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(54) Benævnelse: **6,7-UMÆTTET-7-CARBAMOYL-SUBSTITUERET MORPHINANDERIVAT**

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Fortsættes ...

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Description

[0001] The present invention relates to a 6,7-unsaturated-7-carbamoyl-substutaed morphinan derivatives, which are useful as an agent for treating and/or preventing nausea, emesis, vomiting and/or constipation, particularly as an agent for alleviating and/or preventing a side effect (emesis, vomiting and/or constipation etc.) induced by a compound having the opioid receptor (e.g. opioid μ receptor) agonistic activity.

[0002] An opioid receptor agonist such as morphine and the like which is used as an analgesic is very effective in a patient having cancer pain, but as a side effect, induces severe nausea, emesis, vomiting, constipation, anuresis, and itching. Various antiemetics and anti-constipation agents are clinically used, but it can not be said that any of them exhibits the sufficient effect, and an excellent side effect alleviating agent is also demanded for improving QOL of a patient.

[0003] Patent Literatures 1 and 2, and Non-patent Literature 1 describe to the effect that a morphinan derivative is effective in treating or preventing emesis and vomiting induced by an opioid μ agonist, and Non-Patent Literature 2 describes that a 6,7-saturated-7-carbamoyl-sbustituted-morphinan de-rivatives have the opioid δ receptor antagonism. However, none of them describes or suggests the present compound.

[Patent Literature 1] International Patent Application Publication WO 2004-007503
[Patent Literature 2] International Patent Application Publication WO 95/13071
[Non-Patent Literature 1] Journal of Medicinal Chemistry 41, 4177-4180 (1998)
[Non-Patent Literature 2] Chemical and Pharmaceutical Bulletin, 52 (66) 747-750 (2004)

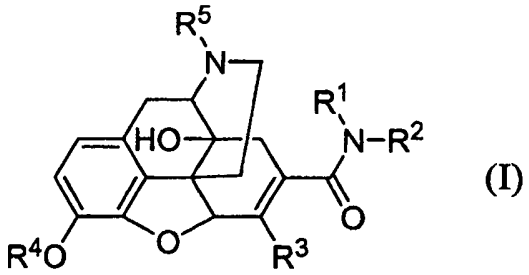
[0004] We found 6,7-unsaturated-7-carbamoyl-substituted morphinan derivatives useful as a composition for treating and/or preventing emesis, vomiting and/or constipation.

[0005] The present invention relates to compounds according to any of claims 1 to 7 and 14, a pharmaceutical composition according to claim 8, a composition having an opioid receptor antagonistic activity according to claim 9, a composition according to any one of claims 10, 11, 13 and 15, and an agent according to claim 12.

[0006] The present invention provides:

(I) a compound represented by the formula (I):

[Chemical formula 1]

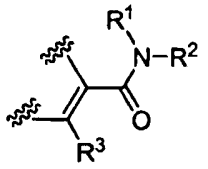


(I)

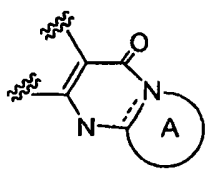
wherein R^1 and R^2 are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkylsulfonyl, optionally substituted acyl , optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, an optionally substituted heterocyclic group, or optionally substituted arylsulfonyl, or R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form optionally substituted heterocycle;

R^3 is hydrogen, hydroxy, optionally substituted lower alkyl, lower optionally substituted lower alkenyl, optionally substituted lower alkynyl optionally substituted lower alkoxy, mercapto, optionally substituted lower alkylthio, optionally substituted amino, optionally substituted carbamoyl, optionally substituted acyl, optionally substituted acyloxy, optionally substituted aryl, or an optionally substituted heterocyclic group, a group represented by the formula:

[Chemical formula 2]



may be



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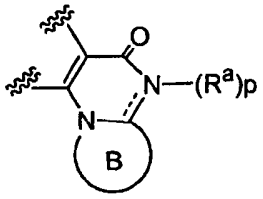
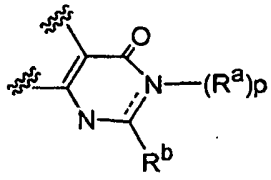
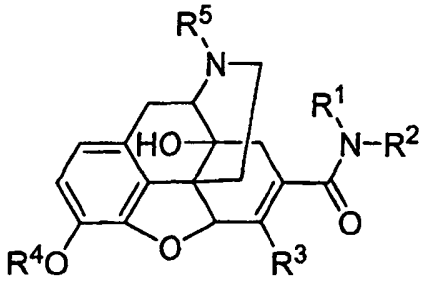


, or



wherein ring A or ring B are each independently optionally substituted nitrogen-containing heterocycle optionally containing additional nitrogen atom, an oxygen atom, and/or a sulfur atom in the ring;
broken line indicates the presence or the absence of a bond;
when a broken line indicates the presence of a bond, p is 0;
when a broken line indicates the absence of a bond, p is 1;
R^a is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted lower alkynyl;
and R^b is hydrogen or oxo;
R^4 is hydrogen or lower alkyl;
R^5 is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl, or a pharmaceutically acceptable salt, or a solvate thereof,
(1') a compound represented by the formula (I):

[Chemical formula 3]



(I)

wherein R^1 and R^2 are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, or an optionally substituted heterocyclic group, or R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form optionally substituted heterocycle;
R^3 is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkoxy, mercapto, optionally substituted lower alkylthio, optionally substituted aryl, or an optionally substituted heterocyclic group;
R^4 is hydrogen or lower alkyl;
and R^5 is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl; or a pharmaceutically acceptable salt, or a solvate thereof,
(2) the compound according to (1) or (1'), wherein R^3 is hydroxy,
or a pharmaceutically acceptable salt, or a solvate thereof,
(3) the compound according to (1) or (1'), wherein R^3 is optionally substituted amino,
or a pharmaceutically acceptable salt, or a solvate thereof,

(4) the compound according to (1) or (1'), wherein R^3 is amino substituted with optionally substituted arylsulfonyl, or a pharmaceutically acceptable salt, or a solvate thereof,
(5) the compound according to any one of (1) to (4), and (1'), wherein R^1 is hydrogen or lower alkyl, R^2 is optionally substituted lower alkyl, optionally substituted phenyl, optionally substituted cycloalkyl, or an optionally substituted heterocyclic group, and R^5 is cyclopropylmethyl;
or a pharmaceutically acceptable salt, or a solvate thereof,
(6) the compound according to any one of (1) to (5), and (1'), wherein R^1 is hydrogen, R^2 is lower alkyl optionally substituted with lower alkoxy or with a heterocyclic group that is optionally substituted with aryl, phenyl optionally substituted with lower alkyl or lower alkoxy, cycloalkyl substituted with lower alkylcarbonyl, or a heterocyclic group substituted with lower alkoxy or aryl, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
or a pharmaceutically acceptable salt, or a solvate thereof,
(7) a pharmaceutical composition containing the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,
(8) a composition having opioid receptor antagonistic activity containing the compound according to (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,
(9) a composition for treating and/or preventing emesis, vomiting and/or constipation containing the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,
(10) a composition for alleviating and/or preventing a side effect induced by a compound having the opioid receptor agonistic activity, containing the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,
(11) a composition for treatment and/or prevention according to (10), wherein the side effect is emesis, vomiting and/or constipation,
(12) an agent for treatment and/or prevention according to (10) or (11), wherein the compound having the opioid receptor agonistic activity is morphine, oxycodone, or a pharmaceutically acceptable salt, or a solvate thereof,
(13) use of the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt ,or solvate thereof for producing a medicament for treating and/or preventing emesis, vomiting and/or constipation,
(14) use of the compound according to any one of (1) to (6), and (1'),or a pharmaceutically acceptable salt, or solvate thereof, for producing a medicament for alleviating and/or preventing a side effect induced by a compound having the opioid receptor agonistic activity,
(15) a method for treating and/or preventing emesis, vomiting and/or constipation, comprising administering the compound according to any one of (1) to (6) and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,
(16) a method for alleviating and/or preventing a side effect induced by a compound having the opioid receptor agonistic activity, comprising administering the compound according to any one of (1) to (6) and (1'), its pharmaceutically acceptable salt, or a solvate thereof,
(17) a composition for analgesic containing
a compound having an opioid receptor agonistic activity,
and an effective amount of compound according to any one of (1) to (6) and (1'), or a pharmaceutically acceptable salt, or a solvate thereof, for alleviating and/or preventing a side effect induced by administration of the compound having an opioid receptor agonistic activity,
(18) a composition for analgesic containing
a compound having an opioid receptor agonistic activity,
and an effective amount of compound according to any one of (1) to (6) and (1'), or a pharmaceutically acceptable salt or a solvate thereof, for treating and/or preventing emesis, vomiting and/or constipation induced by administration of the compound having an opioid receptor agonistic activity, ,
(19) the analgesic according to (17) or (18), wherein the compound having the opioid receptor agonistic activity, is morphine, oxycodone, its pharmaceutically acceptable salt, or a solvate thereof.

[0007] The compound (I) of the present invention has the activity of treating/or preventing emesis, vomiting and/or constipation, particularly emesis, vomiting and/or constipation induced by a compound having the opioid receptor (e.g. opioid μ receptor) agonistic activity, and is useful as a compositon for alleviating a side effect of a patient to whom a compound having the opioid receptor agonistic activity is administered or is in the middle of administration.

[0008] As used herein, the "halogen" includes fluorine, chlorine, bromine and iodine. A halogen part of the "halogeno lower alkyl", the "halogeno lower alkoxy", and the "halogeno lower alkylthio" is the same.

[0009] The "lower alkyl" is a straight or branched alkyl of a carbon number of 1 to 10, preferably a carbon number of 1 to 6, further preferably 1 to 3, and examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl and n-decyl. Preferable are methyl, ethyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and 1-ethylpropyl.

[0010] A substituent of the "optionally substituted lower alkyl" is selected from halogen, hydroxy, lower alkoxy, halogeno

lower alkoxy, hydroxy lower alkoxy, lower alkylthio, lower alkylamino, acylamino, acyl, acyloxy, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, cyanocarbamoyl, lower alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, sulfamoyl, lower alkylsulfamoyl, lower alkylsulfonyl, cycloalkyl optionally substituted with one or more substituents selected from Substituent group α (wherein Substituent group α is halogen, hydroxy, lower alkyl, halogeno lower alkyl, hydroxy lower alkyl, lower alkoxy lower alkyl, carboxy lower alkyl, lower alkoxycarbonyl lower alkyl, amino lower alkyl, lower alkylamino lower alkyl, acylamino lower alkyl, cyano lower alkyl, lower alkoxy, halogeno lower alkoxy, hydroxy lower alkoxy, lower alkylthio, halogeno lower alkylthio, acyl, acyloxy, amino, lower alkylamino, acylamino, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, arylcarbamoyl, cyanocarbamoyl, lower alkylsulfonylcarbamoyl, sulfamoyl, lower alkylsulfamoyl, lower alkylsulfonyl, aryl optionally substituted with lower alkylenedioxy, and a heterocyclic group), cycloalkenyl optionally substituted with one or more substituents selected from Substituent group α, aryl optionally substituted with one or more substituents selected from Substituent group α, aryloxy optionally substituted with one or more substituents selected from Substituent group α, arylthio optionally substituted with one or more substituents selected from Substituent group α, a heterocyclic group optionally substituted with one or more substituents selected from Substituent group α, and heterocyclic oxy optionally substituted with one or more substituents selected from Substituent group α.

[0011] A lower alkyl part of the "halogeno lower alkyl", the "hydroxy lower alkyl", the "amino lower alkyl", the "acylamino lower alkyl", the "acyloxy lower alkyl", the "cycloalkyl lower alkyl", the "lower alkoxy", the "halogeno lower alkoxy", the "hydroxy lower alkoxy", the "lower alkoxy lower alkyl", the "lower alkoxycarbonyl", the "carboxy lower alkyl", the "lower alkoxycarbonyl lower alkyl", the "lower alkylthio", the "halogeno lower alkylthio", the "lower alkylamino", the "lower alkylamino lower alkyl", the "lower alkylcarbamoyl", the "lower alkylsulfamoyl", the "lower alkylsulfonyl", the "aryl lower alkyl", the "tri lower alkylsilyl", the "lower alkyldiarylsilyl", the "triaryl lower alkylsilyl", the "lower alkoxy lower alkoxy lower alkyl", the "lower alkylthio lower alkyl", the "aryl lower alkoxy lower alkyl", the "lower alkylsulfonyl", the "lower alkylsulfonylcarbamoyl", the "lower alkylcarbonyl", the "cyano lower alkyl", the "lower alkoxycarbonylamino", the "lower alkylenedioxy", and the "heterocyclic lower alkyl" is the same as that of the aforementioned "lower alkyl".

[0012] A substituent of the "optionally substituted lower alkoxy", the "optionally substituted lower alkylthio", and the "optionally substituted lower alkylsulfonyl" is the same as the aforementioned substituent of the "optionally substituted lower alkyl".

[0013] The "lower alkenyl" is a straight or branched alkenyl of a carbon number of 2 to 10, preferably a carbon number of 2 to 8, further preferably a carbon number of 3 to 6 having one or more double bonds at an arbitrary position. Specifically, examples include vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl and decenyl. The lower alkenyl in R^5 is preferably allyl.

[0014] The substituent of the "optionally substituted lower alkenyl" is the same as that of the "optionally substituted lower alkyl".

[0015] The "lower alkynyl" is straight or branched alkynyl of a carbon number of 2 to 10, preferably a carbon number of 2 to 8, further preferably a carbon number of 3 to 6 having one or more triple bonds at an arbitrary position. Specifically, examples include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, and decynyl. These may further have a double bond at an arbitrary position.

[0016] The substituent of the "optionally substituted lower alkynyl" is the same as that of the "optionally substituted lower alkyl".

[0017] The substituent of the "optionally substituted amino" is selected from lower alkyl optionally substituted with one or more substituents selected from Substituent group α, cycloalkyl optionally substituted with one or more substituents selected from Substituent group α, acyl optionally substituted with one or more substituents selected from Substituent group α, amino optionally substituted with one or more substituents selected from Substituent group α, aryl optionally substituted with one or more substituents selected from Substituent group α, sulfamoyl, lower alkylsulfamoyl optionally substituted with one or more substituents selected from Substituent group α, arylsulfamoyl optionally substituted with one or more substituents selected from Substituent group α, lower alkylsulfonyl optionally substituted with one or more substituents selected from Substituent group α, arylsulfonyl optionally substituted with one or more substituents selected from Substituent group α, arylamino optionally substituted with one or more substituents selected from Substituent group α, and a heterocyclic group optionally substituted with one or more substituents selected from Substituent group α.

[0018] The substituent of the "optionally substituted carbamoyl" is the same as that of the "optionally substituted amino".

[0019] The "cycloalkyl" is a carbocyclic group of a carbon number of 3 to 10, preferably a carbon number of 3 to 8, more preferably a carbon number of 4 to 8 and, for example, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. These may be further condensed with "aryl" described later or "heterocyclic group" described later at an arbitrary position.

[0020] As the "cycloalkyl" in R^1 and R^2, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl are preferable.

[0021] A cycloalkyl part of the "cycloalkyl lower alkyl" and the "cycloalkylcarbonyl" is the same as the aforementioned "cycloalkyl".

[0022] As the "cycloalkyl lower alkyl" in R^5, cyclopropylmethyl is preferable."

[0023] The substituent of the "optionally substituted cycloalkyl" is one or more substituents selected from the aforementioned Substituent group α. The substituent can replace at an arbitrary position, and may replace at a carbon atom having a bond of cycloalkyl.

[0024] The "cycloalkenyl" is cycloalkenyl having one or more double bonds at an arbitrary position in a ring of the aforementioned cycloalkyl, and examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptyl, cyclooctynyl and cyclohexadienyl.

[0025] As the "cycloalkenyl" in R^1 or R^2, cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl are preferable.

[0026] A cycloalkenyl part of the "cycloalkenylcarbonyl" is the same as the aforementioned "cycloalkenyl".

[0027] The substituent of the "optionally substituted cycloalkenyl" is the same as that of the aforementioned "optionally substituted cycloalkyl".

[0028] The "aryl" includes phenyl, naphthyl, anthryl and phenanthryl, and phenyl is particularly preferable.

[0029] An aryl part of the "aryloxy", the "arylthio", the "aryl lower alkyl", the "lower alkyldiarylsilyl", the "triaryl lower alkylsilyl", the "aryl lower alkyloxy lower alkyl", the "arylsulfonyl", the "arylsofamoyl", the "arylamino", the "arylcarbamoyl", and the "arylsulfonylcarbamoyl" is the same as the aforementioned "aryl".

[0030] The substituent of the "optionally substituted aryl", the "optionally substituted phenyl", and the "optionally substituted arylsulfonyl" is selected from the Substituent group α, phenyl substituted with one or more groups selected from Substituent group α, phenoxy substituted with one or more groups selected from Substituent group α, and lower alkylenedioxy.

[0031] The "heterocyclic group" includes a heterocyclic group having one or more heteroatoms arbitrarily selected from O, S and N in a ring, and specifically includes a 5- to 6-membered heteroaryl such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, furyl and thienyl; a bicyclic condensed heterocyclic group such as indolyl, isoindolyl, indazolyl, indolidinyl, indolinyl, isoindolinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthridinyl, quinoxalinyl, purinyl, pteridinyl, benzopyranyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzoisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, quinazolinyl, quinolyl, isoquinolyl, naphthyridinyl, dihydropyridyl, tetrahydroquinolyl, and tetrahydrobenzothienyl; a tricyclic condensed heterocyclic group such as carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, and dibenzofuryl; a non-aromatic heterocyclic group such as dioxanyl, thiiranyl, thioranyl, thietanyl, oxilanyl, oxetanyl, oxathioranyl, azetidinyl, thianyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, dihydropyridyl, dihydrofuryl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolyl, and tetrahydroisothiazolyl. Preferable is a 5- to 6-membered heteroaryl or a non-aromatic heterocyclic group.

[0032] As the "heterocyclic group" in R^1 and R^2, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, isoxazolyl, thiazolyl, thiadiazolyl, furyl, thienyl, indolyl, indazolyl, quinolyl, isoquinolyl, benzoxazolyl, benzothiazolyl, oxetanyl, tetrahydrofuryl, and tetrahydropyranyl are preferable. Pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl are more preferable. Pyridyl and pyrimidinyl are particularly preferable.

[0033] As the heterocyclic group of the "optionally substituted lower alkyl" in R^1 and R^2, isoxazolyl, oxazolyl, and oxadiazolyl are preferable. Oxadiazolyl is particularly preferable.

[0034] A heterocyclic part of the "heterocyclic oxy" and the "heterocyclic lower alkyl" is the same as the aforementioned "heterocyclic group".

[0035] The substituent of the "optionally substituted heterocyclic group" is one or more groups selected from the group consisting of the Substituent group α and oxo. The substituent can replace at an arbitrary position, or may replace at a carbon atom or a nitrogen atom having a bond of the heterocyclic group.

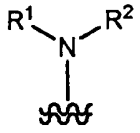
[0036] The "acyl" includes straight or branched chain-like aliphatic acyl of a carbon number of 1 to 10, preferably a carbon number of 1 to 6, further preferably a carbon number of 1 to 4, cyclic aliphatic acyl of a carbon number of 4 to 9, preferably a carbon number of 4 to 7, aroyl and heterocyclic carbonyl. Herein, the "chain-like aliphatic" includes the aforementioned "lower alkyl", the aforementioned "lower alkenyl", and the aforementined "lower alkynyl". The "cyclic aliphatic" includes the aforementioned "cycloalkyl" and the aforementioned "cycloalkenyl". A heterocyclic part of the heterocyclic carbonyl is the same as the aforementioned "heterocyclic group". Examples of the acyl include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, pivaloyl, hexanoyl, acryloyl, propioloyl, methacryloyl, crotonoyl, cyclopropylcarbonyl, cyclohexylcarbonyl, cyclooctylcarbonyl, benzoyl, pyridinecarbonyl, piperidinecarbonyl, piperazinecarbonyl, morpholinocarbonyl, and the like.

[0037] An acyl part of the "acyloxy", the "acylamino", the "acylamino lower alkyl" and the "acyloxy lower alkyl" is the same as the aforementioned "acyl".

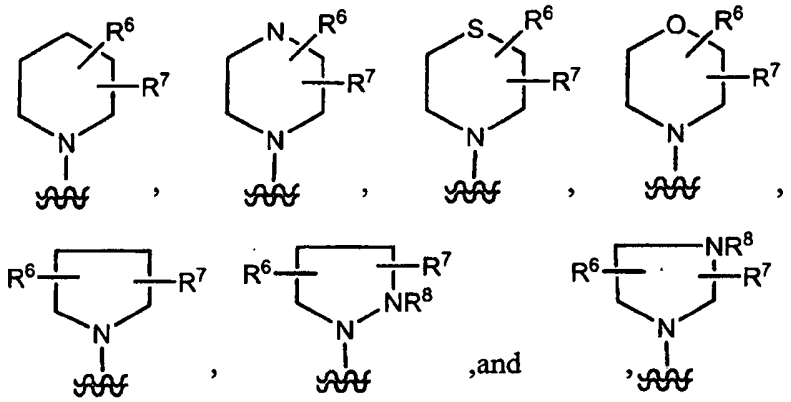
[0038] The substituent of the "optionally substituted acyl" or the "optionally substituted" is the same as the substituent of the aforementioned "optionally substituted lower alkyl" when the "acyl" is chain-like aliphatic acyl, and includes one or more groups selected from the Substituent group α when the "acyl" is cyclic aliphatic acyl, aroyl or heterocyclic carbonyl.

