Claim 101 wherein said compound is selected from the group consisting of (+)-Z-$NHCH_2C(O)OH$ and (-)-Z-$NHCH_2C(O)OH$.

103. A composition according to Claim 102 wherein said compound is (+)-Z-$NHCH_2C(O)OH$.

104. A composition according to Claim 89 wherein said compound is a substantially pure stereoisomer.

105. A composition according to Claim 89 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone,

levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

106. A composition according to Claim 105 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

107. A composition according to Claim 89 which is in a single dosage unit form.

108. A composition according to Claim 89 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 2 mg/day to about 1000 mg/day.

109. A composition according to Claim 108 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 4 mg/day to about 1000 mg/day.

110. A composition according to Claim 108 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 12 mg/day to about 1000 mg/day.

111. A composition according to Claim 89 wherein, in use, said opioid is administered to the patient in an amount of from about 15 mg/day to about 200 mg/day and said compound of formula (I) is administered to the patient in an amount of from about 0.1 mg/day to about 4 mg/day.

112. A pharmaceutical composition comprising an opioid, a peripheral mu opioid antagonist compound, and a pharmaceutically acceptable carrier wherein, in use, said opioid is administered to a patient in an amount of from about 0.1 mg/day to about 1000 mg/day and said peripheral mu opioid antagonist is administered to the patient in an amount of from about 0.1 mg/day to about 1000 mg/day, wherein said peripheral mu opioid antagonist compound is selected from the group consisting of a piperidine-N-alkylcarboxylate, an opium alkaloid derivative, a quaternary benzomorphan compound, and a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

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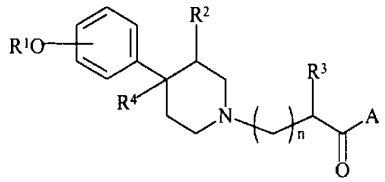
113. A composition according to Claim 112 wherein said peripheral mu opioid antagonist compound is a piperidine-N-alkylcarboxylate compound.

114. A composition according to Claim 113 wherein said piperidine-N-alkylcarboxylate compound has the following formula (I):



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is

C(=O)W or NR^8R^9;

wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or,

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together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

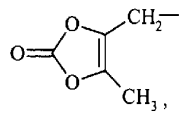
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

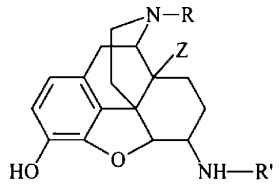
R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

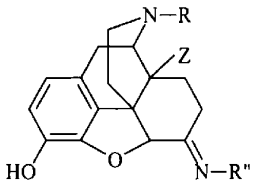
115. A composition according to Claim 112 wherein said peripheral mu opioid antagonist compound is an opium alkaloid derivative.

116. A composition according to Claim 112 wherein said opium alkaloid derivative has the following formula (III) or (IV):



III

or



IV

wherein:

R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl;

Z is hydrogen or OH;

R' is X'-J(L)(T), wherein:

J is alkylene or alkenylene;

L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl; and

T is CO_2H, SO_3H, amino or guanidino;

X' is a direct bond or C(=O); and

R" is NH-J(L)(T) or guanidino;

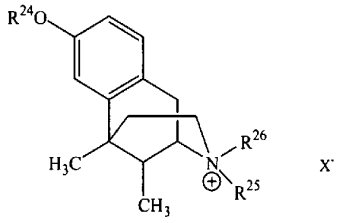
or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

117. A composition according to Claim 116 wherein R is C_1-C_3alkyl, allyl or cyclopropylmethyl; Z is OH; J is C_1-C_5alkylene, C_2-C_6alkylene interrupted by an oxygen atom, or C_2-C_5alkenylene; L is hydrogen or amino; and T is CO_2H or guanidino.

118. A composition according to Claim 117 wherein R is cyclopropylmethyl, R' is $C(=O)(CH_2)_2CO_2H$, $C(=O)(CH_2)_3CO_2H$, $C(=O)CH=CHCO_2H$, $C(=O)CH_2OCH_2CO_2H$, $C(=O)CH(NH_2)(CH_2)_3NHC(=NH)NH_2$, $C(=O)CH(NH_2)CH_2CO_2H$ or CH_2CO_2H and R" is $NHCH_2CO_2H$.

119. A composition according to Claim 112 wherein said peripheral mu opioid antagonist compound is a quaternary benzomorphan compound.