[0039] The "optionally substituted heterocycle" formed when R^1 and R^2 are taken together with the nitrogen atom to which they are atttached, includes a 5-membered or 6-membered heterocycle containing the nitrogen atom to which R^1 and R^2 are attached and, further, optionally containing one or more heteroatoms selected from N, S and O. For example, the case where

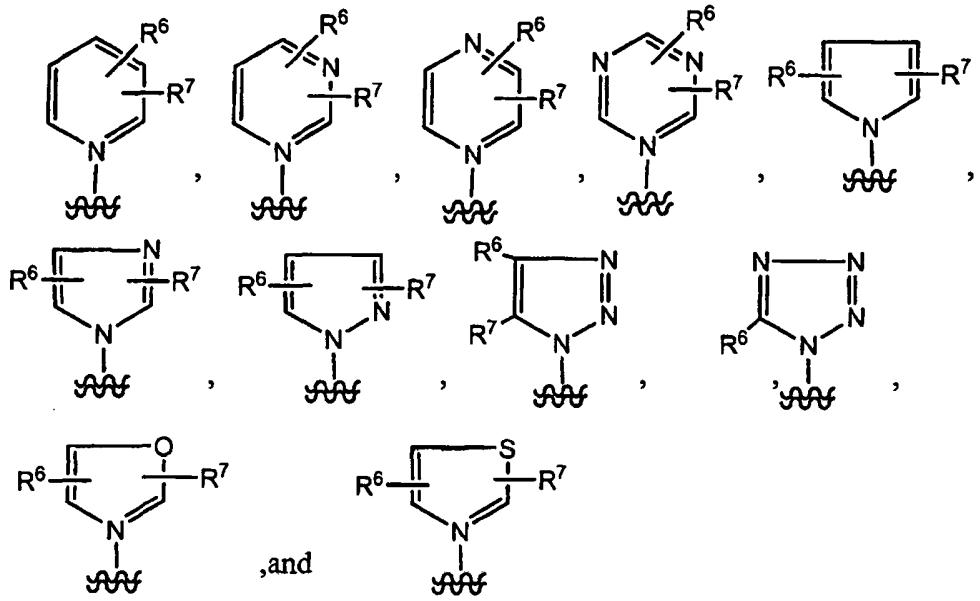
[Chemical formula 4]



is a saturated heterocycle group such as



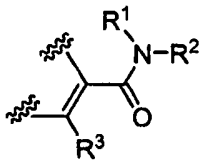
, or an unsaturated heterocycle group such as



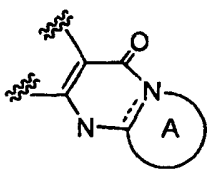
wherein R^6, R^7 and R^8 are each independently hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, lower alkylthio, acyl, acyloxy, amino, lower alkylamino, acylamino, lower alkoxycarbonylamino, carboxy or lower alkoxycarbonyl, is included and the preferable is a saturated heterocycle group such as morpholine ring, pyrrolidine ring, piperidine ring, piperazine ring, and the like optionally substituted with hydrogen, halogen, hydroxy or lower alkyl.

[0040] The substituent of the "optionally substituted heterocycle, which is formed when R^1 and R^2 are taken together with the nitrogen atom to which they are attached" is the same as the substituent of the "optionally substituted heterocyclic group".

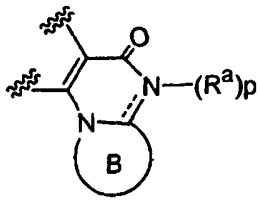
[Chemical formula 5]



is

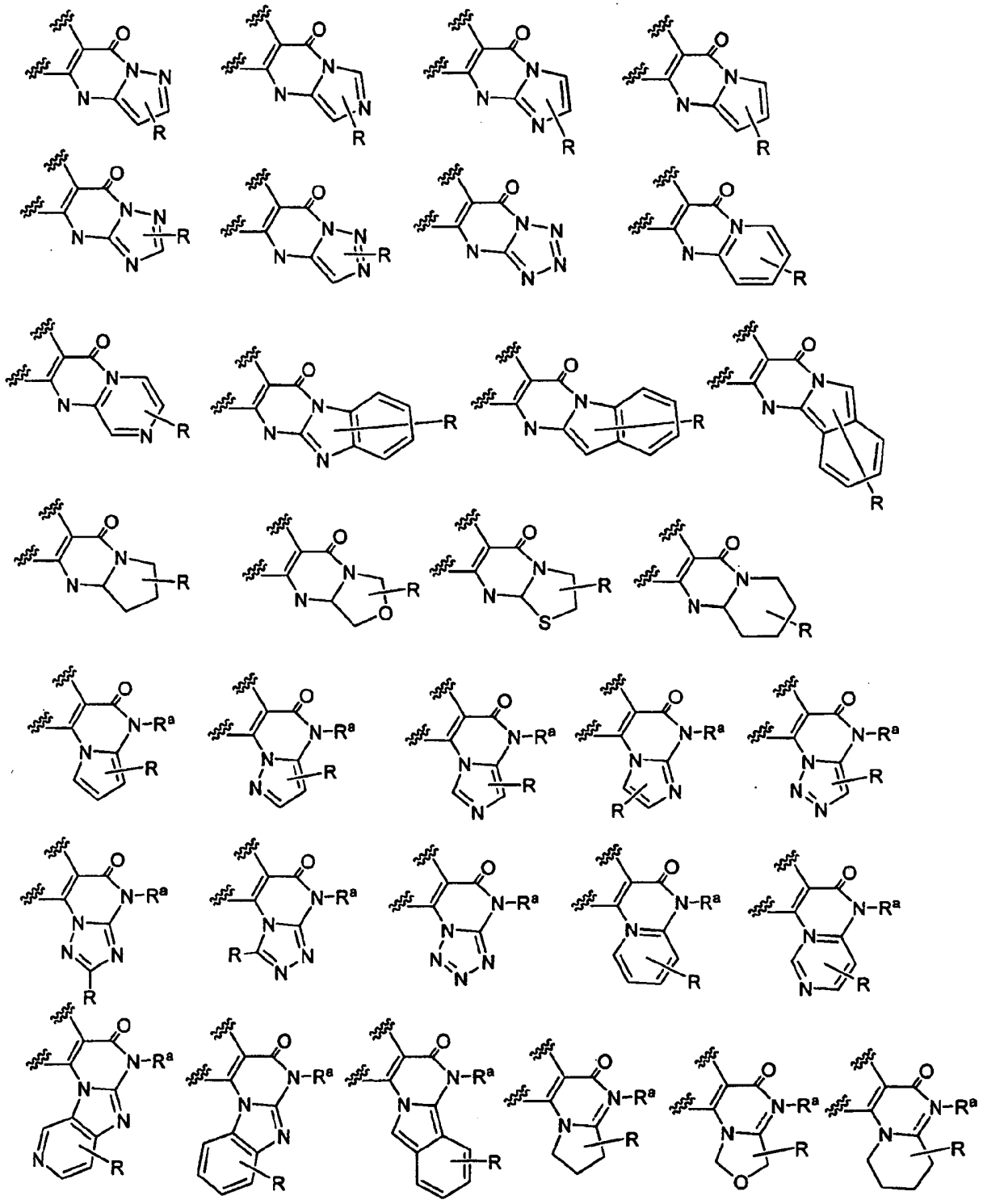


or



includes, for example, the following:

[Chemical formula 6]



wherein R^a is as defined above, and R is hydrogen or a group selected from Substituent group α.

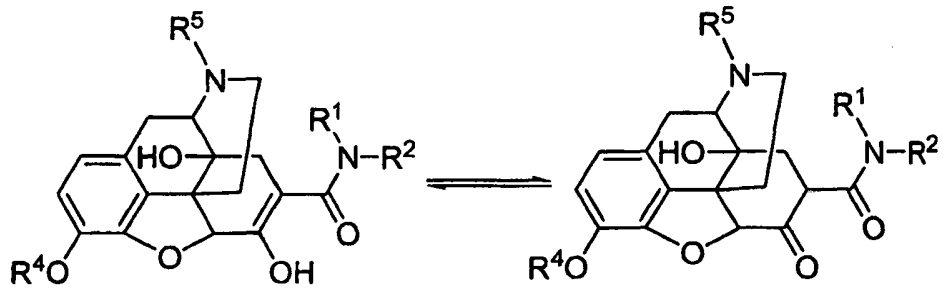
[0041] Herein, the "solvate" includes, for example, a solvate with an organic solvent, a hydrate and the like. When a hydrate is formed, any number of water molecules may be coordinated.

[0042] The compound (I) includes a pharmaceutically acceptable salt. Examples include salts with alkali metals (lithium, sodium or potassium), alkaline earth metals (magnesium or calcium), ammonium, organic bases or amino acids, and salts with inorganic acids (hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid and hydroiodic acid), or organic acids (acetic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric

acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid). Particularly, hydrochloric acid, phosphoric acid, tartaric acid, or methanesulfonic acid is preferable. These salts can be formed by a conventional method.

[0043] In addition, the compound (I) is not limited to a specific isomer, but includes all possible isomers and racemates. For example, when R^3 of the compound (I) is hydroxy, the compound (I) includes other tautomer, that is, the following compound (I').

[Chemical formula 7]



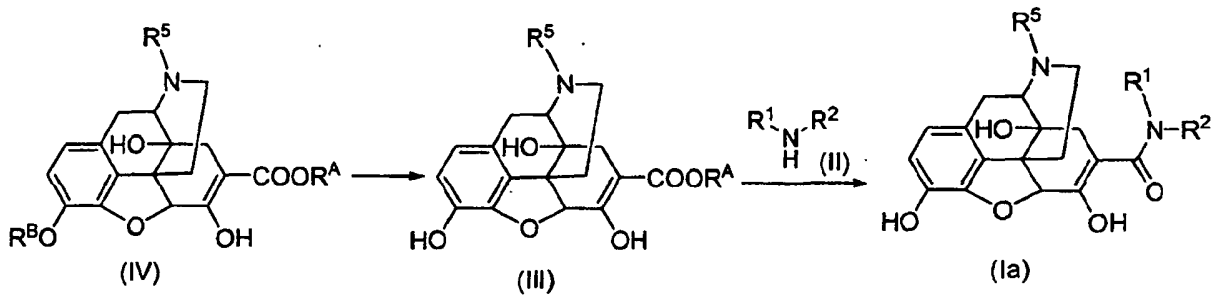
(I) (I')

[0044] The present compound (I) can be produced by the following process.

(A process)

[0045]

[Chemical formula 8]



(IV) (III) (Ia)

wherein R^A is an ester residue , R^B is hydrogen or hydroxy protecting group, and other symbols are as defined above..

[0046] Herein, the ester residue includes lower alkyl such as methyl, ethyl and the like, aryl lower alkyl such as benzyl, phenethyl and the like, acyloxy lower alkyl such as acetyloxymethyl and the like, etc.

[0047] The hydroxy protecting group is not limited to, but includes lower alkyl (methyl, tert-butyl etc.), aryl lower alkyl (triphenylmethyl, benzyl etc.), tri lower alkylsilyl (trimethylsilyl, tert-butyldimethylsilyl, triethylsilyl, triisopropylsilyl etc.), lower alkyldiarylsilyl (tert-butyldiphenylsilyl etc.), triaryl lower alkylsilyl (tribenzylsilyl etc.), lower alkoxy lower alkyl (methoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxyehtyl etc.), lower alkoxy lower alkoxy lower alkyl (methoxyethoxymethyl etc.), lower alkylthio lower alkyl (methylthiomethyl etc.), optionally substituted tetrahydropyranyl (tetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl etc.), tetrahydrothiopyranyl (tetrahydrothiopyran-2-yl etc.), tetrahydrofuranyl (tetrahydrofuran-2-yl etc.), tetrahydrothiofuranyl (tetrahydrothiofuran-2-yl etc.), aryl lower alkyloxy lower alkyl (benzyloxymethyl etc.), lower alkylsulfonyl (methanesulfonyl, ethanesulfonyl etc.), acyl (acetyl etc.) and arylsulfonyl (p-toluenesulfonyl etc.).

(First step)

[0048] First, the known compound or compound (IV) derived therefrom is deprotected by a conventional method.

[0049] For example, when a protecting group is benzyl, the compound is dissolved or suspended in a suitable solvent (ethyl acetate, methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide, acetic acid, dilute hydrochloric acid, or

a mixture thereof), and a hydrogenation reaction using a palladium catalyst (palladium hydroxide, palladium-carbon, palladium-barium sulfate, palladium-aluminum oxide, palladium black etc.) affords compound (III). A reaction may be performed at about 0°C to about 100°C, preferably about 20°C to about 50°C for about 15 minutes to about 24 hours, preferably about 1 hour to about 5 hours.

(Second step)

[0050] Then, the resulting compound (III) is directly amidated to obtain compound (Ia).

[0051] For example, compound (III) and compound (II) may be reacted by heating in a suitable solvent (methanol, ethanol, tetrahydrofuran, dimethylformamide, diethyl ether, dichloromethane, dichloroethane, toluene, xylene, chlorobenzene, orthodichlorobenzene, 2-methoxyethanol or diethylene glycol dimethyl ether or a mixture thereof) or without a solvent at about 0°C to about 250°C, preferably about 80°C to about 200°C for about 30 minutes to about 24 hours, preferably about 1 to 12 hours in the presence or the absence of an amine compound (ammonia, dimethylamine, triethylamine, pyridine, dimethylaniline, dimethylaminopyridine, lutidine etc.).

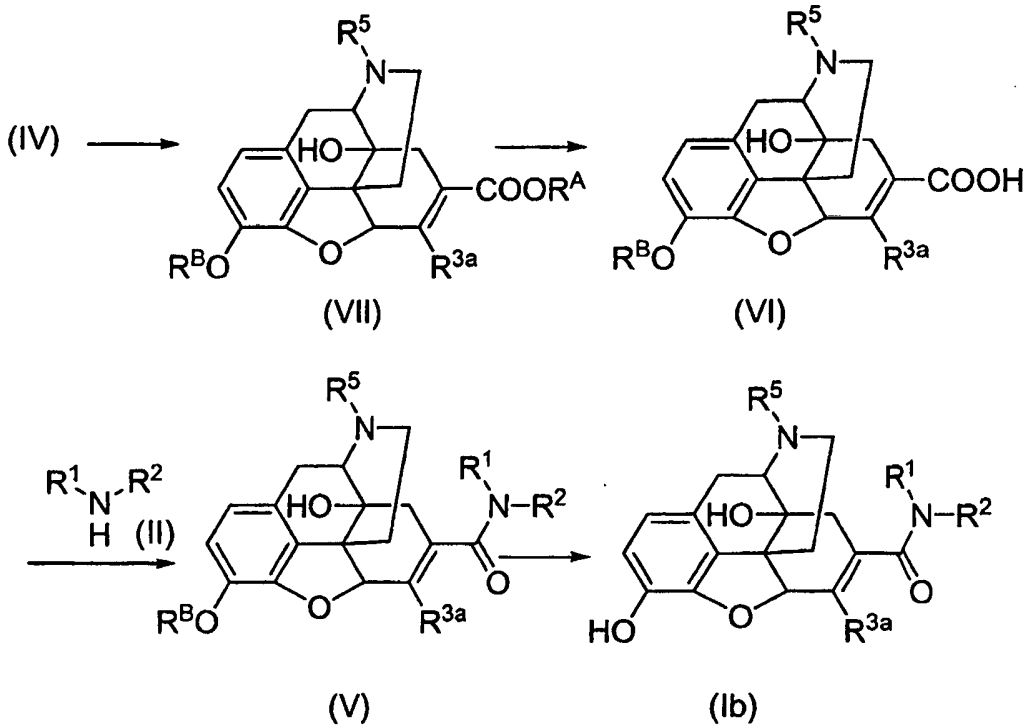
[0052] In order to effectively carry a reaction forward, the reaction may be performed by microwave irradiation. A reaction temperature, and an irradiation time are not particularly limited, but are about 100°C to about 200°C and about 5 minutes to about 5 hours, preferably about 10 minutes to about 1 hour. It is preferable to use, as a solvent, a polar solvent such as methanol, ethanol, 1-propanol, ethylene glycol, glycerin, 2-methoxyethanol, 2-ethoxyethanol, N,N-dimethylformamide, diethylene glycol dimethyl ether and the like.

[0053] When R^4 of objective compound (I) is lower alkyl, an objective compound can be obtained by the conventional etherization reaction at an arbitrary stage.

(B process)

[0054]

[Chemical formula 9]



wherein R^{3a} is hydroxy, or optionally substituted lower alkoxy, and other symbols are as defined above.

(First step)

[0055] When R^3 of objective compound (I) is optionally substituted lower alkoxy, first, the known compound (IV) is

etherized by a conventional method.

[0056] For example, the compound is reacted with an alkylating agent or an alcohol having a R^{3a} group corresponding to an objective compound in the presence of a base (sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium bicarbonate or metal sodium), or under the condition of Mitsunobu reaction in a suitable solvent (N,N-dimethylformamide, dimethyl sulfoxide, toluene, benzene, xylene, a mixture thereof, or the like) cyclohexane, hexane, dichloromethane, 1,2-dichloroethane, tetrahydrofuran, dioxane, acetone, methyl ethyl ketone, acetonitrile, water or a mixture thereof) to obtain compound (VII). The reaction may be performed at -70 to 180°C, preferably about 0 to 150°C for about 15 minutes to about 24 hours, preferably about 1 hour to about 5 hours.

(Second step)

[0057] Then, compound (VII) is hydrolyzed to obtain compound (VI). The reaction may be performed under ice-cooling to at a reflux temperature of a solvent for about 15 minutes to about 24 hours, preferably, 1 hour to about 5 hours using an inorganic base (sodium hydroxide, lithium hydroxide or potassium hydroxide) in a suitable solvent (methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide or a mixture thereof).

(Third step and Fourth step)

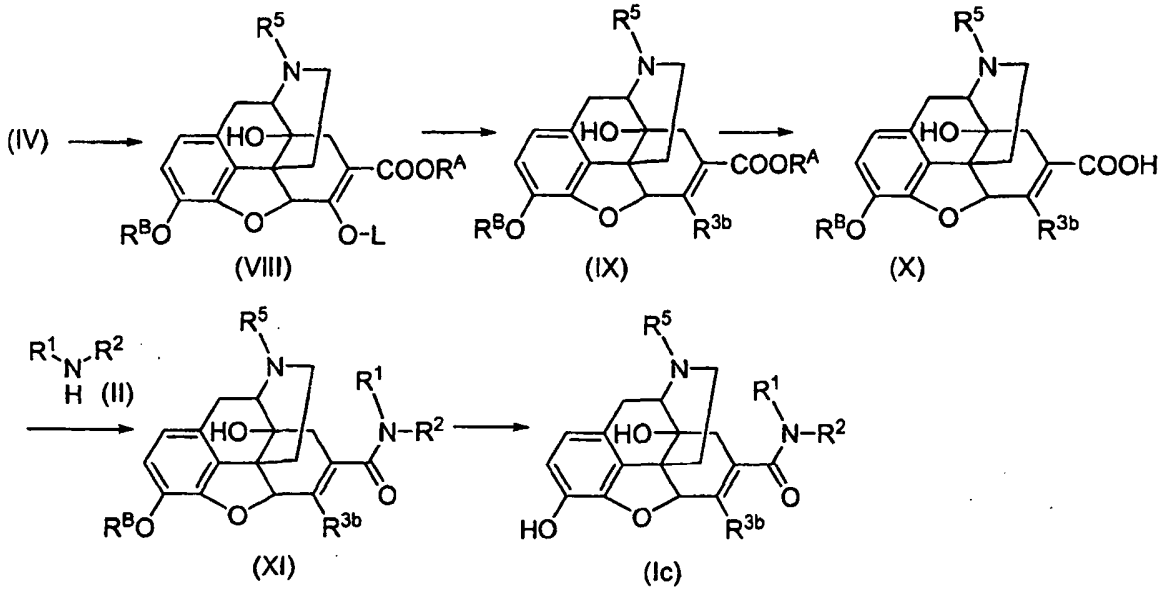
[0058] Then, compound (VI) is amidated, and the resulting compound (V) is deprotected to obtain objective compound (Ib). These reactions may be performed by the same methods as those of the second step and the first step in A process, respectively. In an amidation step, the reaction may be performed, if necessary, in the presence of a condensing agent (N,N'-dicyclohexylcarbodiimide, N-dimethylaminopropyl-N'-ethylcarbodiimide, diethyl phosphoryl cyanide, diphenyl phosphoryl azide etc.).

[0059] In addition, when R^4 of objective compound (I) is lower alkyl, an etherization reaction may be performed at an arbitrary stage as described above.

(C process)

[0060]

[Chemical formula 10]



wherein L is a leaving group, R^{3b} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl,

optionally substituted lower alkynyl, optionally substituted lower alkoxy, mercapto, optionally substituted lower alkylthio, optionally substituted amino, optionally substituted carbamoyl, optionally substituted aryl, or optionally substituted heterocyclic group, and other symbols are as defined above..

(First step)

[0061] When R^3 of objective compound (I) is the R^{3b}, a leaving group L (e.g. trifluoromethanesulfonyl, methanesulfonyl, phosphoric acid ester etc.) is introduced into the known compound (IV). For example, the compound is reacted with trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride, methanesulfonyl chloride, methanesulfonic anhydride, p-toluenesulfonyl chloride, N-phenyltrifluoromethanesulfonimide or various phosphoric acid esterifying reagents in the presence of a base (pyridine, triethylamine, ammonia, dimethylamine, dimethylaniline, dimethylaminopyridine, 2,6-lutidine or 2,6-di-tert-butylpyridine) using dichloromethane, chloroform, tetrahydrofuran, benzene, toluene, dimethylformamide, ethyl acetate or a mixture thereof as a solvent.

(Second step)

[0062] The thus obtained compound (VIII) is subjected to the known substituent introducing reaction to obtain compound (IX).

(Third step, Fourth step and Fifth step)

[0063] The compound (IX) is hydrolyzed, amidated, and deprotected by the same methods as those of the second step in B process,, the second step in A process and the first step in A step, respectively, to obtain objective the compound (Ic).

[0064] In addition, when R^4 of the objective compound (I) is lower alkyl, an etherization reaction may be performed at an arbitrary stage as described above.

(D process)

[0065] compound (VIII) is obtained by the first step in C process, amidated according to the method of the fourth step in C process, and subjected to introduction of a substituent R^{3b}, deprotection, and a hydrolysis reaction according to the methods of the second step, third step and fifth step in C process, respectively, thereby, objective compound (I) may be also obtained.

[0066] All of thus obtained present compounds have the opioid receptor antagonistic activity, and are useful as a drug, and among compounds represented by the formula (I), the following compounds are particularly preferable.

a) a compound in which R^1 is hydrogen or lower alkyl,
b) a compound in which R^1 is hydrogen or C1-C3 alkyl,
c) a compound in which R^2 is:

(c-i) lower alkyl optionally substituted with one or more groups selected from Substituent group β (herein, Substituent group β is cycloalkyl optionally substituted with hydroxy, halogen, hydroxy, lower alkoxy, halogeno lower alkoxy, lower alkylthio, amino, lower alkylamino, carboxy, lower alkoxycarbonyl, cyano, lower alkylsulfonyl, aryl, aryloxy and lower alkylenedioxy),
(c-ii) phenyl optionally substituted with one or more groups selected from group consisting of Substituent group β, lower alkyl and halogeno lower alkyl,
(c-iii) aryl lower alkyl optionally substituted with one or more groups selected from Substituent group β,
(c-iv) cycloalkyl optionally substituted with one or more groups selected from Substituent group β,
(c-v) heterocyclic group optionally substituted with one or more groups selected from Substituent group β, or
(c-vi) heterocyclic lower alkyl optionally substituted with one or more groups selected from Substituent group β,

d) a compound in which R^2 is:

(d-i) lower alkyl optionally substituted with hydroxy, cycloalkyl optionally substituted with hydroxy, lower alkoxy, lower alkylthio, lower alkylamino or aryloxy,
(d-ii) phenyl optionally substituted with halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, halogeno lower alkoxy, lower alkylthio, amino, lower alkylamino, cyano, lower alkylsulfonyl or lower alkylenedioxy,
(d-iii) aryl lower alkyl optionally substituted with lower alkoxy or lower alkylthio,

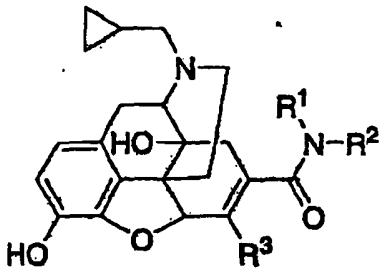
(d-iv) cycloalkyl optionally substituted with lower alkyl, carboxy or lower alkoxycarbonyl,
(d-v) a heterocyclic group optionally substituted with lower alkyl, lower alkoxy or phenyl, or
(d-vi) heterocyclic lower alkyl optionally substituted with lower alkyl or aryl,

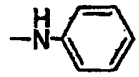
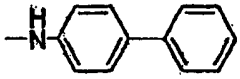
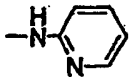
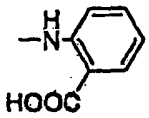
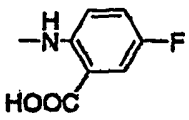
e) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle,
f) a compound in which R^3 is hydroxy or lower alkoxy,
g) a compound in which R^3 is hydroxy,
h) a compound in which R^3 is amino optionally substituted with one or more groups selected from Substituent group α,
i) a compound in which R^3 is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy,
j) a compound in which R^4 is hydrogen or methoxy,
k) a compound in which R^5 is cycloalkyl lower alkyl or lower alkenyl,
l) a compound in which R^5 is cyclopropylmethyl or allyl,
m) a compound in which R^5 is cyclopropylmethyl,
n) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-i), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
o) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-i), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
p) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-i), R^3 is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
q) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-i), R^3 is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
r) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-ii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
s) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-ii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
t) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
u) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
v) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iv), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
w) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iv), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
x) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-v), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
y) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-v), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
z) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-vi), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
aa) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-vi), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
ab) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle, R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl group or lower alkenyl,
ac) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle, R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,

or a pharmaceutically acceptable salt or a solvate thereof.

[0067] In a compound represented by the formula (I), a compound in which R^4 is hydrogen, R^5 is cyclopropylmethyl, and a combination of NR^1R^2 and R^3 (NR^1R^2, R^3) is the following.

[Table 1]



	NR1R2	CR9R10			NR1R2	CR9R10
AA	-NHiPr	-		BJ	-NHCR9R10CONMe2	Ri
AB		-		BK	-NHCR9R10CONMe2	Rk
AC		-		BL	-NHCR9R10CONMe2	Rl
AD		-		BM	-NHCR9R10CONMe2	Rm
AE		-		BN	-NHCR9R10CONMe2	Rn
AF		-		BO	-NHCR9R10CONMe2	Ro
AG	-NHCR9R10CONH2	Ra		BP	-NHCR9R10CONMe2	Rp
AH	-NHCR9R10CONH2	Rb		BQ	-NHCR9R10CONMe2	Rq
AI	-NHCR9R10CONH2	Rc		BR	-NHCR9R10CONMe2	Rr
AJ	-NHCR9R10CONH2	Rd		BS	-NHCR9R10CONMe2	Rs
AK	-NHCR9R10CONH2	Re		BT	-NHCR9R10CONMe2	Rt
AL	-NHCR9R10CONH2	Rf		BU	-NHCR9R10COOH	Ra
AM	-NHCR9R10CONH2	Rg		BV	-NHCR9R10COOH	Rb
AN	-NHCR9R10CONH2	Rh		BW	-NHCR9R10COOH	Rc
AO	-NHCR9R10CONH2	Ri		BX	-NHCR9R10COOH	Rd
AP	-NHCR9R10CONH2	Rj		BY	-NHCR9R10COOCH	Re
AQ	-NHCR9R10CONH2	Rk		BZ	-NHCR9R10COOH	Rf
AR	-NHCR9R10CONH2	Rl		CA	-NHCR9R10COOH	Rg
AS	-NHCR9R10CONH2	Rm		CB	-NHCR9R10COOH	Rh
AT	-NHCR9R10CONH2	Rn		CC	-NHCR9R10COOH	Ri
AU	-NHCR9R10CONH2	Ro		CD	-NHCR9R10COOH	Ri
AV	-NHCR9R10CONH2	Rp		CE	-NHCR9R10COOH	Rk

(continued)

	NR1R2	CR9R10			NR1R2	CR9R10
AW	-NHCR9R10CONH2	Rq		CF	-NHCR9R10COOH	Rl
AX	-NHCR9R10CONH2	Rr		CG	-NHCRSR10COOH	Rm
AY	-NHCR9R10CANH2	Rs		CH	-NHCR9R10COOH	Rn
AZ	-NHCR9R10CONH2	Rt		CI	-NHCR9R10COOH	Ro
BA	-NHCR9R10CONMe2	Ra		CJ	-NHCR9R10COOH	Rp
BB	-MHCR9R10CONMe2	Rb		CK	-NHCMR10COOH	Rq
BC	-NHCR9R10CONMe2	Rc		CL	-NHCR9R10COOH	Rr
BD	-NHCR9R10CONMe2	Rd		CM	-NHCR9R10COOH	Rs
BE	-NHCR9R10CONMe2	Re		CN	-NHCR9R10COOH	Rt
BF	-NHCR9R10CONMe2	Rf		CO	-NHCR9R10COOMe	Ra
BG	-NHCR9R10CONMe2	Rg		CP	-NHCR9R10COOMe	Rb
BH	-NHCR9R10CONMe2	Rh		CQ	-NHCR9R10COOMe	Rc
B1	-NHCR9R10CONMe2	Ri		CR	-NHCR9R10COOMe	Rd

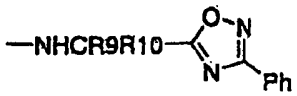
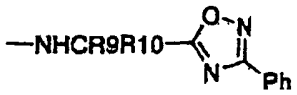
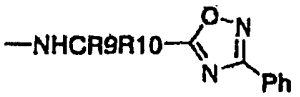
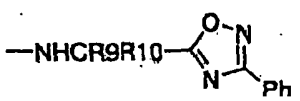
[Table 2]

	NR1R2	CR9R10			NR1R2	CR9R10
CS	-NHCR9R10COOMe	Re		EY	-NHCR9R10CONHMe	Rc
CT	-NHCR9R10COOMe	Rf		EZ	-NHCR9R10CONHMe	Rd
CU	-NHCR9R10COOMe	Rg		FA	-NHCR9R10CONHMe	Re
CV	-NHCR9R10COOMe	Rh		FB	-NHCR9R10CONHMe	Rf
CW	-NHCR9R10COOMe	Ri		FC	-NHCR9R10CONHMe	Rg
CX	-NHCR9R10COOMe	Rj		FD	-NHCR9R10CONHMe	Rh
CY	-NNOR9R10COOMe	Rk		FE	-NHCR9R10CONHMe	Ri
CZ	-NHCR9R10COOMe	Rl		FF	-NHCR9R10CONHMe	Ri
DA	-NHCR9R10COOMe	Rm		FG	-NHCR9R10CONHMe	Rk
DB	-NHCR9R10COOMe	Rn		FH	-NHCR9R10CONHMe	Rl
DC	-NHCR9R10COOMe	Ro		FI	-NHCR9R10CONHMe	Rm
DD	-NHCR9R10COOMe	Rp		FJ	-NHCR9R10CONHMe	Rn
DE	-NHCR9R10COOMe	Rq		FK	-NHCR9R10CONHMe	Ro
DF	-NHCR9R10COOMe	Rr		FL	-NHCR9R10CONHMe	Rp
DG	-NHCR9R10COOMe	Rs		FM	-NHCR9R10CONHMe	Rq
DH	-NHOR9R10GOOMe	Rt		FN	-NHCR9R10CONHMe	Rr
DI	-NHCR9R10COOEt	Ra		FO	-NHOR9R10CONHMe	Rs
DJ	-NHCR9R10COOEt	Rb		FP	-NHCR9R10CONHMe	Rt
DK	-NHCR10COOEt	Rc		FQ	-NHCR9R10CONHiPr	Ra
DL	-NHCR9R10COOEt	Rd		FR	-NHCR9R10CONHiPr	Rb
DM	-NHCR9R10COOEt	Re		FS	-NHCR9R10CONHiPr	Rc

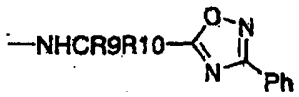
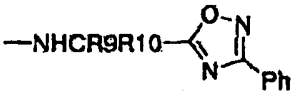
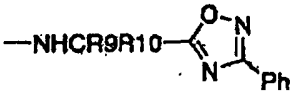
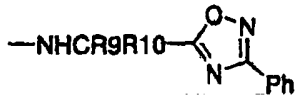
(continued)

	NR1R2	CR9R10			NR1R2	CR9R10
DN	-NHCR9R10COOEt	Rf		FT	-NHCR9R10CONHiPr	Rd
DO	-NHCR9R10COOEt	Rg		FU	-NHCR9R10CONHiPr	Re
DP	-NHCR9R10COOEt	Rh		FV	-NHCR9R10CONHiPr	Rf
DQ	-NHCR9R10COOEt	Ri		FW	-NHCR9R10CONHiPr	Rg
DR	-NHCR9R10COOEt	Rj		FX	-NHCR9R10CONHiPr	Rh
DS	-NHCR9R10COOEt	Rk		FY	-NHCR9R10GONHiPr	Ri
DT	-NHCR9R10COOEt	Rl		FZ	-NHCR9R10CONHiPr	Rj
DU	-NHCR9R10COOEt	Rm		GA	-NHCR9R10CONHiPr	Rk
DV	-NHCR9R10COOEt	Rn		GB	-NHCR9R10CONHiPr	Rl
DW	-NHCR9R10COOEt	Ro		GC	-NHCR9R10CONHiPr	Rm
DX	-NHCR9R10COOEt	Rp		GD	-NHCR9R10CONHiPr	Rn
DY	-NHCR9R10COOEt	Rq		GE	-(NHCR9R10CONHiPr	Ro
DZ	-NHCR9R10COOEt	Rr		GF	-NHCR9R10CONHiPr	Rp
EA	-NHCR9R10COOEt	Rs		GG	-NHCR9R10CONHiPr	Rq
EB	-NHCR9R10COOEt	Rt		GH	-NHCR9R10CONHiPr	Rr
EC	-NHCR9R10COOiPr	Ra		GI	-NHCR9R10CONHiPr	Rs
ED	-NHCR9R10COOiPr	Rb		GJ	-NHCR9R10OONHiPr	Rt
EE	-NHOR9R10COOiPr	Rc		GK	-NHCR9R10CONHPh	Ra
EF	-NHCR9R10COOiPr	Rd		GL	-NHCR9R10CONHPh	Rb
EG	-NHCR9R10COOiPr	Re		GM	-NHCR9R10CONHPh	Rc
EH	-NHCR9R10COOiPr	Rf		GN	-NHCR9R10CONHPh	Rd
EI	-NHCR9R10COOiPr	Rg		GO	-NHCR9R10CONHPh	Re
EJ	-NHCR9R10COOiPr	Rh		GP	-NHCR9R10CONHPh	Rf
EK	-NHCR9R10COOiPr	Ri		GQ	-NHCR9R10CONHPh	Rg
EL	-NHCR9R10COOiPr	Rj		GR	-NHCR9R10CONHPh	Rh
EM	-NHCR9R10COOiPr	Rk		GS	-NHCR9R10CONHPh	Ri
EN	-NHCR9R10COOiPr	Rl		GT	-NHCR9R10CONHPh	Rj
EO	-NHCR9R10COOiPr	Rm		GU	-NHCR9R10CONHPh	Rk
EP	-NHCR9R10COOiPr	Rn		GV	-NHCROR10CONHPh	Rl
EQ	-NHCR9R10COOiPr	Ro		GW	-NHCR9R10CONHPh	Rm
ER	-NHCR9R10COOiPr	Rp		GX	-NHCR9R10CONHPh	Rn
ES	-NHCR9R10COOiPr	Rq		GY	-NHCR9R10CONHPh	Ro
ET	-NHCR9R10COOiPr	Rr		GZ	-NHCR9R10CONHPh	Rp
EU	-NHCR9R10COOiPr	Rs		HA	-NHCR9R10CONHPh	Rq
EV	-NHCR9R10COOiPr	Rt		HB	-NHCR9R10CONHPh	Rr
EW	-NHCR9R10CONHMe	Ra		HC	-NHCR9R10COMHPh	Rs
EX	-NHCR9R10CONHMe	Rb		HD	-NHCR9R10CONHPh	Rt

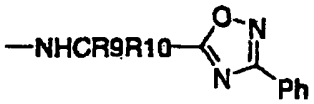
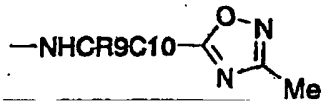
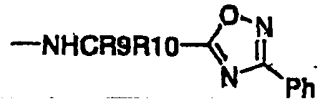
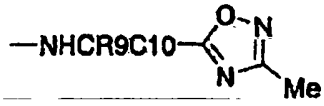
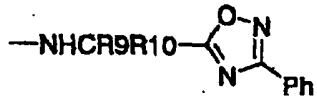
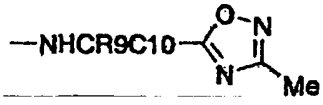
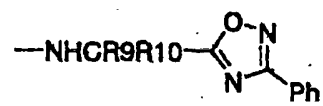
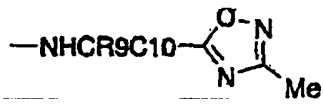
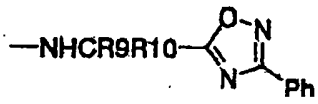
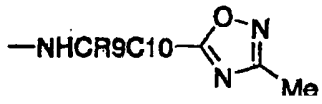
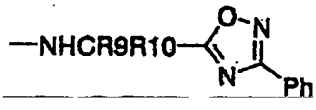
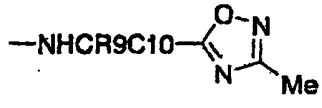
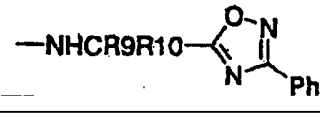
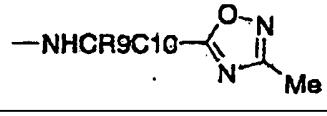
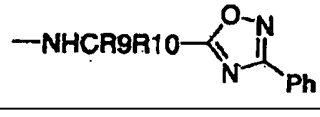
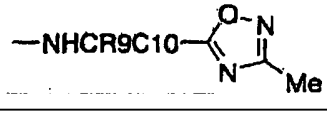
[Table 3]

	NR1R2	CR9R10		NR1R2	CR9R10
HE	-NHCR9R10CONHCN	Ra	IM	-NHCR9R10CONHS02Me	Ro
HF	-NHCR9R10CONHCN	Rb	IN	-NHCR9R10CONHSO2Me	Rp
HG	-NHCR9F10CONHCN	Rc	IO	-NHCR9R10CONHSO2Me	Rq
HH	-NHCR9R10CQNHCN	Rd	IP	-NHGR9R10CONHSO2Me	Rr
HI	-NHCR9R10CONHCN	Re	IQ	-NNCR9R10CONHSO2Me	Rs
HJ	-NHCR9R10CONHCN	Rf	IR	-NHCR9R10CONHSO2Me	Rt
HK	-NHCR9R10CONHCN	Rg	IS	-NHCR9R10CH2OMe	Ra
HL	-MHCR9R10CONHCN	Rh	IT	-NHCR9R10CH2OMe	Rb
HM	-NHCR9R10CONHCN	Ri	IU	-NHCR9R10CH2OMe	Rc
HN	-NHCR9R10CONHCN	Rj	IV	-NHCR9R10CH2OMe	Rd
HO	-NHCR9R10CONHCN	Rk	IW	-NHCR9R10CH2OMe	Re
HP	-NHCR9R10CONHCN	Rl	IX	-NHCR9R10CH2OMe	Rf
HQ	-NHCR9R10CONHCN	Rm	IY	-NHCR9R10CH2OMe	Rg
HR	-NHCR9R10CONHCN	Rn	IZ	-NHCR9R10CN2OMe	Rh
HS	-NHCR9R10CONHCN	Ro	JA	-NHCR9R10CH2OMe	Ri
HT	-NHCR9R10CONHCN	Rp	JB	-NHCR9R10CH2OMe	Rj
HU	-NHCR9R10CONHCN	Rq	JC	-NHCR9R10CH2OMe	Rk
HV	-NHCR9R10CONHCN	Rr	JD	-NHCR9R10CH2OMe	Rl
HW	-NHCR9R10CONHCN	Rs	JE	-MHCR9R10CH2OMe	Rm
HX	-NHCR9R10CONHCN	Rt	JF	-NHCR9R10CH2OMe	Rn
HY	-NHCR9R10CONHSO2Me	Ra	JG	-NHCR9R10CH2OMe	Ro
HZ	-NHCR9R10CONHSO2Me	Rb	JH	-NHGR9R10CH2OMe	Rp
IA	-NHCR9R10CONHSO2Me	Rc	JI	-NHCR9R10CH2OMe	Rq
IB	-NHCR9R10CONHSO2Me	Rd	JJ	-NHCR9R10CH2OMe	Rr
IC	-NHCR9R10CONHSO2Me	Re	JK	-NHCR9R10CH2OMe	Rs
ID	-NHCR9R10CONHSO2Me	Rf	JL	-NHCR9R10CH2OMe	Rt
IE	-NHCR9R10CONHSO2Me	Rg	JM		Ra
IF	-NHCR9R10CONHSO2Me	Rh	JN		Rb
IG	-NHCR9R10CONHSO2Me	Ri	JO		Rc
IH	-NHCR9R10CONHSO2Me	Rj	JP		Rd

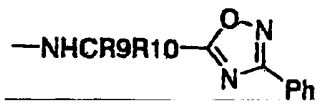
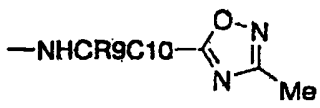
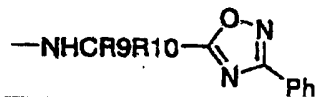
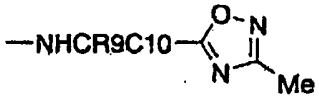
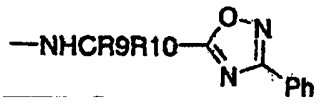
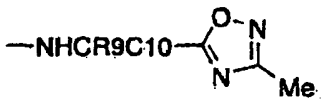
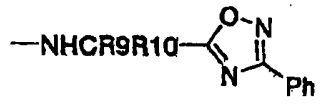
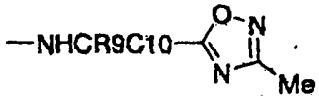
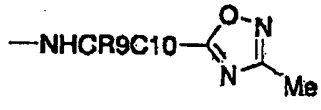
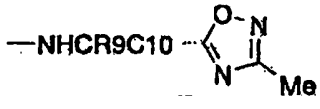
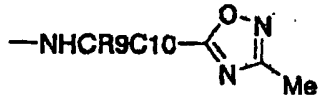
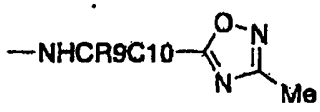
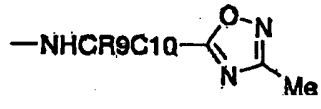
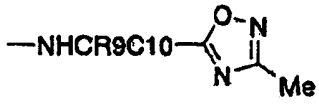
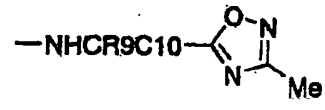
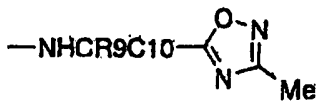
(continued)

	NR1R2	CR9R10		NR1R2	CR9R10
II	-NHCR9R10CONHSO2Me	Rk	JQ		Re
IJ	-NHCR9R10CONHSO2Me	RI	JR		Rf
IK	-NHCR9R10CONHSO2Me	Rm	JS		Rg
IL	-NHCR9R10CONHSO2Me	Rn	JT		Rh

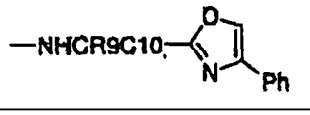
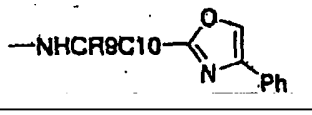
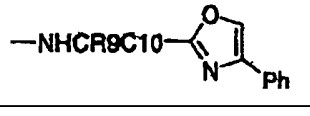
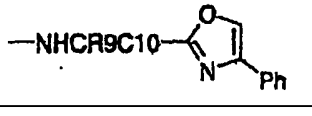
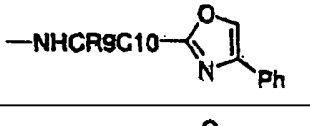
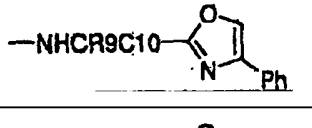
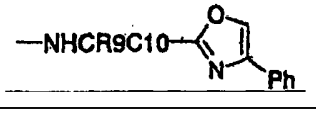
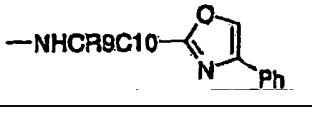
[Table 4]

	NR1R2	CR9R10		NR1R2	CR9R10
JU		Rj	KK		Re
JV		Rj	KL		Rf
JW		Rk	KM		Rg
JX		RI	KN		Rh
JY		Rm	KO		Ri
JZ		Rn	KP		Ri
KA		Ro	KQ		Rk
KB		Rp	KR		RI