120. A composition according to Claim 119 wherein said quaternary benzomorphan compound has the following formula (V):



V

where:

R^{24} is hydrogen or acyl;

R^{25} is alkyl or alkenyl;

R^{26} is alkyl or alkenyl; and

X^- is a counter ion;

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or a stereoisomer, prodrug, or pharmaceutically acceptable hydrate or N-oxide thereof.

121. A composition according to Claim 120 wherein R^{24} is hydrogen or C_1-C_2 acyl and R^{25} and R^{26} are independently C_1-C_3 alkyl or C_2-C_3 alkenyl.

122. A composition according to Claim 121 wherein R^{24} is hydrogen or acetoxy, R^{25} is propyl or allyl and R^{26} is propyl or methyl.

123. A composition according to Claim 120 wherein the quaternary benzomorphan compound is selected from the group consisting of 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2,2-di-n-propyl-6,7-benzomorphanium bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

124. A composition according to Claim 112 wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

125. A composition according to Claim 112 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

126. A composition according to Claim 125 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

127. A composition according to Claim 111 which is in a single dosage unit form.

128. A composition according to Claim 111 wherein, in use, said opioid is administered to the patient in an amount of from about 15 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered to the patient in an amount of from about 0.1 mg/day to about 4 mg/day.

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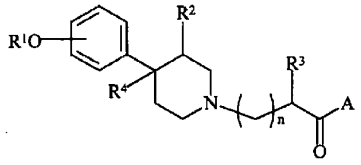
129. A pharmaceutical kit when used for preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system, or for treating or preventing pain, comprising one or more containers containing pharmaceutical dosage units comprising an opioid and a compound of formula (I) wherein, in use, said opioid is administered to a patient in an amount of from about 0.1 mg/day to about 1000 mg/day and said compound of formula (I) is administered to the patient in an amount of from about 0.1 mg/day to about 1000 mg/day:



wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

A is OR^5 or NR^6R^7; wherein:

R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

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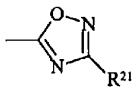
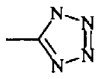
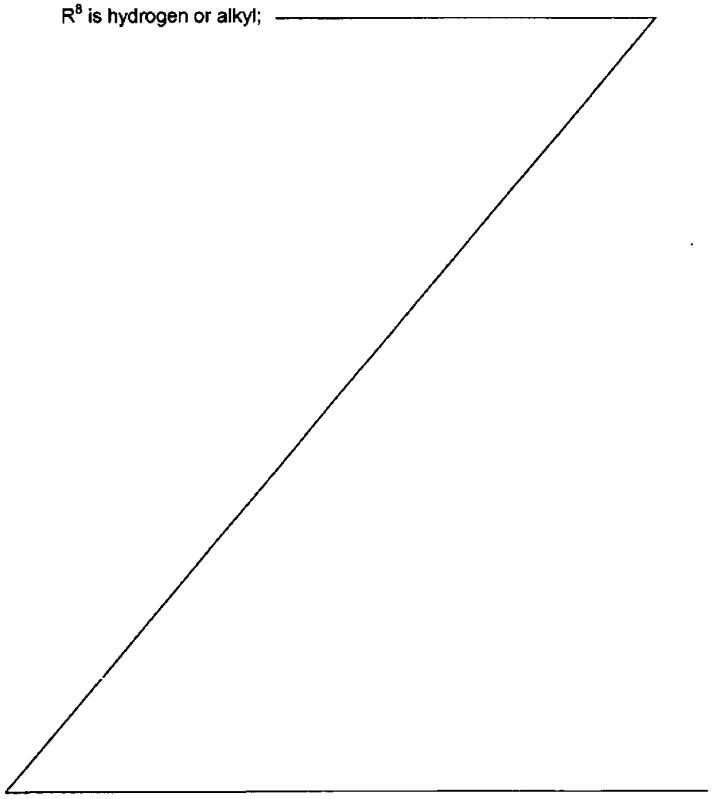
B is

C(=O)W or NR^8R^9;

wherein;

R^8 is hydrogen or alkyl;



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R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

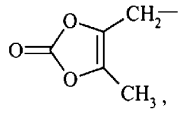
W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is



alkylene substituted (C=O)D, or $-R^{13}OC(=O)R^{14}$;

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or,

together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

130. A kit according to Claim 129 wherein the compound of formula (I) is a trans 3,4-isomer.

131. A kit according to Claim 129 wherein R^1 is hydrogen; R^2 is alkyl; n is 1 or 2; R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl; and R^4 is alkyl.