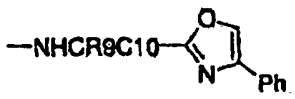
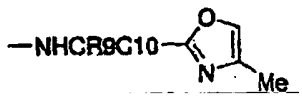
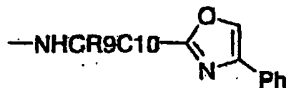
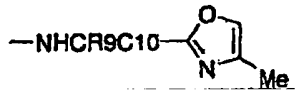
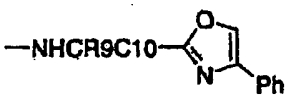
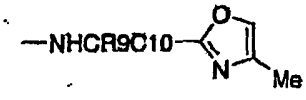
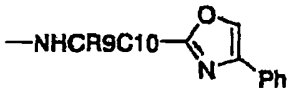
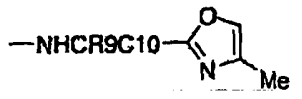
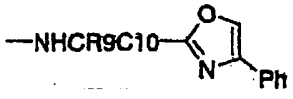
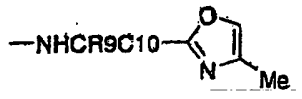
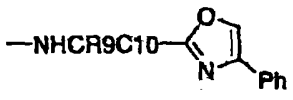
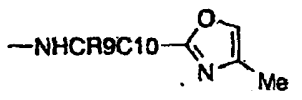
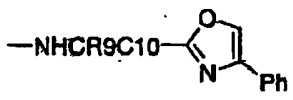
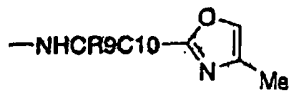
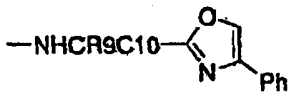
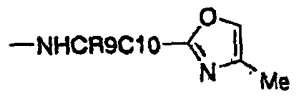
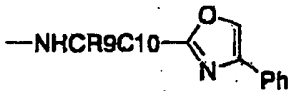
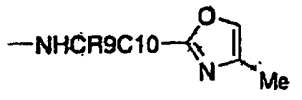
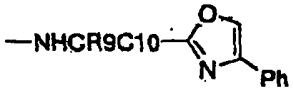
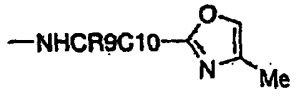
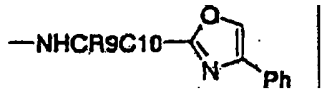
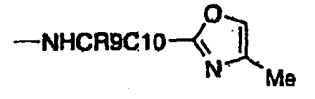
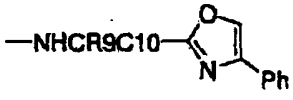
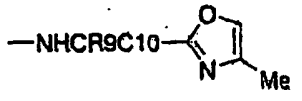
(continued)

	NR1R2	CR9R10		NR1R2	CR9R10
KC		Rq	KS		Rm
KD		Rr	KT		Rn
KE		Rs	KU		Ro
KF		Rt	KV		Rp
KG		Ra	KW		Rq
KH		Rb	KX		Rr
KI		Rc	KY		Rs
KJ		Rd	KZ		Rt

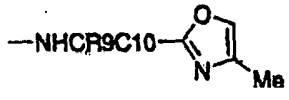
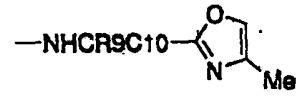
[Table 5]

	NR1R2	CR9R10		NR1R2	CR9R10
LA		Ra	LQ		Rq
LB		Rb	LR		Rr
LC		Rc	LS		Rs
LD		Rd	LT		Rt

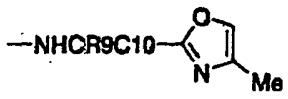
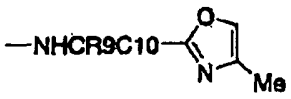
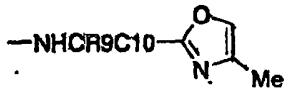
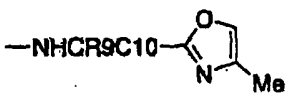
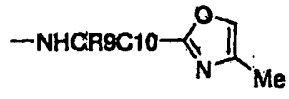
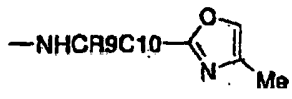
(continued)

	NR1R2	CR9R10		NR1R2	CR9R10
LE		Re	LU		Ra
LF		Rf	LV		Rb
LG		Rg	LW		Rc
LH		Rh	LX		Rd
LI		Ri	LY		Re
LJ		Rj	LZ		Rf
LK		Rk	MA		Rg
LL		Rl	MB		Rh
LM		Rm	MC		Ri
LN		Rn	MD		Rj
LO		Ro	ME		Rk
LP		Rp	MF		Rl

[Table 6]

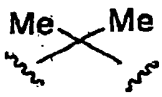
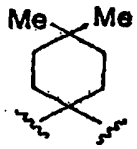
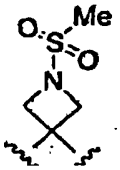
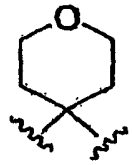
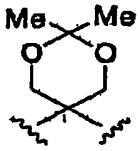
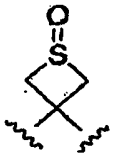
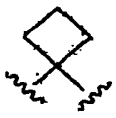
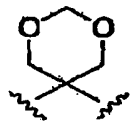
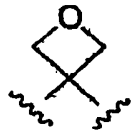
	NR1R2	CR9R10		NR1R2	CR9R10
MG		Rm	MK		Rq

(continued)

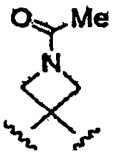
	NR1R2	CR9R10		NR1R2	CR9R10
MH		Rn	ML		Rr
MI		Ro	MM		Rs
MJ		Rp	MN		Rt

In the above Tables, CR^9CR^{10} is represented by the following symbol.

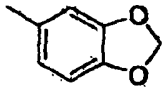
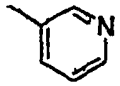
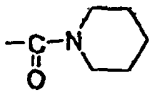
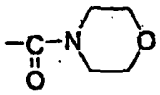
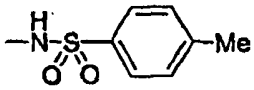
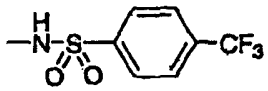
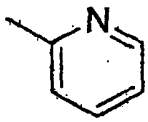
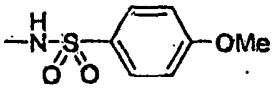
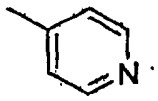
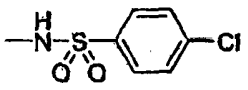
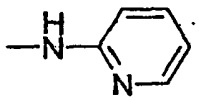
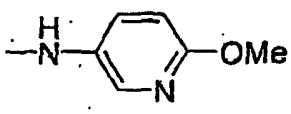
[Table 7]

	CR9R10		CR9R10		CR9R10
Ra		Rg		Rn	
Rb		Rh		RQ	
Rc		Ri		Rp	
Rd		Rj		Rq	
Re		Rk		Rr	
Rf		Rl		Rs	

(continued)

	CR9R10			CR9R10			CR9R10
			Rm			Rt	

[Table 8]

	R3			R3			R3
VA	H		VJ	Ph		VT	NHCOPh
VB	Me		VK			VU	CONHMe
VC	OH		VL			VV	CONMe2
VD	OMe		VM			VW	NHMe
VE	CONH2		VN			VX	NHiPr
VF	CONHIPr		vo			VY	NHPh
VG	NH2		VP			VZ	
VH	NHAc		VQ			WA	
VI	NHSO2Me		VR			WB	
			VS	NHSO2Ph		WC	

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[0081] As used herein, the "emesis, vomiting and/or constipation" includes nausea, emesis, vomiting and/or constipation which are induced by ingestion of a compound having the opioid receptor (particularly, opioid receptor) agonistic activity. Specifically, examples of the "compound having the opioid receptor agonistic activity" include morphine, oxycodone, fentanyl, methadone, codeine, dihydrocodeine, hydromorphone, levorphanol, meperidine, propoxyphene, dextropropoxyphen, tramadol, and a pharmaceutically acceptable salt, or a solvate thereof. Particularly, when the compound is morphine, oxycodone, or a pharmaceutically acceptable salt, or a solvate thereof, the present compound is particularly effective.

[0082] Influence of the present compound on emesis or vomiting can be confirmed, for example, by the following test.

[0083] At thirty minutes after ingestion of a diet, each test substance is administered to a ferret. The test compound is dissolved in 5% xylitol, and is administered at 5 mg/kg. At thirty minutes after administration of the test compound, 0.6 mg/kg of morphine was subcutaneously administered, and the vomiting symptom is observed visually until 30 minutes after administration of morphine.

[0084] For each of emesis (rhythmic construction movement at an abdominal part) and vomiting (vomiting conduct of excreting a vomiting substance or a similar conduct), an appearance time, a latent time (time from morphine administration to initial appearance of vomiting symptom) and a sustaining time (time from initial vomiting to final vomiting) are colleted.

[0085] In addition, influence of the present compound on constipation can be confirmed, for example, by the following test.

1) Preparation of test diet (dye)

[0086] Using a 0.5 w/v% Evans Blue aqueous solution, a 2.5 w/v% carboxymethylcellulose salt solution is prepared, and this is used as a test diet.

2) Animal

[0087] For example, a Wistar male rat (6 to 7 week old) may be used. The animal is fasted from about 20 or more hours before test initiation, and water is given ad lib.

3) Test compound and medium

[0088] The test compound is dissolved in a solvent (DMAA/Solutol/5% meglumine= 15/15/70).
DMAA: N,N-dimethylacetamide
Solutol (registered trademark) HS15
Meglumine: D (-)-N-methylglucamine

[0089] Morphine hydrochloride is dissolved in a physiological saline.

[0090] The test compound, the solvent and morphine are all administered at a liquid amount of 2 mL/kg.

4) Method

[0091] The test compound 0.03, 0.1, 0.3, 1 or 3 mg/kg (test compound administration group) or the solvent (solvent administration group) is subcutaneously administered, and amount of 3 mg/kg of morphine is subcutaneously adminis-

tered to all groups after 75 minutes. As a control group, the solvent is subcutaneously administered, and a physiological saline is administered after 75 minutes.

[0092] The test diet 2 mL/rat is orally administered at 30 minutes after administration of morphine. At fifteen minutes after the test diet (at 120 minutes after administration of the test substance), the rats are isolated from esophagus to an ileocecal part near a stomach cardia part. A distance from pyloric part of the stomach to an ileocecal part (full length of small intestine) and a distance until a dye reaching front part (dye movement distance) are measured.

5) Data processing

[0093]

$$\text{Transport rate (\%)} = (\text{dye movement distance (cm)}) / \text{full length of small intestine (cm)}) \times 100$$

$$\text{M.P.E. (\%)} = \{(\text{small intestine transport rate (\%) of each individual of test compound administration group} - \text{average small intestine transport rate (\%) of solvent administration group}) / (\text{average small intestine transport rate (\%) of control group} - \text{average small intestine transport rate (\%) of solvent administration group})\} \times 100$$

[0094] An ED_{50} value is calculated by reverse estimation of regression a SAS program using %MPE and letting a value of a control group to be 100%.

[0095] The present compound has the opioid receptor (particularly, opioid 8 and μ receptors) antagonistic activity. Therefore, the present compound is effective in treating and/or preventing digestive tract passage disorder which occurs by a cause such as acute dyspepsia, acute alcoholism, food poisoning, cold, stomach ulcer, duodenum ulcer, stomach cancer, ileus, appendicitis, peritonitis, cholelithiasis, hepatitis, liver inflammation, encephalitis, meningitis, increased brain pressure, head trauma, motion sickness, vomiting of pregnancy, side effect due to chemotherapy, side effect due to radiation therapy, side effect due to anti-cancer agent, pressure - stenosis of digestive tract, and intestinal tract coalescence after operation, treating and/or preventing emesis and vomiting which occurs by a cause such as increase in brain pressure due to brain tumor - brain bleeding - meningitis - irradiation of brain with radiation, and treating and/or preventing acute constipation derived from a cause such as ileus, duodenum ulcer or appendicitis, relaxing constipation derived from a cause such as nervous disorder, low nutrient, general prostration, vitamin deficiency, anemia, sensitivity reduction or mechanical stimulation insufficiency, or convulsive constipation derived from a cause such as stress, in addition to emesis · vomiting · constipation induced'by a compound having the opioid receptor agonistic activity.

[0096] Since the present compound has low brain transition, it exhibits the high alleviating effect on a side effect such as emesis, vomiting, constipation and the like induced by an opioid receptor agonistic activity almost without inhibiting the analgesic activity of a compound having the opioid receptor agronistic activity which is administered to the patient with a decease accompanying pain (e.g. cancerous.pain (pain due to bone transition, nervous pressure, increased intracranial pressure, soft tissue infiltration, pain due to constipation or spasm of muscle, pain of internal organ, muscle, fascia, waist or shoulder joint periphery, chronic pain after operation), AIDS etc.). In addition, the present compound has pure antagonistic activity on an opioid receptor, and also has an advantage in safety point that the hERG channel inhibitory activity is low, there is no cardiac toxicity, and so on. Further, the present compound also has an advantageous characteristic in dynamics in a body such as high oral absorbability, high stability in human plasma, high bioavailability and the like, and is very effective as a medicament.

[0097] When the present compound is administered against emesis, vomiting, or constipation induced by a compound having the opioid receptor agonistic activity, the administration may be any of before, after or at the same time with administration of the compound having the opioid receptor agonistic activity. An administration interval between these two kinds of drugs is not particularly limited. For example, when the present compound is administered after administration of the compound having the opioid receptor agonistic activity, if the administration is immediately after to in about 3 days,

preferably immediately after to in about 1 day from administration of the compound having the opioid receptor agonistic activity, the present compound works more effectively. In addition, when the present invention is administered before administration of the compound having the opioid receptor agonistic activity, if the administration is immediately before to before about 1 day, preferably immediately before to before about 12 hours from administration of the compound having the opioid receptor agonistic activity, the present compound works more effectively.

[0098] When the present compound is administered as an agent for treating and/or preventing emesis, vomiting and/or constipation, it may be used jointly with other agent for treating and/or preventing emesis, vomiting and/or constipation. For example, it is possible to administer the agent jointly with ondansetrone hydrochloride, adrenal cortical steroid (methylprednisolone, prednisolone, dexamethasone etc.), prochlorperazine; haloperidol, thymiperone, perphenazine, metoclopramide, domperidone, scopolamine, chlorpromazine hydrochloride, droperidol, stimulating laxative (sennoside, picosulfate sodium etc.), osmotic laxative (lactulose etc.), or salt laxative (magnesium oxide etc.).

[0099] Alternatively, a combination agent between the present compound and a compound having the opioid receptor agonistic activity, or a combination agent between the present compound and other agent for treating and/or preventing emesis, vomiting and/or constipation can be administered.

[0100] When the present compound is administered to a human, it can be administered orally as powders, granules, tablets, capsules, pills, solutions, or the like, or parenterally as injectables, suppositories, transdermal absorbable agents, absorbable agents, or the like. Oral agents are preferable.

[0101] In addition, the present compound can be formulated into pharmaceutical preparations by adding pharmaceutical additives such as excipients, binders, wetting agents, disintegrating agents, lubricants and the like, which are suitable for formulations and, an effective amount of the present compound.

[0102] The present compound may be formulated into medical mixtures in which a compound having the opioid receptor agonistic activity and/or other agent for treating and/or preventing emesis, vomiting and/or constipation and, if necessary, various pharmaceutical additives.

[0103] A dose is different depending on state of a disease, an administration route, and an age and a weight of a patient, and is usually 0.1 μg to 1 g/day, preferably 0.01 to 200 mg/day when orally administered to an adult, and is usually 0.1 μg to 10 g/day, preferably 0.1 to 2 g/day when parenterally administered.

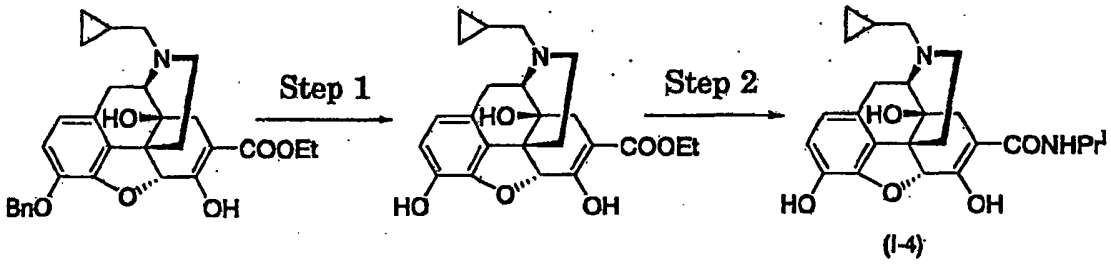
[0104] Following Examples and Test Examples illustrate the present invention in more detail, but the present invention is not limited by these Examples.

[Example 1]

Production of Compound (I-4)

[0105]

[Chemical formula 11]



wherein Bn indicates benzyl, Et indicates ethyl, and Pr^i indicates isopropyl.

(First step) 7-Ethoxycarbonylnaltrexone

[0106] To a suspension of 3-b-benzyl-7-ethoxycaxbonylnaltrexone described in Non-Patent Literature 2 (11.16 g, 22.15 mmol) in ethyl acetate (50 mL) and methanol (50 mL) was added palladium hydroxide (Perlman's catalyst) (1.2 g), and the mixture was vigorously stirred for 2 hours under a hydrogen atmosphere. After filtration of the catalyst, the filtrate was concentrated, and the residue was crystallized from ethyl acetate and hexane to obtain 8.96 g (92%) of the title compound as colorless crystals.

NMR (300MHz, $CDCl_3$)

δ 0.14-0.17 (m, 2H), 0.55-0.58 (m, 2H), 0.86 (m, 1H), 1.23-1.29 (m, 3H), 1.67 (d, 1H, J = 9.6 Hz), 2.02 (dd, 1H, J = 1.2,

16.2 Hz), 2.20-2.79 (m, 8H), 3.08 (d, 1H, J = 18.6 Hz), 3.24 (br, 1H), 4.12-4.20 (m, 2H), 4.96 (s, 1H), 5.17 (br, 1H), 6.59 (d, 1H, J = 8.1 Hz), 6.72 (d, 1H, J = 8.1Hz), 12.12 (s, 1H).
Elemental analysis ($C_{23}H_{27}NO_6 \cdot 0.2H_2O$)
(Calculated value) C, 66.24; H, 6.62; N, 3.36.
(Found value) C, 66.29;H, 6.50; N, 3.45.

(Second step) 7-Isopropylaminocarbonylnaltrexone

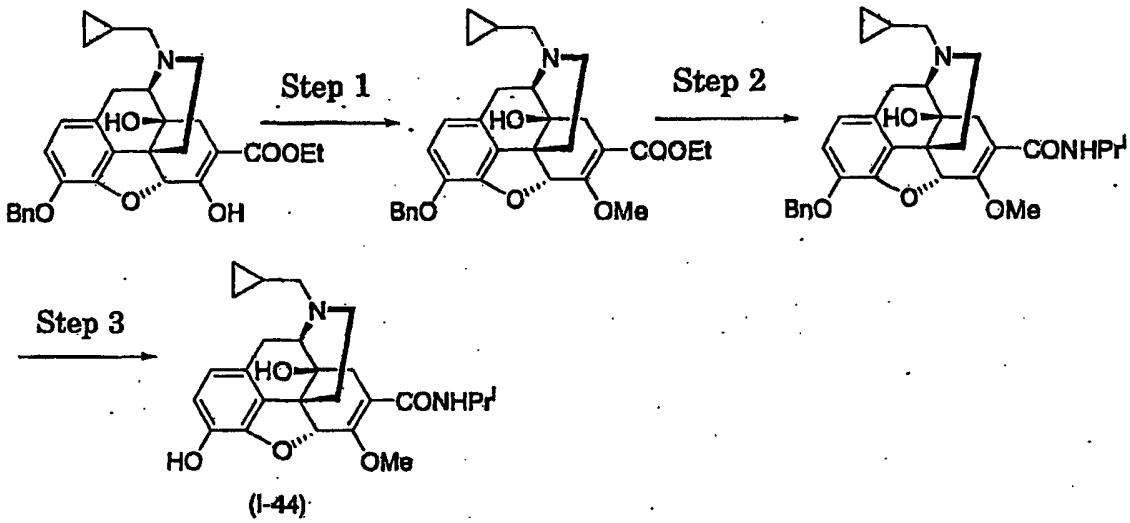
[0107] A solution of 7-ethoxycarbonylnaltrexone obtained in the first step (200 mg, 0.484 mmol), isopropylamine (0.412 mL, 4.84 mmol) and triethylamine (0.202 mL, 1.45 mmol) in 2-methoxyethanol (1.5 ml) was stirred at 180°C for 45 minutes under microwave irradiation. After cooled to room temperature, 7 mL of 5mol/L hydrochloric acid was added to the reaction mixture, and stirring was continued at 70°C for 20 minutes. After the reaction solution was cooled, pH value was adjusted to 8.5 with aqueous ammonia, followed by extraction with ethyl acetate. The organic layer was washed with water, and dried, and the solvent was evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol= 99:1 to 94:6) to obtain 140 mg of the title compound at a yield of 68%.
NMR (300MHz, d6-DMSO)
δ 0.12-0.15 (m, 2H), 0.44-0.53 (m, 2H), 0.83 (m, 1H), 1.02 (d, 3H, J = 6.6Hz), 1.08 (d, 3H, J = 6.6 Hz), 1.41 (d, 1H, J =11.4 Hz), 1.85 (d, 1H, J = 15.6 Hz), 2.04-2.62 (m, 8H), 3.04 (d, 1H, J = 18.6 Hz), 3.24 (m, 1H), 3.96 (m, 1H), 4.71 (s, 1H), 4.74 (s, 1H), 6.51 (d, 1H, J = 8.4 Hz), 6.56 (d, 1H, J = 8.4Hz), 7.40 (br d, 1H, J = 7.2 Hz), 9.16 (s, 1H), 14.50 (s, 1H).
Elemental analysis ($C_{24}H_{30}N_2O_5 \cdot 0.2H_2O$)
(Calculated value) C, 67.02; H, 7.12; N, 6.51.
(Found value) C, 67.02;H, 7.20; N, 6.49.

[Example 2]

Preparation of Compound (I-44)

[0108]

[Chemical formula 12]



(I-44)

wherein Bn indicates benzyl, Me indicates methyl, Et indicates ethyl, and Pr^i indicates isopropyl.