132. A kit according to Claim 131 wherein A is OR^5 in which R^5 is hydrogen or alkyl.

133. A kit according to Claim 131 wherein A is NR^6R^7 in which R^6 is hydrogen and R^7 is alkylene substituted B wherein B is C(O)W.

134. A kit according to Claim 133 wherein R^7 is $(CH_2)_q$-B in which q is about 1 to about 3; and W is OR^{10} in which R^{10} is hydrogen, alkyl, phenyl-substituted alkyl, cycloalkyl or cycloalkyl-substituted alkyl.

135. A kit according to Claim 131 wherein W is $NR^{11}R^{12}$ in which R^{11} is hydrogen or alkyl, and R^{12} is hydrogen, alkyl or alkylene substituted C(=O)Y.

136. A kit according to Claim 135 wherein R^{12} is $(CH_2)_mC(O)Y$ in which m is 1 to 3 and Y is OR^{18} or $NR^{19}R^{20}$ wherein R^{18}, R^{19} and R^{20} are independently hydrogen or alkyl.

137. A kit according to Claim 133 wherein W is OE in which E is $CH_2C(=O)D$ wherein D is OR^{15} or $NR^{16}R^{17}$ in which R^{15} is hydrogen or alkyl, R^{16} is methyl or benzyl and R^{17} is hydrogen.

138. A kit according to Claim 133 wherein W is OE in which E is $R^{13}OC(=O)R^{14}$, wherein R^{13} is $-CH(CH_3)-$ or $-CH(CH_2CH_3)-$ and R^{14} is alkyl.

139. A kit according to Claim 129 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

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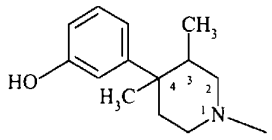
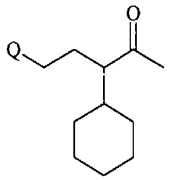
140. A kit according to Claim 129 wherein said compound is selected from the group consisting of Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OCH_2CH_2$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)OH$, G-$NH(CH_2)_3C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NHCH_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)OH$, Q-$CH_2CH(CH_2(C_6H_{11}))C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-$NH(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$ or Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$; wherein:

Q represents

trans-3,4-dimethyl  ;

G represents

 ;

and Z represents

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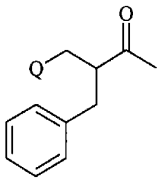

141. A kit according to Claim 140 wherein said compound is selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)-Z-$NHCH_2C(O)OH$, (-)-Z-$NHCH_2C(O)OH$, (3R,4R,R)-Z-$NHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-Z-$NHCH_2C(O)NHCH_2(C_6H_5)$ or (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

142. A kit according to Claim 141 wherein said compound is selected from the group consisting of (+)-Z-$NHCH_2C(O)OH$ and (-)-Z-$NHCH_2C(O)OH$.

143. A kit according to Claim 142 wherein said compound is (+)-Z-$NHCH_2C(O)OH$.

144. A kit according to Claim 129 wherein said compound is a substantially pure stereoisomer.

145. A kit according to Claim 129 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

146. A kit according to Claim 145 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

147. A kit according to Claim 129 further comprising conventional pharmaceutical kit components.

148. A kit according to Claim 129 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 2 mg/day to about 1000 mg/day.

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149. A kit according to Claim 148 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 4 mg/day to about 1000 mg/day.

150. A kit according to Claim 148 wherein, in use, said compound of formula (I) is administered to the patient in an amount of from about 12 mg/day to about 1000 mg/day.

151. A kit according to Claim 129 wherein, in use, said opioid is administered to the patient in an amount of from about 15 mg/day to about 200 mg/day and said compound of formula (I) is administered to the patient in an amount of from about 0.1 mg/day to about 4 mg/day.

152. A pharmaceutical kit when used for preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system, or for treating or preventing pain, comprising one or more containers containing pharmaceutical dosage units comprising an opioid and a peripheral mu opioid antagonist wherein, in use, said opioid is administered to a patient in an amount of from about 0.1 mg/day to about 1000 mg/day and said peripheral mu opioid antagonist is administered to the patient in an amount of from about 0.1 mg/day to about 1000 mg/day, wherein said peripheral mu opioid antagonist compound is selected from the group consisting of a piperidine-N-alkylcarboxylate, an opium alkaloid derivative, a quaternary benzomorphan compound, and a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

153. A kit according to Claim 152 wherein said peripheral mu opioid antagonist compound is a piperidine-N-alkylcarboxylate compound.