(First step) 3-O-Benzyl-7-ethoxycarbonyl-6-O-methylnaltrexone

[0109] To a solution of 3-O-benzyl-7-ethoxycarbonylnaltrexone described in Non-Patent Literature 2 (504 mg, 1 mmol) in tetrahydrofuran (10 mL) were successively added 1,1'-azodicarbonylpiperidine (379 mg, 1.5 mmol), tri-n-butylphosphine (370 μL, 1.5 mmol) and methanol (41 μl, 1 mmol), and the mixture was stirred at room temperature for 7 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography (hexane/ethyl acetate) to obtain the title compound (421 mg, 81%) as colorless oiL
^{1}H NMR ($CDCl_3$, δ ppm): 0.10-0.20 (m, 2H), 0.50-0.65 (m, 2H) 0.88 (m, 1H), 1.26 (t, J = 6.6 Hz, 3H), 1.67 (d, J = 11.4 Hz, 1H), 2.15-2.80 (m, 8H), 3.00-3.30 (m, 2H), 3.93 (s, 3H), 4.05-4.20 (m, 2H), 4.86 (br s, 1H), 5.15 (s, 2H), 5.18 (br s, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 7.28-7.45 (m, 5H)

(Second step) 3-O-Benzyl-7-isopropylaminocarbonyl-6-O-methylnaltrexone

[0110] To a mixed solution of 3-O-benzyl-7-ethoxycarbonyl-6-O-methylnaltrexone obtained in the first step (145 mg, 0.28 mmol) in methanol (6 mL) and dioxane (2 mL) was added a 50% potassium hydroxide aqueous solution (2 mL), and the mixture was stirred at 50°C for 30 minutes. The reaction solution was cooled to room temperature, and adjusted to pH=4 with 0.5M an aqueous citric acid solution, followed by extraction with ethyl acetate. The organic layer was successively washed with water, brinebrine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crystalline residue, 3-O-benzyl-7-carboxy-6-O-methylnaltrezone was used in the next reaction without purification, To a solution of the above residue in dimethylformamide (3 mL) were successively added 1-ehtyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (40 mg, 0.2 mmol), 1-hydrozybenzotriazole (27 mg, 0.2 mmol) and isopropylamine (16 μL, 0.182 mmol), and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water and this was extracted with ethyl acetate, and the organic layer was washed with water, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform / methanol = 9/1) to obtain the title compound (39 mg, 44%) as a colorless foam.
^{1}H NMR ($CDCl_3$, δ ppm): 0.10-0.20 (m, 2H), 0.50-6.65 (m, 2H), 0.88 (m, 1H), 1.13 (d, J = 2.1 Hz, 3H), 1.15 (d, J = 1.8 Hz, 3H), 1.58 (d, J =11.4 Hz, 1H), 2.08-2.80 (m, 8H), 2.99-3.30 (m, 2H), 3.94 (s, 3H), 4.06 (m, 1H), 4.83 (br s, 1H), 5.14 (d, J = 2.4 Hz, 2H), 5.23 (br s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.28-7.45 (m, 6H)

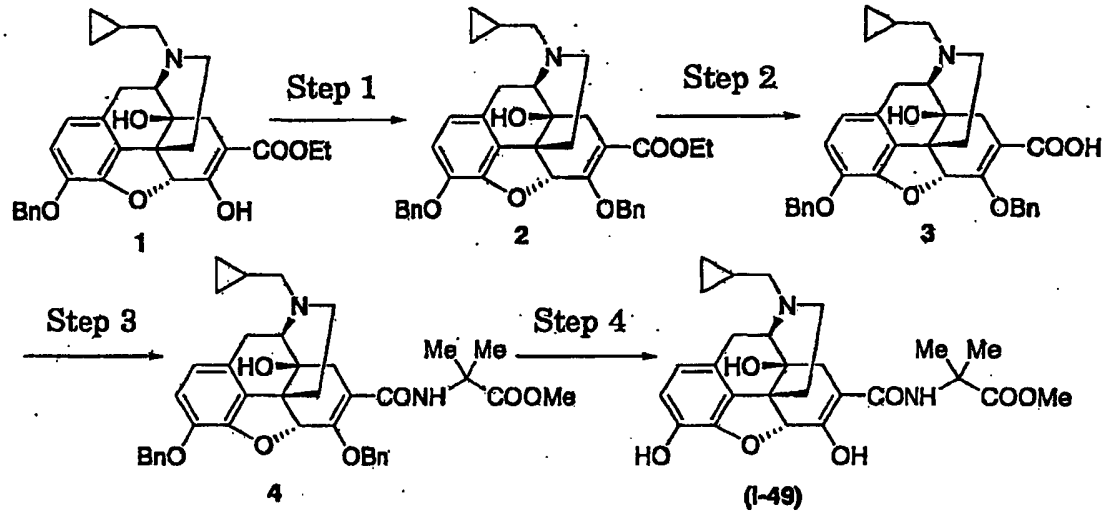
(Third step) 7-Isopropylaminocarbonyl-6-O-methylnaltrexone

[0111] To a solution of 3-O-benzyl-7-isopropylaminocarbonyl-6-O-methylnaltrexone obtained in the second step (33 mg, 0.073 mmol) in tetrahydrofuran (5 mL) was added palladium hydroxide (33 mg), and the mixture was stirred for 1 hour under a hydrogen atmosphere. The reaction solution was filtered with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform / methanol = 9/1) to obtain the title compound (13 mg, 41%) as a colorless foam.
^{1}H NMR ($CDCl_3$, δ ppm): 0.10-0.15 (m, 2H), 0.50-0.70 (m, 2H), 0.85 (m, 1H), 1.12 (d, J = 0.9 Hz, 3H), 1.14 (d, J = 0.9 Hz, 3H), 1.66 (d, J = 11.4 Hz, 1H), 2.06-2.80 (m, 8H), 3.00-3.30 (m, 2H), 3.92 (s, 3H), 4.05 (m, 1H), 4.80 (br s, 1H), 5.26 (br s, 1H), 6.56 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H)

[Example 3]

[0112]

[Chemical formula 13]



wherein Bn indicates benzyl, Me indicates methyl, and Et indicates ethyl.

(First step)

[0113] A solution of compound (1) (28.7 g, 57.0 mmol) in tetrahydrofuxan (250 ml) was cooled to -10°C and to the solution were 1,1'-azodicarbonylpiperidine (21.6 g, 85.5 mol), tri-n-butylphosphine (21.4 mL, 85.5 mmol) and benzyl alcohol (6.50 mL, 62.7 mmol) successively added, and the mixture was stirred at room temperature for 6 hours and 45 minutes. The reaction solution was filtered and the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform → chloroform/methanol= 50/1) to obtain quantitatively the objective compound (2) (33.8 g) as a pale yellow oil.
^{1}H NMR ($CDCl_3$, δ ppm): 0.10-0.20 (m, 2H), 0.50-0.65 (m, 2H), 0.88 (m, 1H), 0.94 (t, J = 7.2 Hz, 3H), 1.20-3.60 (m, 11H), 4.14 (q, J = 7.2 Hz, 2H), 5.10-5.35 (m, 5H), 6.58 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 7.15-7.50 (m, 10H)

(Second step)

[0114] To a mixed solution of compound (2) obtained in the first step (33.8 g, 57.0 mmol) in methanol (130 mL) and dioxane (43 mL) was added a 4N-potassium hydroxide aqueous solution (43 mL), and the mixture was stirred at 50°C for 14 hours and 35 minutes. The reaction solution was cooled to room temperature, and concentrated under reduced pressure, and the residue was adjusted to pH = 3 to 4 with ice-water and 2N-hydrochloric acid, followed by extraction with a mixed solution of ethyl acetate and tetrahydrofuran. The organic layer was successively washed with water, and brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was converted into a powder with ether to obtain the objective compound (3) (24.8 g, 77%) as a colorless powder.
^{1}H NMR (DMSO-d_6, δ ppm): 0.20-0.40 (m, 2H), 0.50.0.65 (m, 2H), 0.95 (m, 1H), 1.30-3.60 (m, 11H), 5.00-5.25 (m, 5H), 5.39 (s, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.27-7.52 (m, 10H)

(Third step)

[0115] To a solution of compound (3) obtained in the second step (350 mg, 0.619 mmol) in tetrahydrofuran (4 mL) were successively added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (142 mg, 0.743 mmol), 1-hydroxybenzotriazole (100 mg, 0.743 mmoL), dimethylglycine methyl ester hydrochloride (114 mg, 0.743 mmol) and N-methylmorpholine (82 μL, 0.743 mmol), and the mixture was stirred at room temperature overnight. The reaction solution was poured into ice-water snd a saturated sodium bicarbonate aqueous solution, followed by extracted with ethyl acetate, and the organic layer was washed with brine, dried with anhydrous sodium sulfate, and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (chloroform / methanol = 50/1) to obtain the objective compound (4) (300 mg, 73%) as a pale yellow foam.
^{1}H NMR ($CDCl_3$, δ ppm): 0.08-0.20 (m, 2H), 0.50-0.60 (m, 2H), 0.87 (m, 1H), 1.13 (s, 3H), 1.22 (s, 3H), 1.55-2.80 (m, 11H), 3.62 (s, 3H), 4.85 (br s, 1H), 5.13-5.40 (m, 5H), 6.58 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 7.26-7.48 (m, 10H), 7.94 (s, 1H)

(Fourth step)

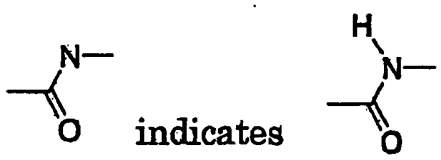
[0116] To a solution of compound (4) obtained in the third step (290 mg, 0.436 mmol) in methanol (4 mL) was added palladium hydroxide (60 mg), followed by stirring for 3 hours under a hydrogen atmosphere. The reaction solution was filtered with Celite, and the filtrate was concentrated under reduced pressure. The residue was crystallized with hexane / ethyl acetate to obtain the objective compound (I-49) (181 mg, 86%) as colorless crystals.
^{1}H NMR (DMSO-d_6, ppm): 0.10-0.20 (m, 2H), 0.40-0.57 (m, 2H), 0.84 (m, 1H), 1.33 (s, 3H), 1.37 (s, 3H), 1.40-3.40 (m, 11H), 3.55 (s, 3H), 4.72 (s, 1H), 4.77 (br s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 7.68 (br s, 1H), 9.18 (br s, 1H), 13.78 (br s, 1H)

[0117] According to the same procedure, other compounds (I) can be synthesized. Structural formulas and physical constants are shown below.

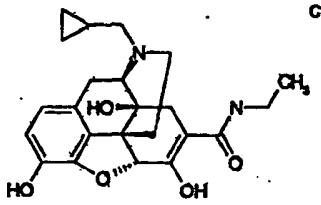
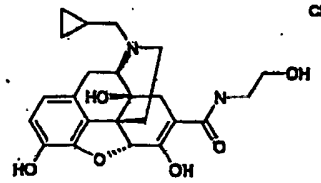
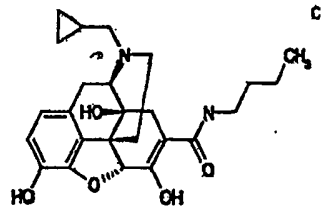
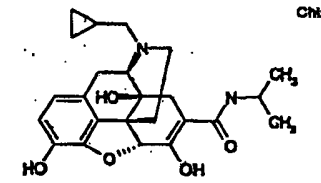
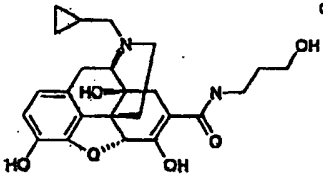
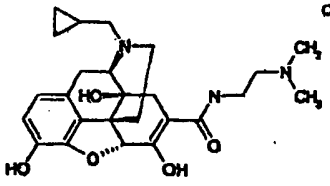
[0118] In Tables, Me indicates methyl, Et indicates ethyl, Pr^i indicates isopropyl, and Ph indicates phenyl.

[0119] In addition, in Tables,

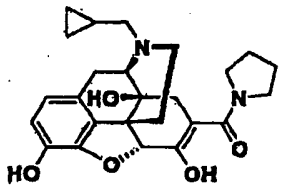
[Chemical formula 14]



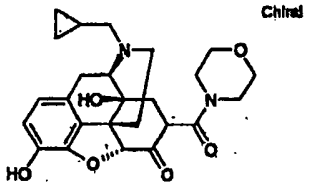
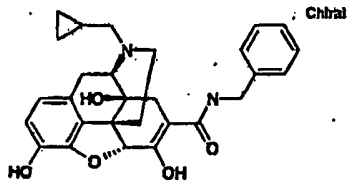
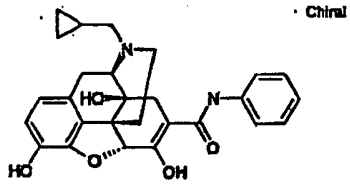
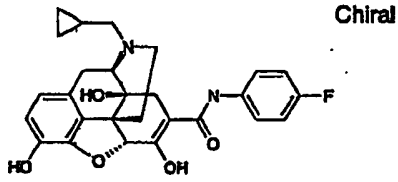
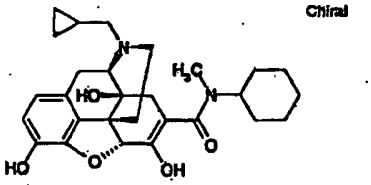
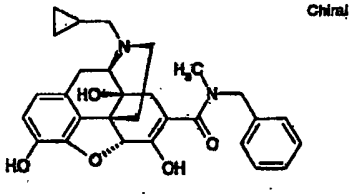
[Table 9]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-1		0.10-025 (m, 2H), 050-0.60 (m 2H), 1.87 (m, 1H). 1.13 (t J = 7.2 Hz, 3H), 1.66 (d, J = 11.4 Hz, 1H). 2.20-2.80 (m, 7H), 3.00-3.35 (m, 5H), 4.84 (s, 1H), 5.40 (m, 1H), 6.57 (d J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 14.20 8br s, 1H)
I-2		0.1.0-0.20 (m, 2H), 0,40-0.60 (m, 2H), 0.85 (m, 1H), 1.41 (d, J = 11.4 Hz, 1H), 1.90-3.40 (m, 14H), 4.71 (s, 1H), 4.73 (br s, 1H), 6.50 (d, J = 8.1 Hz, 1H), 8.35 (d, J = $_8$.1 Hz, 1H), 7.77 (br s, 1H)
I-3		(CDCl3) 0.10-0.25 (m, 2H), 0.50-0.62 (m, 2H), 0.81-0.98 (m, 4H), 1.24-1.74 (m, 9H), 2.21-2.77 (m, 7H). 3.05-3.30 (m, 5H), 4.93 (s, 1H), 5.40 (br t, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 8.7Hz, 1H), 14.21 (s, 1H).
I-4		0.12-0.15 (m, 2H), 0.44-0.53 (m, 2H), 0.83 (m, 1H), 1.02 (d, 3H, J = 6.6Hz), 1.08 (d, 3H, J = 6.6 Hz), 1.41 (d, 1H, J = 11.4 Hz), 1.85 (d, 1H, J = 15.6 Hz), 2.04-2.62 (m, 8H), 3.04 (d, 1H, J = 18.6 Hz), 3.24 (m, 1H), 3.96 (m, 1H), 4.71 (s, 1H), 4.74 (s, 1H), 6.51 (d, 1H, J = 8.4 Hz), 6.56 (d, 1H, J = 6.4Hz), 7.40 (br d, 1H, J = 7.2 Hz), 9.10 (s, 1H), 14.50 (s, 1H)
I-6		0.10-0.25 (m, 2H), 0.50-0.62 (m, 2H), 0.85 (m, 1H), 1.40-1.60 (m, 4H), 1.83-3.20 (m, 11H), 4.41 (br s, 1H), 4.72 (s, 1H), 4.74 (s, 1H), 6.51 (d, J = 8.7 Hz), 6.56 (d, J = 8.7Hz, 1H), 7.70 (s, 1H), 8.15 (br s, 1H), 14.42 (s, 1H).
I-6		0.10-0.25 (m, 2H), 0.50-0.82 (m, 2H), 0.85 (m, 1H), 1.42 (d, J = 11.7 Hz, 1H), 1.83-2.64 (m, 10H), 2.10 (s, 6H), 3.00-3.18 (m, 3H), 4.72 (s, 1H), 4.74 (s, 1H), 8.51 (d, J = 6.7 Hz), 6.56 (d, J = 8.7Hz, 1H), 7.65 (s. 1H), 9.10 (br s, 1H).

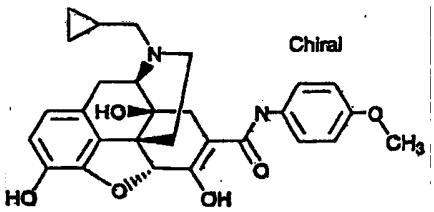
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-7		0.10-0.25 (m, 2H). 0.50-0.40 (m, 2H), 1.80 (m, 1H), 1.57 (dd. J = 2.4, 12.6 Hz. 2H), 1.85-2.80 (m, 10H), 3.00-9.25 (m, 3H), 3.35-3.60 (m, 3H), 4.20 (m, 1H), 4,78 (br s, 1H), 5.85 (br s, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H)

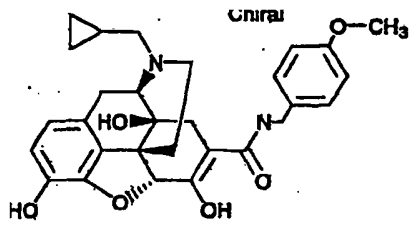
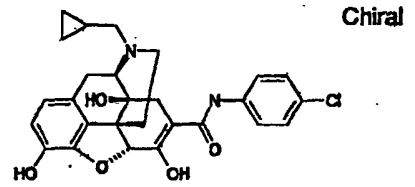
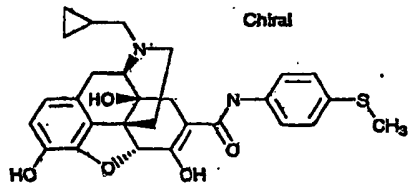
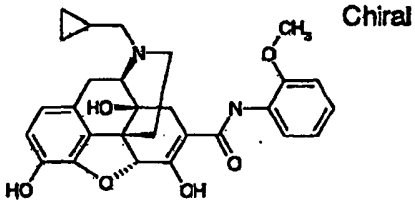
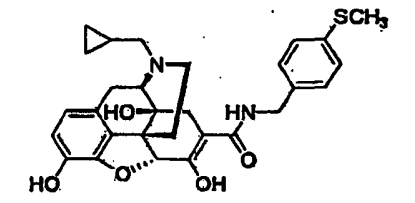
[Table 10]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-8		0.10-0.20 (m, 2H), 0.45-0.68 (m, 2H), 1.88 (m, 1H). 1.35 (,d J = 11.4 Hz, 1H), 1.65-2.20 (m, 4H), 2.30-3.60 (m, 13H). 4.29 (dd, J = 4.8, 12.6 Hz, 1H), 5.08 (s, 1H), 5.23 (br, s, 1H). 6.53 (d. J = 8.1 Hz, 1H) 8.1 (d, J = 8.1 Hz, 1H), 9.25 (br s, 1H)
I-9		(CDCl3) 0.10-0.25 (m, 2H), 0.50-0.62 (m, 2H), 0.85 (m, 1H), 1.62--2.77 (m, 6H), 3.07 (d, J = 1 8.6 Hz, 1H), 3.23 (d, J = 7.2 Hz, 1H), 4.42 (d, J = 5.4 Hz, 2H), 4.93 (s, 1H), 5.66 (br s, 1H), 8.55 (d, J = 8.7 Hz), 6.72 (d, J = 8.7Hz, 1H), 7.22-7.39 (m, 5H), 14.15 (s, 1H),
I-10		0.10-0.24 (m. 2H), 0.45-0.60 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 11.1 Hz, 1H), 1.70-3.40 (m, 10H), 4.78 (s, 1H), 4.82 (s, 1H), 6.54 (d, J 8.4 Hz, 1 H), 6.58 (d, J = 8.4 Hz, 1H), 7.05 (m, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 9.14 (s, 1H), 9.24 (br s, 1H).13.90 (br s, 1H)
I-11		0.10-022 (m, 2H), 0.44-0.58 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.75-3.40 (m, 10H), 4.79 (s, 1H), 4.83 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d,J = 8.1 Hz, 1H), 7.13 (t, J = 8.7 Hz, 2H), 7.48-7.58 (m, 2H), 9.17 (s, 1H), 9.27 (br s, 1H), 13.90 (br s, 1H)
I-12		0.10-0.18 (m, 2H), 0.52-0.60 (m, 2H), 0.80-0.98 (m, 2H), 0.98-3.21 (m, 26H), 4.41 (br, s, 1H), 4.70 (d, J = 12.3 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.65 (d, J 8.1 Hz. 1H)
I-13		0.10-0.25 (m, 2H), 0.50-0.60 (m, 2H), 0.87 (m, 1H), 1.58 (d, J = 111.7 Hz, 1H), 2.65-2.50 (m, 6H), 2.55-2.90 (m, 5H), 3.00-3.30 (m, 2H), 4.42 (s, 1H), 4.81-4.87 (m, 2H), 5.55 (br s, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 1H), 7.20-7.40 (m, 5H)

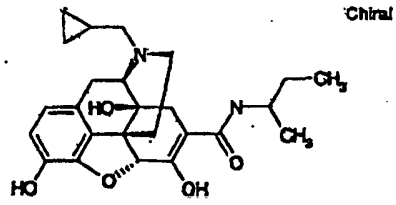
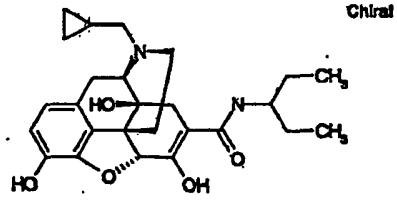
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-14		0.10-0.22 (m, 2H), 0.45-0.80 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 2.10-3.40 (m, 10H), 3.76 (s, 3H), 496 (s, 1H), 8.36 (br s, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 6.98 (br s, 1H), 7.29 (d, J = 9.0 Hz, 2H), 14.00 (br s, 1H)

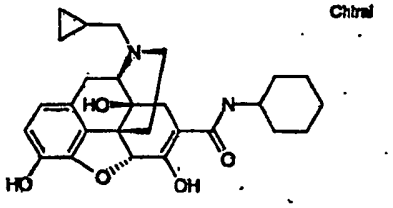
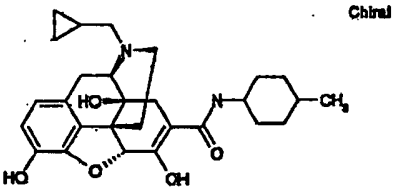
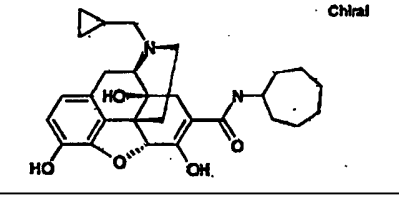
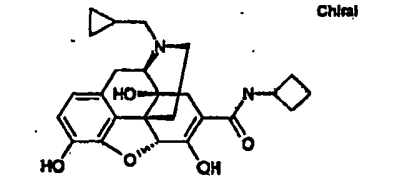
[Table 11]

Compound No.	Chemical structure	NMR (1H-NMR(d6-DMSO) δ)
I-15		0.05-020 (m, 2H), 0.46-0.60 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 2.00-3.35 (m, 10H), 3.78 (s, 3H), 4.34 (d, J = 5.1 Hz, 2H). 4.91 (s, 1H), 5.81 (br s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 8.85 (d, J = 8.4 Hz, 2H) 7.19 (d, J = 8.4 Hz, 2H), 14.13 (br s, 1H)
I-16		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.77 (s, 1H), 4.84 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.58 (d, J = 8.1 Hz, 1H), 7.36-7.38 (m, 2H), 7.53-7.80 (m, 2H), 9.17 (s, 1H), 9.38 (br s, 1H), 13.80 (br s, 1H)
I-17		0.10-025 (m, 2H), 0.44-0.80 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 13H), 4.77 (s, 1H), 4.82 (s, 1H), 8.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J 8.1 Hz, 1H), 7.20 (d, J = 6.7 Hz, 2H), 7.48 (d, J = 9.7 Hz, 2H), 9.17 (s, 1H), 9.27 (br s, 1H), 13.90 (br s, 1H)
I-18		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.69 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.65-3.40 (m, 10H), 3.80 (s, 3H), 4.81 (br s, 2H), 8.52 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 6.87 (m, 1H), 6.98-7.10 (m, 2H), 7.82 (m, 1H), 9.19 (s, 1H), 9,70 (br s, 1H), 12.90 (br s, 1H)
I-19		

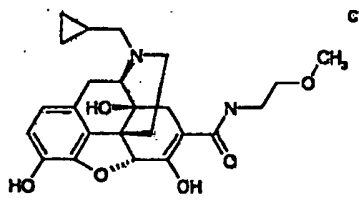
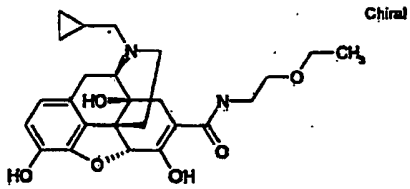
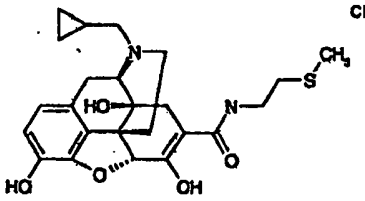
(continued)

Compound No.	Chemical structure	NMR (1H-NMR(d6-DMSO) δ)
I-20		0.12-0.14 (d, J = 4.5 Hz, 2H), 0.46-0.52 G J = 8.3 Hz, 2H), 0.71-0-85 (m, 4H), 0.98-1.06 (dd, J = 6.8, 17.3 Hz, 4H), 1.35-1.45 (m, 4H), 1.82-1.92 (m, 2H), 2.44-2.61 (m), 3.04 (d, J = 18.9 Hz, 1H). 3.19-3.24 (m, 1H), 3.71-3.82 (m, 1H), 4.71-4.76 (m, 2H), 6.50-8.57 (dd, J = 8.1, 14.4 Hz, 2H), 7.31-1.38 (m, 1H). 9.15 (br-a. 1H), 14.52 (br s, 1H)
I-21		0.12-0.14 (d, J = 4.2 Hz, 2H), 0.49 (t, J = 8.1 Hz, 2H), 0.69-0.88 (m, 6H), 132-141 (m, 5H), 1.88 (d, J = 15.3 Hz, 1H), 2.06-2.30 (m, 4H), 2.46-2.61 (m), 3.04 (d, J = 18.0 Hz, 1H), 3.19-3.24 (m, 1H), 4.71-4.75 (m, 2H), 6.05-6.58 (dd, J = 8.8, 14.4 Hz, 2H), 7.24 (d, J = 7.8 Hz, 1H), 9.15 (br s, 1H), 14.55 (br s, 1H)

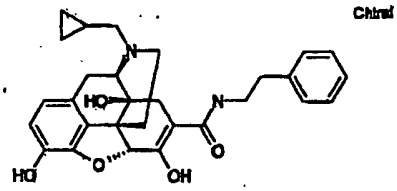
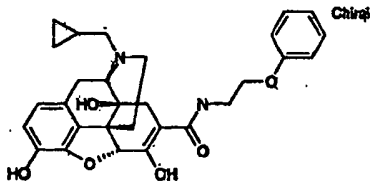
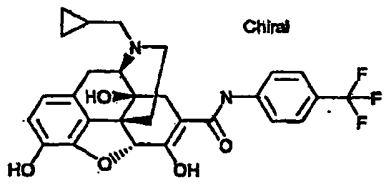
[Table 12]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-22		0.12-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 8.1 Hz, 2H), 0.85 (m, 1H), 1.08 (m, 1H), 1.16-1.28 (m, 4H), 1.39-1.43 (d, J = 11.4 Hz, 1H), 1.54-1.70 (m, 6H), 1.84-1.89 (d, J = 15.6 Hz, 1H), 2.08-2.60 (m, 6H), 3.00-3.07 (d, J = 18.6 Hz, 1H), 3.17-3.24 (m, 1H), 3.60 (br s, 1H), 4.71-4.76 (m 2H), 6.49-6.57 (dd, J = 8.1, 14.7 Hz, 2H), 7.37 (d, J = 9.0 Hz, 1H), 9.13 (br s, 1H), 14.47 (br s, 1H)
I-23		0.12-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 7.8 Hz, 2H), 0.83-0.92 (m, 4H), 1.19-1.70 (m, 9H), 1.83-1.93 (m, 1H), 2.06-2.61 (m, 9H), 3.01-3.07 (d, J = 18.3 Hz, 1H), 3.18-3.20 (d, J = 4.2 Hz, 1H), 3.67 (m, 1H), 4.71-4.76 (m, 2H), 6.52-6.55 (dd, J = 8.1, 14.4 Hz, 2H), 9.13 (br s, 1H), 14.48 (br s, 1H)
I-24		0.12-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 8.0 Hz, 2H), 0.83-0.87 (m, 1H), 1.34-1.55 (m, 12H), 1.84-1.89 (d, J = 15.6 Hz, 1H), 2.09-2.60 (m, 9H), 3.00-3.07 (d, J = 18.3 Hz, 1H), 3.17-3.19 (d, J = 6.0 Hz, 1H), 3.78-3.81 (m, 1H), 4.71-4.76 (m, 2H), 6-49-6.57 (dd, J = 8.1, 14.7 Hz, 2H), 7.39 (d, J = 6.1 Hz, 1H), 9.13 (br s, 1H), 14.46 (br s, 1H)
I-25		0.13-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 7.8 Hz, 2H), 0.85 (m, 1H), 1.39-1.43 (d, J = 11.1 Hz, 1H), 1.56-1.64 (m, 2H), 1.85-2.32 (m, 12H), 2.43-2.61 (m), 3.01-3.07 (d, J = 18.3 Hz, 1H), 3.18-3.20 (d, J = 6.0 Hz, 1H), 4.16-4.27 (m, 1H), 4.72-4.73 (m, 2H), 6.50 (dd, J = 8.1, 16.9 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 9.12 (br s, 1H), 14.41 (br s, 1H)

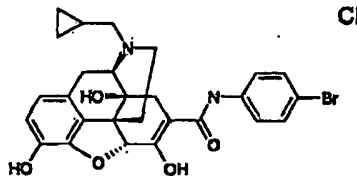
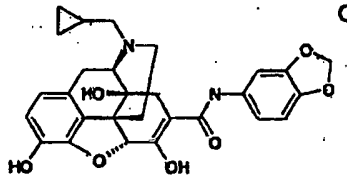
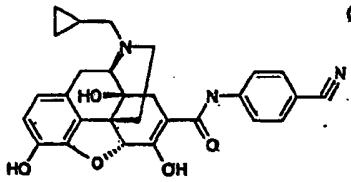
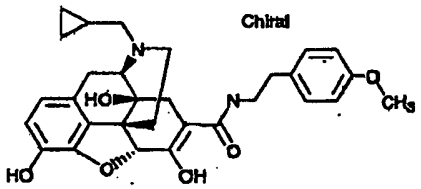
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-26		0.16-0.19 (m, 2H), 0.48-0.57 (m, 2H), 0.88 (m, 1H), 1.46 (d J = 11.2 Hz, 1H), 1.92 (d, J = 15.6 Hz, 1H), 2.04-2.66 (m, 6H), 3.08 (d, J = 18.8 Hz, 1H), 3.17-3.40 (m, 6H), 3.24 (s, 3H), 4.77 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 7.76 (br t, 1H), 9.15 (s, 1H), 14.33 (s, 1H),
I-27		0.16-0.19 (m, 2H), 0.48-0.57 (m, 2H), 0.90 (m, 1H), 1.10 (t. J = 6.8 Hz, 3H), 1.46 (d, J = 11.2 Hz, 1H), 1.92 (d, J = 15.6 Hz, 1H), 2.04-2.66 (m, 6H), 3.08 (d, J = 18.8 Hz, 1H), 3.17-3.46 (m, 8H), 4.77 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 7.77 (br, 1H), 9.15 (s, 1H), 14.32 (s, 1H).
I-28		0.16-0.17 (m, 2H), 0.50-0.63 (m, 2H), 0.89 (m, 1H), 1.46 (d, J = 12.0 Hz. 1H), 1.92 (d, J = 15.2 Hz, 1H), 2.06 (s, 3H), 2.06-2.70 (m, 6H), 3.08 (d, J = 18.4 Hz, 1H), 3.20-3.32 (m, 6H), 4.77 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H). 6.62 (d, J = 8.0 Hz, 1H), 7.76 (br s, 1H), 9.16 (s, 1H), 14.31 (s, 1H).

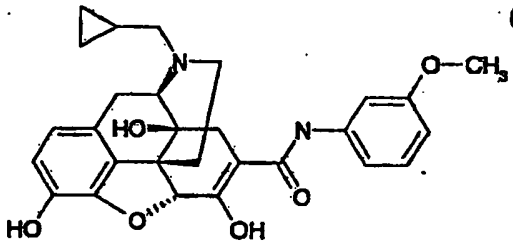
[Table 13]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-29		0.17-0.18 (m. 2H), 0.51-0.57 (m, 2H), 0.90 (m, 1H), 1.46 (d, J = 11.6 Hz, 1H), 1.93 (d, J = 16.0 Hz, 1H), 2.11-2.78 (m, 6H), 3.08 (d, J = 16.4 Hz, 1H), 3.21 (d, J = 6.0 Hz, 1H), 3.27-3.32 (m, 5H), 4.77 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 7.19-7.32 (m, 5H), 7.86 (br s, 1H), 9.16 (s, 1H), 14.38 (s, 1H).
I-30		0.16-0.19 (m, 2H). 0.48-0.57 (m. 2H), 0.88 (m, 1H), 1.46 (d, J = 11.2 Hz, 1H), 1.94 (d, J = 15.6 Hz, 1H), 2.11-2.71 (m, 6H), 3.08 (d, J = 18.8 Hz, 1H), 3.49-3.51 (m, 2H), 3.96-4.4.05 (m, 2H), 4.79 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.94-6.97 (m, 3H), 7.27-7.34 (m, 2H), 7.94 (br, 1H), 9.17 (s, 1H), 14.28 (s, 1H),
I-31		0.10-0.28 (m, 2H), 0.44-0.65 (m, 2H), 0.94 (m, 1H), 1.50 (d, J = 10.8 Hz, 1H), 170-3.40 (m, 10H), 4.72 (br s, 1H), 4.86 (s, 1H). 6.53 (d, J = 8.1 Hz, 1H). 6.58 (d, J = 8.1 Hz, 1H), 7.54-7.80 (m, 4H), 9.16 (s, 1H), 9.32 (s, 1H), 13.90 (br s, 1H)

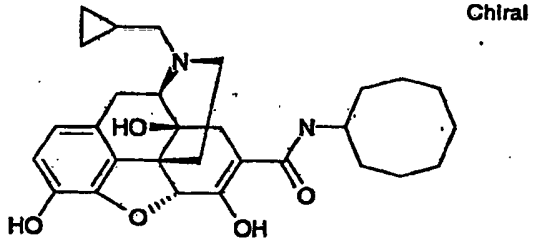
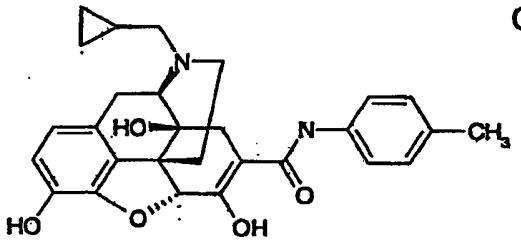
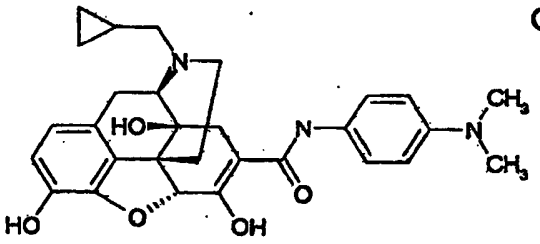
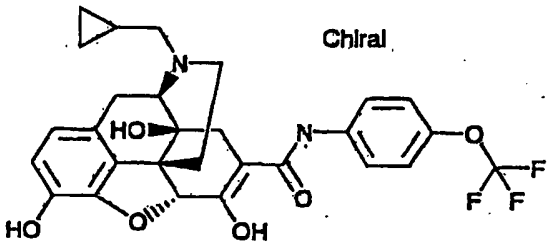
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-32		0.10-0.25 (m, 2H), 0.42-0.62 (m, 2H), 0.90 (m, 1H), 1.45 (d J = 10.6 Hz, 1H), 1.70-3.40 (m, 10H), 4.75 (br s, 1H), 4.84 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.41-7.54 (m, 4H), 9.17 (s, 1H), 9.28 (s, 1H), 13.85 (br s, 1H)
I-33		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.77 (s, 1H), 4.81 (s, 1H), 5.98 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 6.82-6.95 (m, 2H), 7.15 (d, J = 1.8 Hz, 1H), 9.16 (s, 1H), 9.26 (s, 1H), 13.98 (br s, 1H)
I-34		0.20-0.40 (m, 2H), 0.45-0.65 (m, 2H), 0.98 (m, 1H), 1.50 (m, 1H), 1.70-3.40 (m, 10H), 4.65 (br s, 1H), 4.88 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.60-7.80 (m, 4H), 9.17 (s, 1H), 9.30 (s, 1H), 14.00 (br s, 1H)
I-35		0.10-0.20 (m, 2H), 0.50-0.62 (m, 2H), 0.68 (m, 1H), 1.65 (d, J = 10.8 Hz, 1H), 2.00-3.60 (m, 14H), 3.78 (s, 3H), 4.93 (s, 1H), 5.46 (br, s, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 6.4 Hz, 2H), 14.17 (br s, 1H)

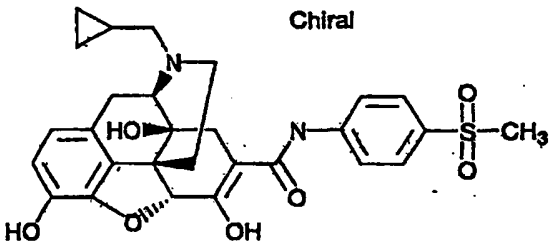
[Table 14]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-36		0.10-0.25 (m, 2H), 0.43-0.63 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 3.71 (s, 3H), 4.77 (s, 1H), 4.82 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.64 (m, 1H), 7.00-7.25 (m, 3H), 9.17 (s, 1H), 9.27 (s, 1H), 13.90 (s 1H), 9.27 1H), (br s, 1H)

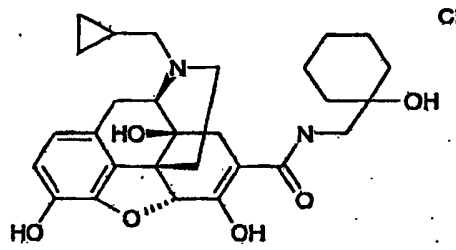
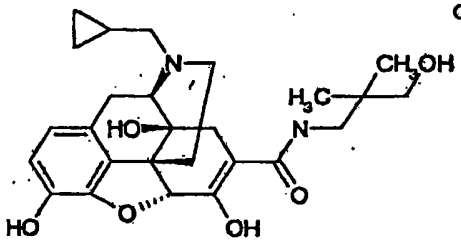
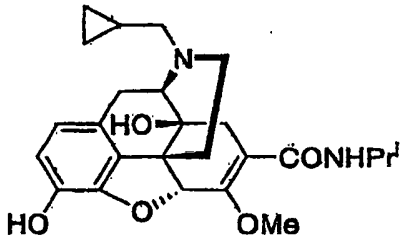
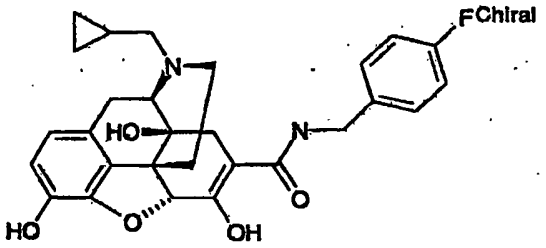
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-37		0.12-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 8.1 Hz, 2H), 0.85 (m, 1H), 1.06 (m, 1H), 1.39-1.62 (m, 18H), 1.84-1.89 (d, J = 15.6 Hz, 1H), 2.08-2.34 (m, 5H), 2.43-2.54 (m), 2.58-2.60 (d, J = 6.9 Hz, 1H), 3.00-3.07 (d, J = 18.6 Hz, 1H), 3.16-3.20 (d, J = 6 Hz, 1 H). 3.87 (br s, 1H), 4,71-4.76 (m, 2H), 8.49-6.57 (dd, J = 8.1, 14.7 Hz, 2H), 7.38 (d J = 7.8 Hz, 1H), 9.13 (br, s, 1H), 14.47 (br s, 1H)
I-38		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 13H), 4.78 (s, 1H), 4.82 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.39 (d J = 8.4 Hz, 2H), 9.17 (s, 1H), 9.27 (s, 1H), 14.00 (br s, 1H)
I-39		0.10-020 (m, 2H), 0.40-0.60 (m, 2H). 0.87 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 16H), 4.76 (s, 1H), 4.80 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 9.0 Hz, 2H), 9.10 (br s, 2H), 14.20 (br s, 1H)
I-40		0.10-0.30 (m, 2H), 0.45-0.65 (m, 2H), 0.90 (m, 1H), 1.48 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.77 (s, 1H), 4.85 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz 1H), 7.25-7.35 (m, 2H), 7.64 (d, J = 9.0 Hz, 2H), 9.18 (s, 1H), 9.29 (s, 1H), 13.90 (br s,

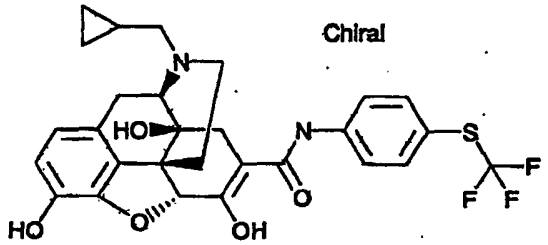
[Table 15]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-41		0.20-0.40 (m, 2H), 0.45-0.70 (m, 2H), 0.96 (m, 1H), 1.50 (m, 1H), 1.70-3.40 (m, 13H), 4.67 (br s, 1H), 4.88 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H). 7.76 (s, 4H), 9.18 (s, 1H), 9.31 (s, 1H), 14.00 (br s, 1H)

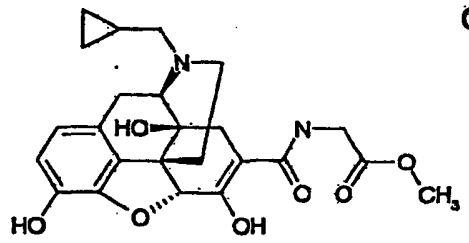
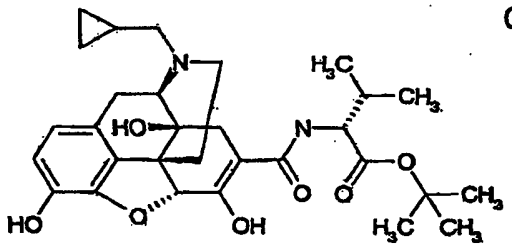
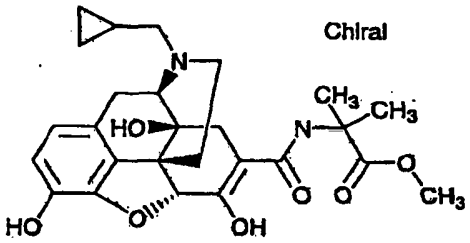
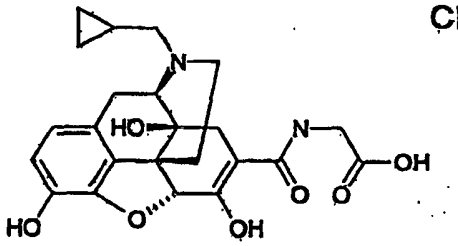
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-42		0.18 (br, s, 2H), 0.42-0.63 (m, 3H), 0.80-0.97 (m, 2H), 1.20-3.43 (m, 24H), 4.92 (s, 1H), 5.89 (br, s, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 14.13 (br, s, 1H)
I-43		0.12-0.19 (m, 2H), 0.41-0.58 (m, 2H), 0.74 (d, J = 3.3 Hz, 6H), 1.43 (m, 1H), 1.88-3.41 (m, 16H), 4.56 (br, s, 1H), 4.65-4.80 (m, 2H), 6.50-6.62 (m, 2H), 7.51 (br, s, 1H), 9.13 (s, 1H), 14.23 (br, s, 1H)
I-44		0.10-0.15 (m, 2H), 0.50-0.70 (m, 2H), 0.85 (m, 1H), 1.12 (d,.J = 0.9 Hz, 3H),).14 (d, J = 0.9 Hz, 3H), 1.66 (d, J = 11.4 Hz, 1H), 2.06-2.80 (m, 8H), 3.00-3.30 (m, 2H), 3.92 (s, 3H), 4.05 (m, 1H), 4.80 (br s, 1H), 5.26 (br s, 1H), 6.56 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H)
I-45		

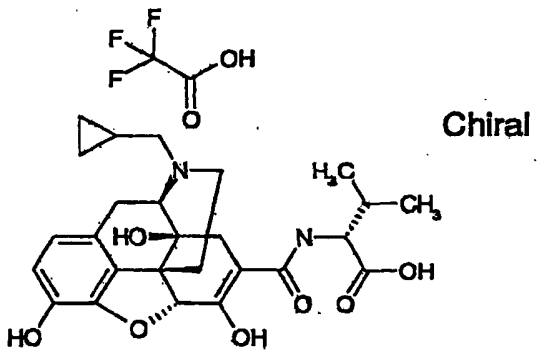
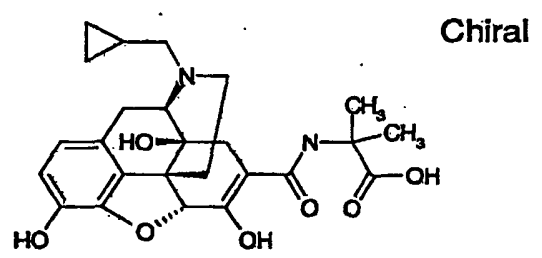
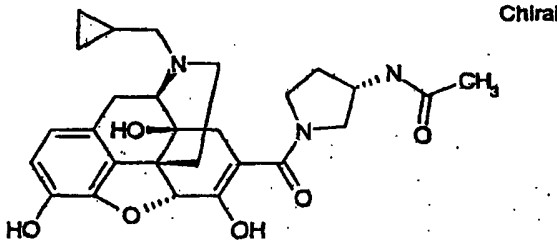
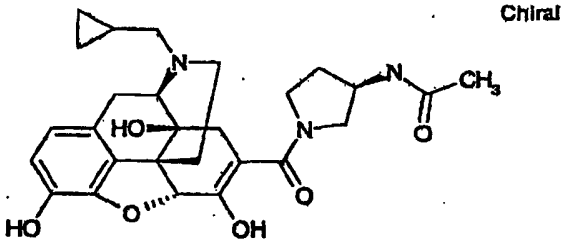
[Table 16]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-46		0.15-0.35 (m. 2H), 0.45-0.70 (m, 2H), 0.92 (m. 1H).1.50 (d, J=10.8 Hz, 1H), 1.70-3.40 (m,10H), 4.72 (br s, 1H), 4.88 (s, 1H), 6.53 (d. J = 8.1 Hz, 1H), 6.58 (d J = 8.1 Hz, 1H). 7.54-7.74 (m, 4H), 9.16 (s, 1H), 9.27 (s, 1H). 14.00 (br s, 1H)