154. A kit according to Claim 153 wherein said piperidine-N-alkylcarboxylate compound has the following formula (I):

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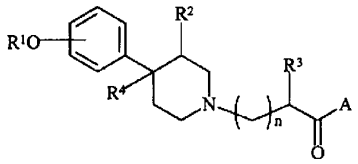


wherein:

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl or alkenyl;

R^3 is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl or aryl-substituted alkyl;

R^4 is hydrogen, alkyl or alkenyl;

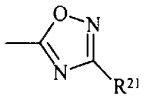
A is OR^5 or NR^6R^7; wherein:

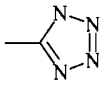
R^5 is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl-substituted alkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl, aryl-substituted alkyl, or alkylene substituted B or, together with the nitrogen atom to which they are attached, R^6 and R^7 form a heterocyclic ring;

B is



,


,

C(=O)W or NR^8R^9;

wherein;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, alkenyl, cycloalkyl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkenyl-substituted alkyl, aryl or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^8 and R^9 form a heterocyclic ring;

W is OR^{10}, $NR^{11}R^{12}$, or OE; wherein

R^{10} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{11} is hydrogen or alkyl;

R^{12} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, aryl-substituted alkyl or alkylene substituted C(=O)Y or, together with the nitrogen atom to which they are attached, R^{11} and R^{12} form a heterocyclic ring;

E is

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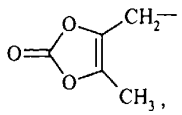


alkylene substituted (C=O)D, or -R^{13}OC(=O)R^{14};

wherein

R^{13} is alkyl substituted alkylene;

R^{14} is alkyl;

D is OR^{15} or $NR^{16}R^{17}$;

wherein:

R^{15} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{16} is hydrogen, alkyl, alkenyl, aryl, aryl-substituted alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl or cycloalkenyl-substituted alkyl;

R^{17} is hydrogen or alkyl or, together with the nitrogen atom to which they are attached, R^{16} and R^{17} form a heterocyclic ring;

Y is OR^{18} or $NR^{19}R^{20}$;

wherein:

R^{18} is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl;

R^{19} is hydrogen or alkyl;

R^{20} is hydrogen, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, cycloalkyl-substituted alkyl, cycloalkenyl-substituted alkyl, or aryl-substituted alkyl or, together with the nitrogen atom to which they are attached, R^{19} and R^{20} form a heterocyclic ring;

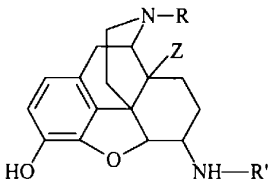
R^{21} is hydrogen or alkyl; and

n is 0 to 4;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

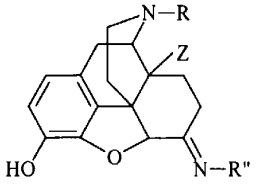
155. A kit according to Claim 152 wherein said peripheral mu opioid antagonist compound is an opium alkaloid derivative.

156. A kit according to Claim 155 wherein said opium alkaloid derivative has the following formula (III) or (IV):



III

or



IV

wherein:

R is alkyl, cycloalkyl-substituted alkyl, aryl, aryl-substituted alkyl or alkenyl;

Z is hydrogen or OH;

R' is X'-J(L)(T), wherein:

J is alkylene or alkenylene;

L is hydrogen, amino, or alkyl optionally substituted with CO_2H, OH or phenyl; and

T is CO_2H, SO_3H, amino or guanidino;

X' is a direct bond or C(=O); and

R" is NH-J(L)(T) or guanidino;

or a stereoisomer, prodrug, or pharmaceutically acceptable salt, hydrate or N-oxide thereof.

157. A kit according to Claim 156 wherein R is C_1-C_3alkyl, allyl or cyclopropylmethyl; Z is OH; J is C_1-C_5alkylene, C_2-C_6alkylene interrupted by an oxygen atom, or C_2-C_5alkenylene; L is hydrogen or amino; and T is CO_2H or guanidino.