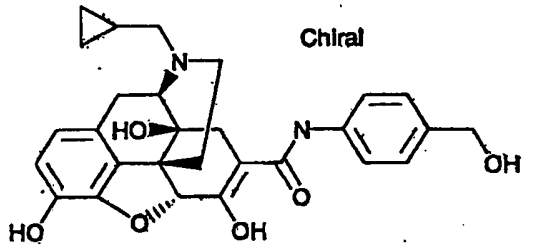
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-47		0,10-0.20 (m, 2H), 0.40-0.60 (m, 2H), 0.86 (m, 1H). 1.42 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 3.61 (s, 3H). 3.82 (d, J = 5.7 Hz, 2H), 4.77 (s, 2H), 6.53 (d, J = 8.1 Hz, 1 H), 8.58 (d, J = 8.1 Hz, 1H), 8.21 (br t, J = 5.7 Hz, 1H), 9.17 (s, 1H), 13.87 (br s, 1H)
I-48		0.10-0.20 (m, 2H). 0.50-0.65 (m, 2H), 0.89 (m, 1H), 0.90 (d, J = 4.5 Hz, 3H), 0.94 (d, J = 4.5 Hz, 3H), 1.45 (s, 9H). 1.66 (d, J = 10.8 Hz, 1H). 2.10-3.40 (m, 11H). 4.43 (dd, J = 4.5, 8.1 Hz, 1H), 4.94 (s, 1H), 6.00 (d, J = 8.1 Hz, 1H). 6.58 (d, J = 8.1 Hz, 1H). 6.71 (d, J = 8.1 Hz. 1H), 13.99 (br s, 1H)
I-49		0.10-0.30 (m, 2H), 0.45-0.70 (m, 2H), 0.90 (m, 1H), 1.34 (s, 3H). 1.38 (s. 3H). 1.50-3.40 (m, 11H). 3.56 (s.3H). 4.77 (br s, 2H). 6.58 (br s, 2H), 7.69 (br s, 1H). 9.20 (br s, 1H), 13.76 (br s, 1H)
I-50		0.10-0.20 (m, 2H), 0.40-p.BO (m, 2H), 0.88 (m, 1H), 1.44 (d, J = 11.7 Hz, 1H).1.90-3.40 (m, 10H), 3.68 (d, J = 4.5 Hz. 2H). 4.77 (s. 1H). 6.52 (d, J = 8.1 Hz, 1H), 6.58 (d. J = 8.1 Hz, 1H), 8.00 (br t, J = 4.6 hz, 1H), 9.18 (br s, 1H), 14.00 (br s, 1H)

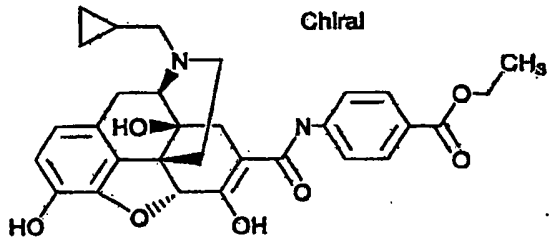
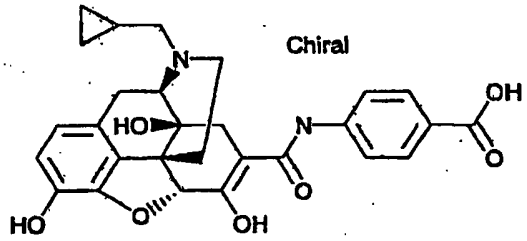
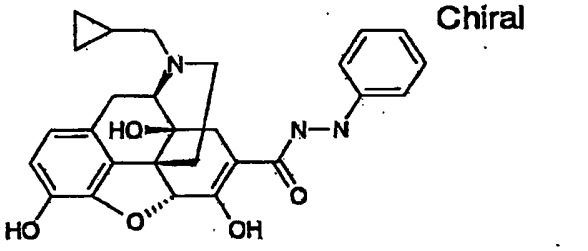
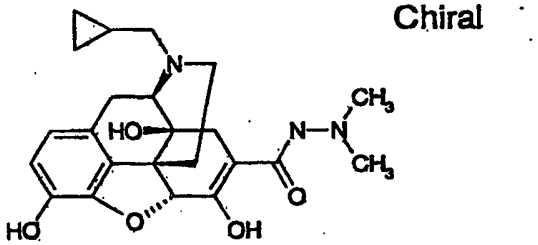
[Table 17]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-51		0.30-0.50 (m, 2H), 0.55-0.75 (m, 2H), 0,89 (d. J = 3.3 Hz, 3H), 0.91 (d, J = 3.3 Hz, 3H), 1.04 (m, 1H), 4.65 (d, J = 13.5 Hz, 1H). 2.00-3.92 (m, 11H), 4.10 (t, J = 6,6 Hz, 1H), 4.95 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 9.43 (s, 1H), 13.66 (br s, 1H)
I-52		0.10-0.25 (m, 2H), 0.45-0.60 (m, 2H), 0.89 (m, 1H), 1.34 (s, 3H), 1.36 (s, 3H), 1.48 (d, J = 9.6 Hz; 1H), 1.90-3.40 (m, 10H), 4.75 (s, 1H), 6.54 (d, J = 6.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.68 (s. 1H), 9.21 (br s. 1H), 14.11 (br s, 1H)
I-53		0.13-0.14 (m, 2H), 0.47-0.49 (m, 2H), 0.88 (m, 1H), H), 1.30 (m, 1H), 1.63-2,10 (m, 6H). 230-2.70 (m, 4H), 2.96-3.58 (m, 6H), 4.06-4.23 (m, 3H). 5.04 (s, 1H), 5.23 (br. 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 8.08 (br, 1H). 9.23 (br, 1H).
I-54		0.13-0.14 (m, 2H), 0.47-0.49 (m, 2H). 0.88 (m, 1H), 1.30 (d, J = 12.0 Hz, 1H), 1.63-2.12 (m, 6H), 2.28-2.70 (m, 4H), 2.97-3.53 (m. 6H), 4.06-4,23 (m, 3H). 5.08 (s, 1H), 5.22 (br, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 6.4Hz, 1H), 8.32 (s, 1H), 9.23 (br, 1H), 10.97 (s, 1H).

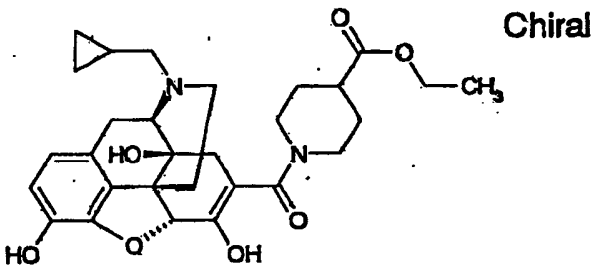
[Table 18]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-55		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.42 (s, 2H), 4.77 (s, 1H), 5.12 (s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 9.20 (s, 1H), 9.28 (s, 1H), 14.00 (br s. 1H)

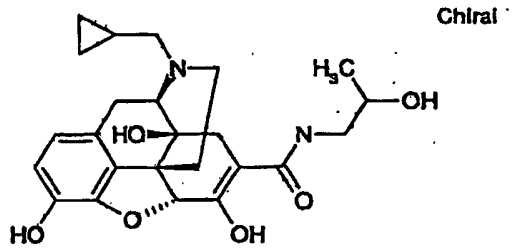
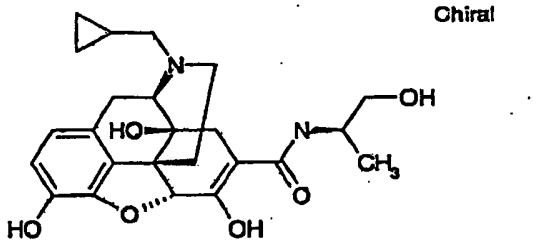
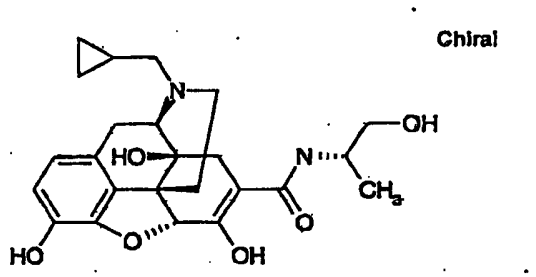
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-56		0.10-0.40 (m, 2H), 0.45-0.70 (m, 2H), 0.92 (m, 1H), 1.29 (t, J=7.2 Hz 3H, 1.49 (d, J = 9.0 Hz, 1H), 1.70-3.40 (m, 10H), 4.26 (q, J = 7.2 Hz, 2H), 4.72 (br s, 1H). 4.86 (s, 1H). 6.54 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.90 (d, J = 9.0 Hz, 2H), 9.18 (s, 1H), 9.29 (s, 1H)
I-57		0.25-0.40 (m, 2H), 0.50-0.70 (m, 2H), 1.00 (m, 1H), 1.56 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.87 (s, 1H), 4.92 (s, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.4 Hz. 2H), 7.86 (d, J = 8.4 Hz, 2H). 9.33 (br s, 2H)
I-58		0.08-0.20 (m, 2H), 0.43-0.57 (m, 2H), 0.88 (m, 1H), 1.22-3.40 (m, 11H), 4.76 (s, 1H), 4.84 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.62-6.81 (m, 3H), 7.06-7.16 (m, 2H), 7.73 (s, 1H), 9.16 (s, 1H), 9.61 (s, 1H), 13.80 (br s, 1H)
I-59		0.08-0.10 (m, 2H), 0.38-0.58 (m, 2H), 0.86 (m, 1H), 1.22-3.40 (m, 17H), 4.71 (s, 2H), 6.51 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 8.1 Hz, 1H), 8.58 (s, 1H), 9.15 (s, 1H), 14.30 (br s, 1H)

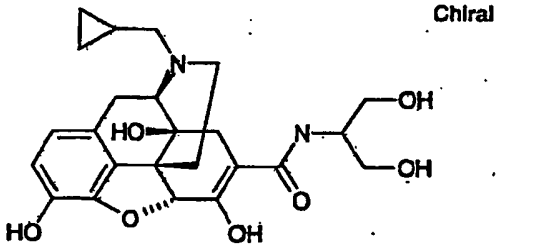
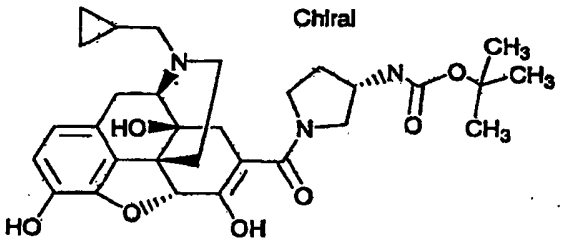
[Table 19]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-60		0.10-0.20 (m, 2H), 0.45-0.55 (m, 2H), 0,88 (m, 1H), 1.81 (t, J = 7.2 Hz, 3H), 1.20-3.75 (m, 20H), 4.07 (q, J = 7.2 Hz, 2H), 5.13 (s, 1H), 1H), 5.21 (br s, 1H), 6.53 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 921b (br s, 1H)

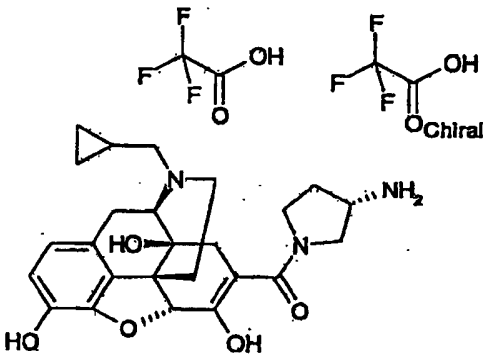
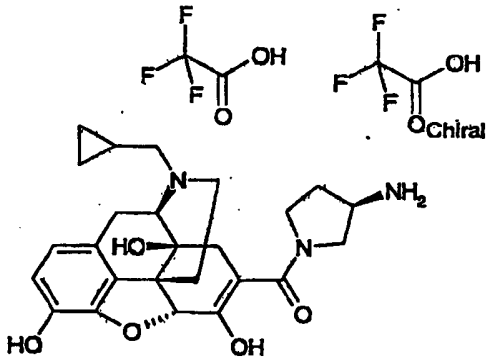
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-61		0.11-0.39 (m, 2H), 0.53-0.70 (m, 2H), 0.95 (m, 1H), 1.10-1.20 (m, 3H). 1.66-1.73 (m, 1H), 1.82-3.99(m. 24H), 4.90 (s, 1H), 6.32 (br, s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.68-6.73 (m, 1H), 14.03 (br, s. 1H)
I-62		0.10-0.18 (m, 2H). 0.42-0.56 (m, 2H), 0.85 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 1.41 (m, 1H), 1.68 (d, J =15.6 Hz, 1H), 204-231 (m, 4H). 2.42-2.62 (m, 6H), 3.04 (d, J = 18.0 Hz, 1H), 3.17-3.35 (m, 7H), 3.87 (m. 1H), 4.64 (t. J = 5.7 Hz, 1H). 4.72 (s, 1H). 6.50-6.57 (m, 2H). 7.27 (d, J = 8.1 Hz, 1H), 9.13 (s, 1H), 14.45 (s, 1H)
I-63		0.13 (d, J = 4.2 Hz, 2H), 0.43-0.55 (m, 2H), 0.85 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 1.41 (d, J = 10.8 Hz, 1H) 1.89 (d, J =15.9 Hz, 1H). 204-232 (m, 4H), 2.43-2.63 (m, 3H). 3.04 (d, J =18.3 Hz, 1H), 3.19-3.40 (m, 11H). 3.86 (m, 1H). 4.72 (s, 1H), 6.50-8.58 (m, 2H), 7.24 (m, 1H), 9.14 (s, 1H), 14.41 (br, s, 1H)

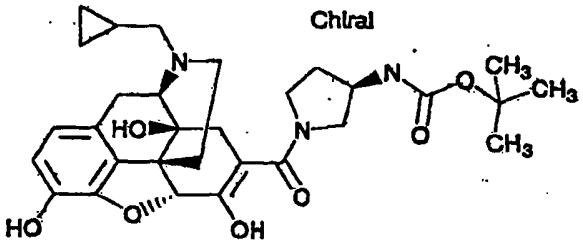
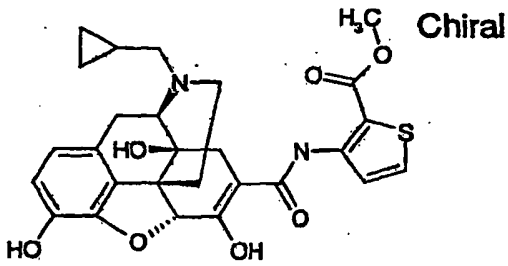
[Table 20]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-64		0.13 (d, J = 4.8 Hz, 2H), 0.43-0.55 (m, 2H), 0.85 (m, 1H), 1.41 (d, J =12.3 Hz, 1H), 1.92 (d, J = 16.2 Hz, 1H), 2.06-2.32 (m, 4H), 2.43-2.61 (m, 3H), 3.04 (d, J= 18.3 Hz. 1H), 3.20 (d, J = 6.6 Hz, 1H), 3.33-3.44 (m, 4H), 3.82 (m, 1H), 4.59 (t, J = 5.7 Hz, 1H), 4.68 (t, J = 5,7 Hz, 1H), 4.73 (s, 2H), 6.50-6.59 (m, 2H), 7.14 (br, s, 1H), 9.14 (s, 1H), 14.33 (br, s, 1H)
I-65		0.17-0.18 (m, 2H), 0.51-0.53 (m, 2H), 0.92 (m, 1H), 1.34 (m, 1H), 1.35 (br s, 9H), 1.71-3.49 (m, 14H), 3.95-4.20 (m, 3H), 5.10 (br, 1H), 5.26 (br, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 7.10 (br, 1H), 8.35 (s, 1H), 9.24 (s, 1H).

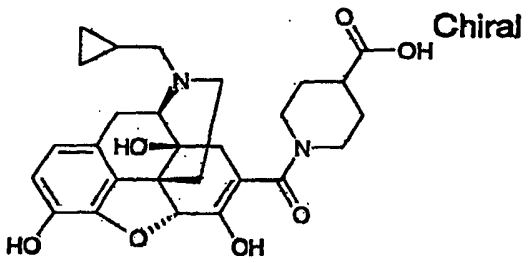
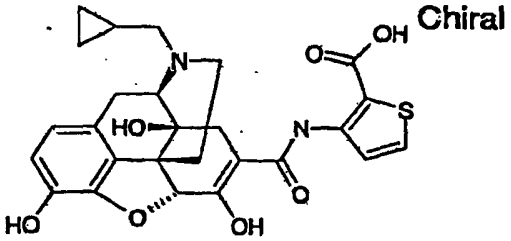
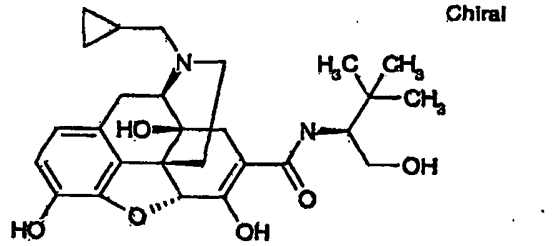
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-66		0.41 (m, 1H), 0.50 (m, 1H), 0.60 (m, 1H), 0.89 (m, 1H), 1.08 (m, 1H), 1.56 (m, 1H), 1.76-4.29 (m, 17H), 5.19 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H). 6.71 (d, J = 8.0 Hz, 1H), 8.14 (br. 1H), 8.20(br, 1H). 8.98 (br, 1H).
I-67		0.41 (m, 1H), 0.50 (m, 1H), 0.59 (m, 1H), 0.69 (m, 1H), 1.09 (m, 1H), 1.30-4.29 (m, 18H), 5.19 (s, 1H), 5.75 (br, 1H), 6.66 (d, J = 8.4 Hz, 1H). 6.71 (d, J = 8.4Hz, 1H), 8.21 (br, 1H), 8.26 (br, 1H), 8.99 (br, 1H).

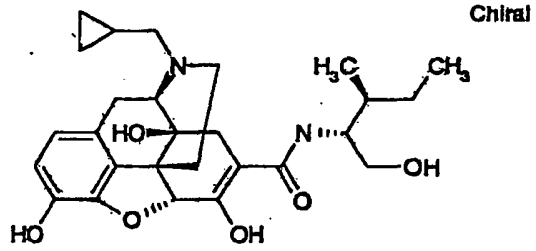
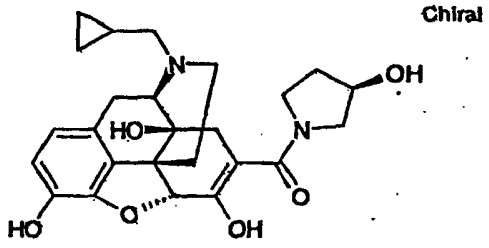
[Table 21]

Compound No.	Chemical stricture	NMR (1H-NMR(d6-DMSO) δ)
I-68		0.17-0.18 (m. 2H), 0.51-0.53 (m, 2H), 0.92 (m, 1H), 1.34 (m, 1H), 1.43 (br s, 9H), 1.71-2.03 (m, 5H), 2.18-2.74 (m, 4H), 2.92-3.69 (m, 5H), 3.95-4.20 (m, 2H). 5.07 (s, 1H), 5.26 (br, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 7.20 (br, 1H), 9.25 (s, 1H).
I-69		0.10-0.26 (m, 2H), 0.42-0.60 (m, 2H), 0.90 (m, 1H), 1.47 (d, J = 10.5 Hz. 1H), 1.90-3.40 (m, 10H), 3.84 (s, 3H). 4.81 (br s, 1H), 6.52 (d, J = 8.1 Hz. 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.80 (br s, 1H), 8.08 (br s, 1H), 9.18 (br s, 1H), 11.60 (br s, 1H)

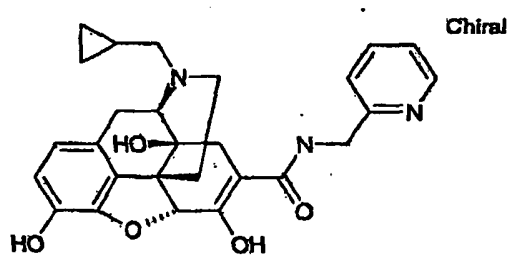
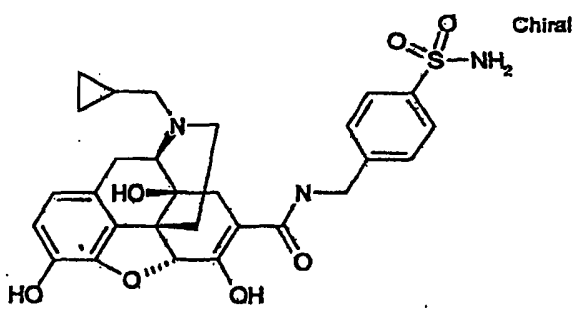
(continued)

Compound No.	Chemical stricture	NMR (1H-NMR(d6-DMSO) δ)
I-70		0.10-0.20 (m, 2H), 0.40-0.55 (m, 2H), 0,88 (m, 1H). 1.30-4.35 (m, 20H), 5.13 (s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 9.20 (br s, 1H)
I-71		0.25-0.45 (m, 2H), 0.45-0.70 (m, 2H), 0.97 (m, 1H), 1.64 (d, J =11.1 Hz, 1H), 2.00-3.40(m, 10H), 4.07 (brs, 1H), 4.97 (s, 1H), 6.63 (d. J = 8.1 Hz,1H), 6.68 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 5.4 Hz, 1H), 7.80 (d, J = 5.4 Hz, 1H). 9.44 (br s, 1H), 13.40 (br s, 1H)
I-72		0.14 (d, J = 4.5 Hz, 2H). 0.40-0.58 (m, 2H), 0.79-0.92 (m, 13H), 1.25 (br. s. 1H), 1.41 (m, 1H), 1.907 (s, 1H), 2.11-2.64 (m, 8H), 3.03 (m, 1H), 3.21-3.77 (m, 4H) 4.53 (br, s, 1H), 4.72-4.80 (m, 2H), 6.50-6.58 (m, 2H), 6.95-7.22 (m, 2H), 9.13 (s, 1H), 14.39 (br, s, 1H)

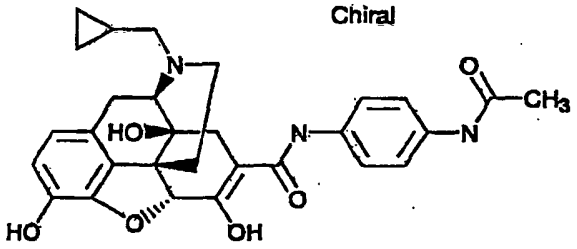
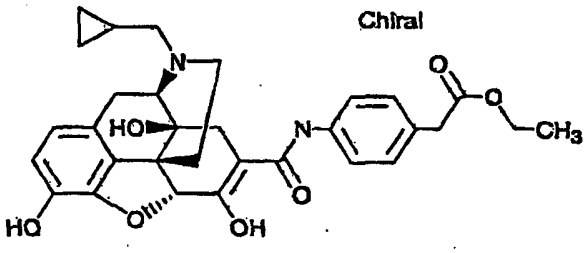
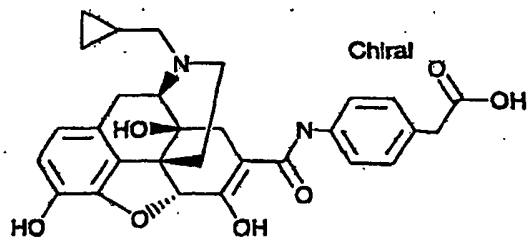
[Table 22]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-73		0.14 (d, J = 4.5 Hz, 2H), 0.40-0.58 (m, 3H), 0.74-1.01 (m, 10H), 1.25-1.61 (m, 4H), 1.88 (m, 1H), 2.06-2.62 (m, 8H), 3.03 (m, 1H), 3.21 (d, J = 6.0 Hz, 1H), 3.45 (t, J = 5.4 Hz, 2H), 3.68 (m, 1H), 4.57 (m, 1H), 4.72 (s, 1H), 4.76 (br, s, 1H), 6.51-6.58 (m, 2H), 7.14-7.27 (m, 2H), 9.15 (s, 1H), 14.44 (s, 1H)
I-74		0.16-0.18 (m, 2H), 0.52 (br d, J = 7.6 Hz, 2H), 0.92(m, 1H), 1.35 (d, J = 11.2 Hz, 1H), 1.72-3.48 (m, 16H), 4.11-4.28 (m, 3H), 4.73-5.25 (m, 2H), 6.57 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 9.23 (s, 1H), 11.16 (s, 1H).