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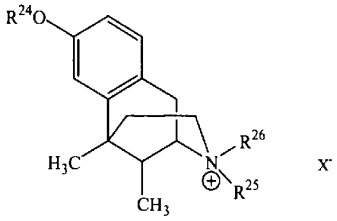
158. A kit according to Claim 157 wherein R is cyclopropylmethyl, R' is $C(=O)(CH_2)_2CO_2H$, $C(=O)(CH_2)_3CO_2H$, $C(=O)CH=CHCO_2H$, $C(=O)CH_2OCH_2CO_2H$, $C(=O)CH(NH_2)(CH_2)_3NHC(=NH)NH_2$, $C(=O)CH(NH_2)CH_2CO_2H$ or CH_2CO_2H and R" is $NHCH_2CO_2H$.

159. A kit according to Claim 152 wherein said peripheral mu opioid antagonist compound is a quaternary benzomorphan compound.

160. A kit according to Claim 159 wherein said quaternary benzomorphan compound has the following formula (V):



V

where:

R^{24} is hydrogen or acyl;

R^{25} is alkyl or alkenyl;

R^{26} is alkyl or alkenyl; and

X^- is a counter ion;

or a stereoisomer, prodrug, or pharmaceutically acceptable hydrate or N-oxide thereof.

161. A kit according to Claim 160 wherein R^{24} is hydrogen or C_1-C_2 acyl and R^{25} and R^{26} are independently C_1-C_3 alkyl or C_2-C_3 alkenyl.

162. A kit according to Claim 161 wherein R^{24} is hydrogen or acetoxy, R^{25} is propyl or allyl and R^{26} is propyl or methyl.

163. A kit according to Claim 160 wherein the quaternary benzomorphan compound is selected from the group consisting of 2'-hydroxy-5,9-dimethyl-2,2-diallyl-6,7-benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2,2-di-n-propyl-6,7-benzomorphanium bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-

benzomorphanium-bromide, 2'-hydroxy-5,9-dimethyl-2-n-propyl-2-propargyl-6,7-benzomorphanium-bromide and 2'-acetoxy-5,9-dimethyl-2-n-propyl-2-allyl-6,7-benzomorphanium-bromide.

164. A kit according to Claim 152 wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnalorphine, N-diallylnormorphine, or N-methylnalmefene.

165. A kit according to Claim 152 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

166. A kit according to Claim 165 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

167. A kit according to Claim 151 further comprising conventional pharmaceutical kit components.

168. A kit according to Claim 152 wherein, in use, said opioid is administered to the patient in an amount of from about 15 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered to the patient in an amount of from about 0.1 mg/day to about 4 mg/day.

169. A method according to Claim 12 wherein said compound is Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

170. A method according to Claim 169 wherein said compound is (3R, 4R, S)-Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

171. A method according to Claim 61 wherein said compound is Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

172. A method according to Claim 171 wherein said compound is (3R, 4R, S)-Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

173. A composition according to Claim 100 wherein said compound is Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

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174. A composition according to Claim 173 wherein said compound is (3R, 4R, S)-Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

175. A kit according to Claim 140 wherein said compound is Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

176. A kit according to Claim 175 wherein said compound is (3R, 4R, S)-Q-$CH_2CH(CH_2(C_6H_5))C(O)OH$.

177. A pharmaceutical composition comprising an effective amount of an opioid, an effective amount of a peripheral mu opioid antagonist compound, and a pharmaceutically acceptable carrier, wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnaltrexone and said composition is formulated for parenteral or transepithelial administration.

178. A pharmaceutical composition comprising an effective amount of an opioid, an effective amount of a peripheral mu opioid antagonist compound, and a pharmaceutically acceptable carrier, wherein said peripheral mu opioid antagonist compound is a quaternary salt of N-methylnaltrexone, said pharmaceutically acceptable carrier is in the form of a liquid, and said composition is formulated for oral, parenteral or transepithelial administration.

179. A composition according to Claims 177 or 178 wherein said parenteral administration comprises intravenous, intramuscular, subcutaneous or intrasynovial administration.

180. A composition according to Claims 177 or 178 wherein said transepithelial administration comprises transdermal, ophthalmic, sublingual or buccal administration.

181. A composition according to any of Claims 177, 178, 179 or 180 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine,

nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

182. A composition according to claim 181 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

183. A method of preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system comprising administering to a patient an effective amount of a pharmaceutical composition according to Claim 177.

184. A method according to Claim 183 wherein said side effect is selected from the group consisting of constipation, nausea and vomiting.

185. A method of preventing or treating an opioid-induced side effect associated with the peripheral nervous system or the gastrointestinal system comprising administering to a patient an effective amount of a pharmaceutical composition according to Claim 178.

186. A method according to Claim 185 wherein said side effect is selected from the group consisting of constipation, nausea and vomiting.

187. A method of treating or preventing pain comprising administering to a patient an effective amount of a pharmaceutical composition according to Claim 177.

188. A method of treating or preventing pain comprising administering to a patient an effective amount of a pharmaceutical composition according to Claim 178.

189. A method according to claim 1 wherein said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 1000 mg/day.

190. A method according to claim 1 wherein said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said compound of

formula (I) is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

191. A method according to claim 29 wherein said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

192. A method according to claim 50 wherein said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 1000 mg/day.

193. A method according to claim 50 wherein said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

194. A method according to claim 74 wherein said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

195. A composition according to claim 89 wherein, in use, said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 1000 mg/day.

196. A composition according to claim 89 wherein, in use, said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

197. A composition according to claim 112 wherein said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said peripheral mu opioid antagonist compound is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

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198. A kit according to claim 129 wherein, in use, said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 1000 mg/day.

199. A kit according to claim 129 wherein, in use, said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

200. A kit according to claim 152 wherein, in use, said opioid is administered in an amount of from about 5 mg/day to about 200 mg/day and said compound of formula (I) is administered in an amount of from about 0.5 mg/day to about 4 mg/day.

Dated this 2nd day of March 2006

Adolor Corporation
Patent Attorneys for the Applicant
PETER MAXWELL & ASSOCIATES

02/03/06

COMS ID No. SBMI-02853123 Received by IP Australia: Time (H:m) 09:29 Date (Y-M-d) 2006-03-03

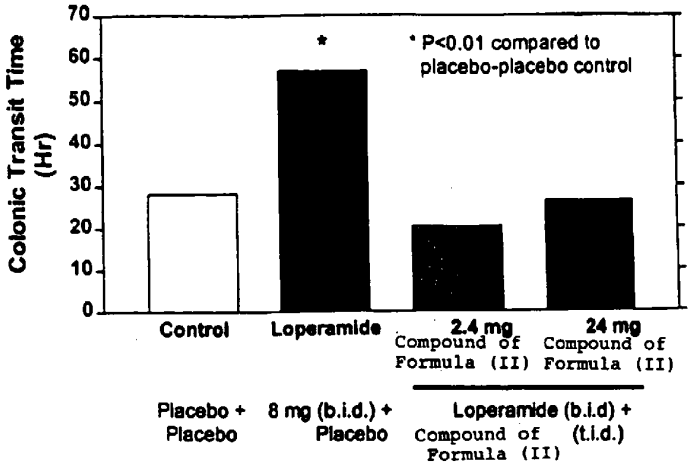
Colonic Transit Time (Hr)
70
60
50
40
30
20
10
0
*
* P<0.01 compared to placebo-placebo control
Control
Loperamide
2.4 mg Compound of Formula (II)
24 mg Compound of Formula (II)
Placebo + Placebo
8 mg (b.i.d.) + Placebo
Loperamide (b.i.d) + Compound of Formula (II) (t.i.d.)

Figure 1

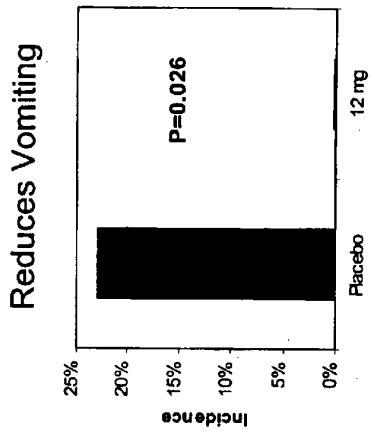

Figure 2B

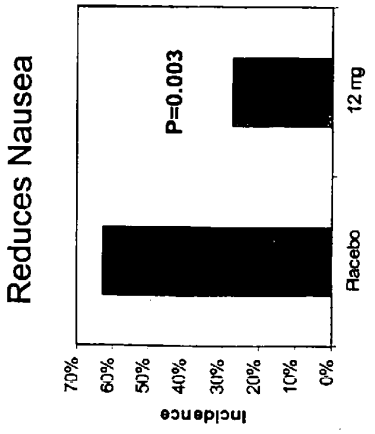

Figure 2A