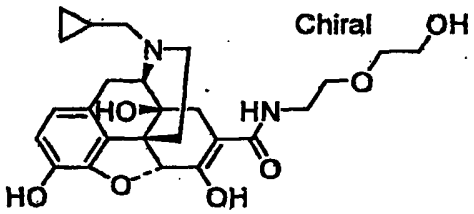
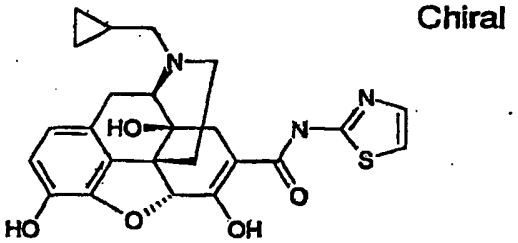
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-75		0.14-0.15 (m, 2H), 0.43-0.57 (m, 2H), 0.87 (m, 1H), 1.44 (d, J = 11.2 Hz, 1H), 1.97 (d, J= 15.6 Hz, 1H), 2.08-3.22 (m, 10H), 4.15-4.48 (m, 2H), 4.76 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 7.23-7.29 (m, 2H), 7.75 (m, 1H), 8.48-8.54 (m, 2H).
I-76		0.16-0.17 (m, 2H), 0.50-0.56 (m, 2H), 0.89 (m, 1H), 1.43 (br d, 1H), 1.97 (d, J =15.6 Hz, 1H), 2.11-3.21 (m, 10H), 4.30-4.46 (m, 2H), 4.77 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 7.29 (s, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 8.42 (br, 1H), 9.17 (br, 1H), 14.19 (s, 1H).

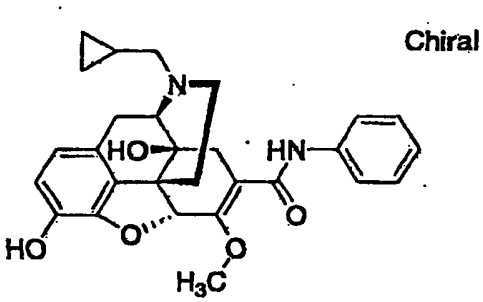
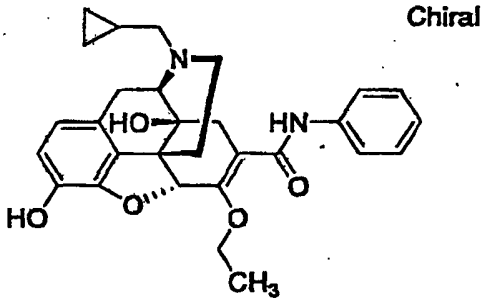
[Table 23]

Compound No:	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-77		-0.10-0.25 (m, 2H), 0.44-0.60 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 11.1 Hz, 1H), 1.70-3.40 (m, 13H), 4.78 (s, 1H), 4.81 (s, 1H), 8.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 9.0 Hz, 2H), 9.15 (s, 1H), 9.25 (s, 1H), 9.88 (s. 1H), 14.00 (br s, 1H)
I-78		0.10-0.25 (m, 2H), 0.44-0.60 (m, 2H), 0.89 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.4 5(d, J= 11.4 Hz, 1H), 1.70-3.40 (m, 10H), 3.60 (s, 2H), 4.00 (q, J = 72 Hz, 2H), 4.78 (s, 1H), 4.83 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.58 (d, J= 8.1 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 9.16 (s, 1H), 9.26 (s, 1H), 13.95 (br s, 1H)
I-79		0.12-0.30 (m, 2H), 0.44-0.62 (m, 2H), 0.90 (m, 1H), 1.48 (d, J = 11.4 Hz, 1H), 1.70-3.40 (m, 10H), 3.51 (s, 2H), 4.81 (s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 9.20 (s, 1H), 9.40 (br s, 1H), 14.00 (br s, 1H)

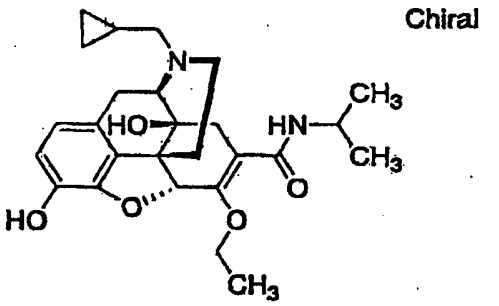
(continued)

Compound No:	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-80		0.10-0.17 (m, 2H), 0.46-0.52 (m, 2H), 0.86 (m, 1H), 1.41 (d, J = 13.2 Hz, 1H), 1.87 (m, 1H), 2.09-2.64 (m, 8H), 3.00-3.50 (m, 15H), 4.57 (m, 1H), 4.73 (br, s, 2H), 6.50-6.57 (m, 2H), 7.73 (br, s, 1H), 9.14 (s, 1H), 14.38 (br, s, 1H)
I-81		0.30-0.50 (m, 2H), 0.50-0.70 (m, 2H), 1.05 (m, 1H), 1.50-3.40 (m, 1H), 4.58 (s, 1H), 5.39 (s, 1H), 6.52 (d, J = 6.0 Hz, 1H), 6.59 (d, J = 6.0 Hz, 1H), 6.84 (br s, 1H), 7.26 (m, 1H), 7.38 (m, 1H), 9.16 (m, 1H)

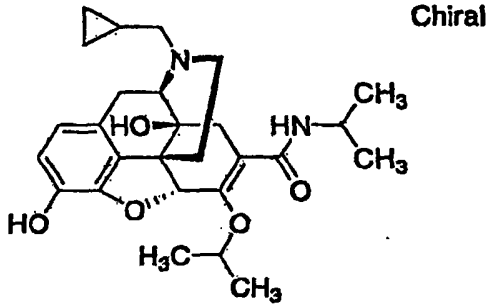
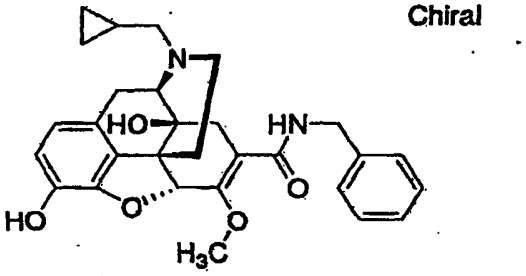
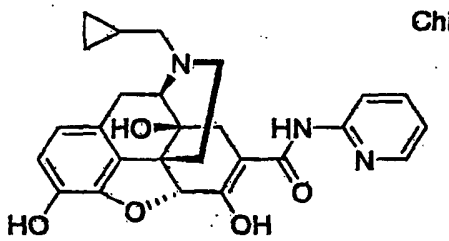
[Table 24]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-82		1H-NMR (CDCl3+CD3OD) d : 0.17 (brs, 2H), 0.59 (brs, 2H), 0.89 (brs, 1H), 1.71 (d, J = 10.8 Hz, 1H), 2.17 (dd, J=17.1 & 1.8 Hz, 1H), 2.22-2.57 (m, 4H), 2.60-2.84 (m, 3H), 3.06 (d, J = 15.6 Hz, 1H), 3.24 (brs, 1H), 4.07 (s, 3H), 5.31 (s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 7.02-7.10 (m, 1H), 7.26-7.32 (m, 2H), 7.39 (d.d, J =8.4 & 0.9 Hz, 2H), 9.61 (s, 1H).
I-83		1H-NMR (CDCl3+CD3OD) d : 0.15 (brs, 2H), 0.58 (brs, 2H), 0.88 (brs, 1H), 1.49 (t, J = 6.9 Hz, 3H), 1.68 (d, J=9.9 Hz, 1H), 2.15 (dd, J=17.1 & 1.5 Hz, 1H), 2.28 (brs, 2H), 2.39 (brs, 2H), 2.60-2.80 (m, 3H), 3.06 (d, J = 18.3 Hz, 1H), 3.26 (brs, 1H), 4.29 (q, J=6.9 Hz, 1H), 4.48 (q, J=6.9 Hz, 1H), 5.27 (s, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.66 (d, J =7.8 Hz, 1H), 7.03-7.09 (m, 1H), 7.26-7.31 (m, 2H). 7.50 (d.d, J =8.7 & 0.9 Hz, 2H),

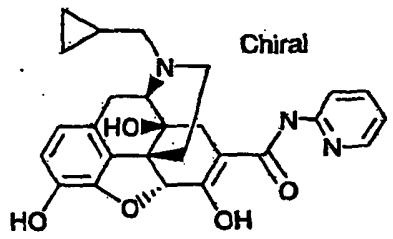
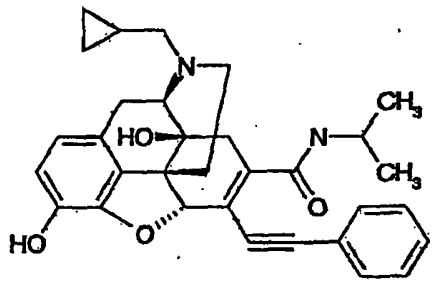
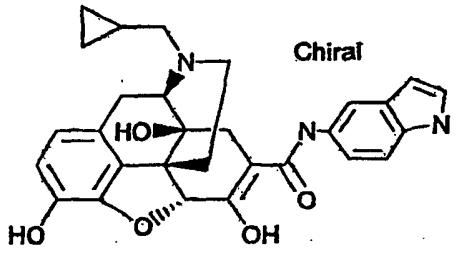
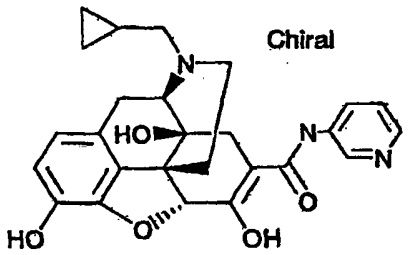
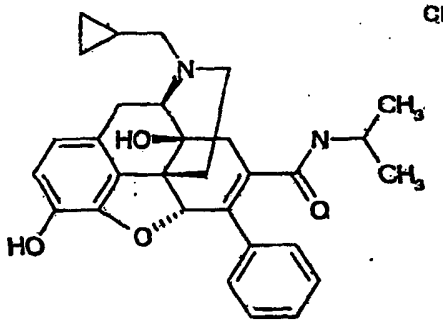
(continued)

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-84		1H-NMR (CDCl3+CD3OD) d : 0.16 (brs, 2H), 0.57 (brs, 2H), 0.86 (brs, 1H), 1.13 (d, J = 6.6 Hz, 3H), 1.14 (d, J=6.6 Hz, 3H), 1.39 (t, J=6.9 Hz, 3H), 1.66 (d, J=9.0 Hz, 1H), 2.08 (d.d, J=17.1 & 1.5 Hz, 1H), 2.21 (brs, 2H), 2.38 (brs, 2H), 2.58-2.77 (m, 3H), 3.03 (d, J =18.6 Hz, 1H), 3.21 (brs, 1H), 4.03 (quint, J=6.6 Hz, 1H), 4.20 (q, J=6.9 Hz, 1H), 4.40 (q, J=6.9 Hz, 1H), 5.19 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.65 (d, J =8.1 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H),

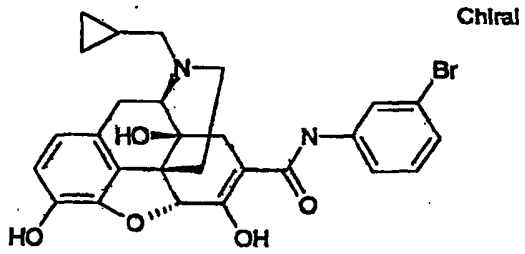
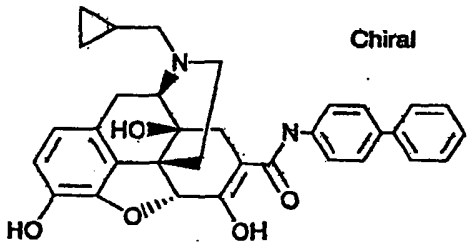
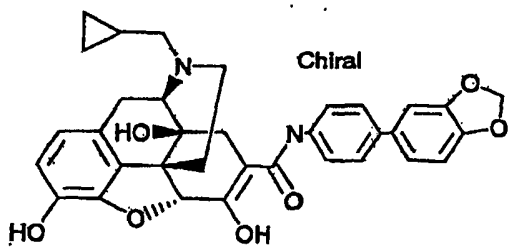
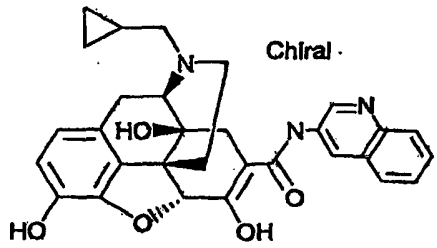
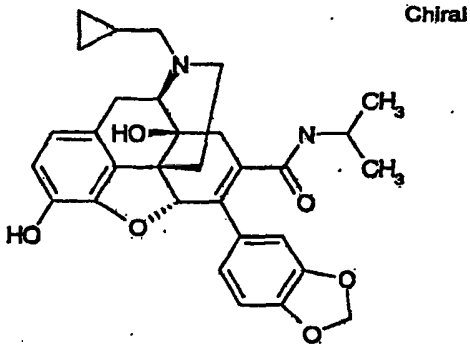
[Table 25]

Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-85		1H-NMR (CDCl3+CD3OD) d : 0.14 (brs, 2H), 0.56 (brs, 2H), 0.86 (brs, 1H), 1.14 (d, J = 6.6 Hz, 3H), 1.15 (d, J=6.6 Hz, 3H), 1.32 (d, J = 4.8 Hz, 1H), 1.34 (d, J=4.8 Hz, 3H), 1.64 (d, J=9.9 Hz, 1H), 2.10 (d.d, J=17.1 & 1.5 Hz, 1H), 2.27 (brs, 2H), 2.39 (brs. 2H), 2.55-2.77 (m, 3H), 3.04 (d, J =18.3 Hz, 1H), 3.22 (brs, 1H), 4.03 (quint, J=6.6 Hz, 1H), 4.81 (quint, J=6.0 Hz, 1H), 5.10 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.67 (d, J =8.4 Hz, 1H), 7.76 (d, J =8.9 Hz, 1H),
I-86		1H-NMR (CDCl3+CD3OD) d : 0.16 (brs, 2H). 0.568 (brs, 2H), 0.87 (brs, 1H), 1.67 (d, J=9.9 Hz, 1H), 2.14 (d.d, J=18.3 & 12 Hz, 1H), 2.27 (brs, 2H), 2.41 (brs, 2H), 3.05 (d, J = 18.8 Hz, 1H), 3.25 (brd, J=4.5 Hz, 1H), 3.92 (s, 1H), 4.46 (d, J=5.7 Hz, 2H), 5.23 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.64 (d, J =6.1 Hz, 1H), 720-7.36 (m, 5H), 8.03 (brt, J =5.7 Hz, 1H).
I-87		1H-NMR (CDCl3+CD3OD) d : 026 (brs, 2H), 0.63 (brs, 2H), 0.94 (brs, 1H), 1.72 (brd, J = 9.0 Hz, 1H), 2.09-2.93 (m, 8H), 3.15 (d, J =18.9 Hz, 1H), 4.97 (s, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.70 (d, J =8.1 Hz, 1H), 7.04-7.08 (m, 1H), 7.69-7.75 (m, 1H), 8.13 (d, J =14.0 Hz, 2H), 8.23 (d, J =3.9 Hz, 1H).

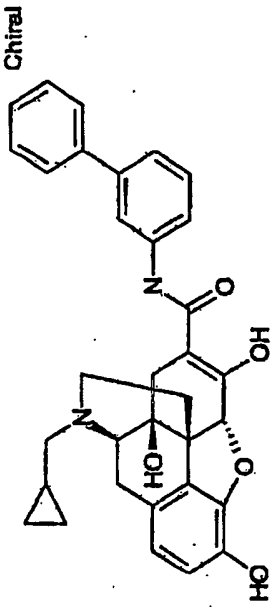
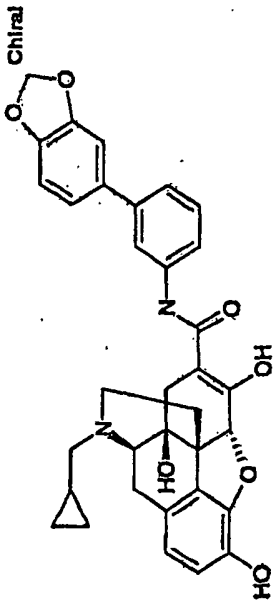
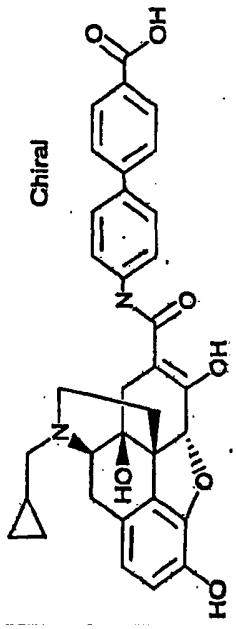
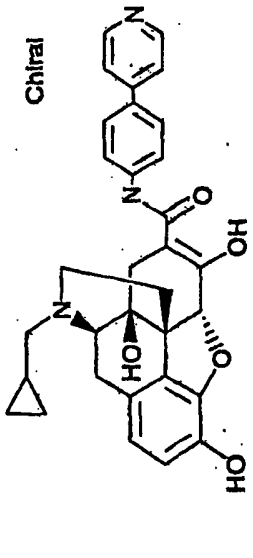
[Table 26]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-89		m/z 462 $[M+H]^+$ 0.94 min	
I-90		m/z 511 $[M+H]^+$ 0.63 min	
I-91		m/z 500 $[M+H]^+$ 0.44 min	
I-92		m/z 462 $[M+H]^+$ 0.44 min	
I-93		m/z 48.7 $[M+H]^+$ 0.50 min	

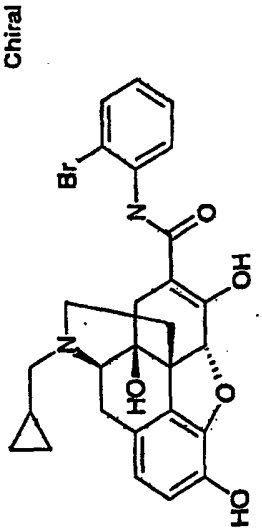
[Table 27]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-94		m/z 540 $[M+H]^+$ 1.07 min	
I-95		m/z 537 $[M+H]^+$ 1.12 min	
I-96		m/z 581 $[M+H]^+$ 1.15 min	
I-97		m/z 512 $[M+H]^+$ 0.50 min	
I-98		m/z 531 $[M+H]^+$ 0.50 min	

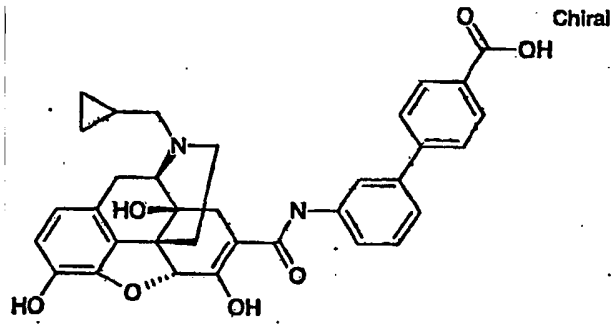
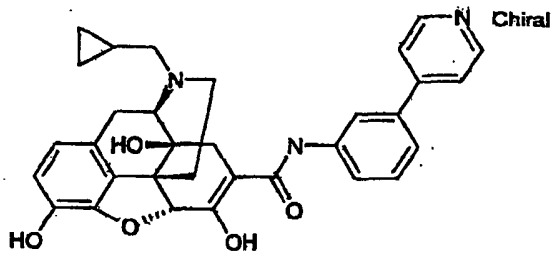
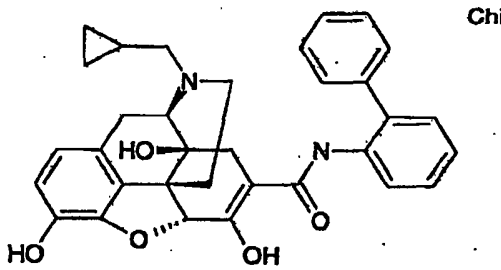
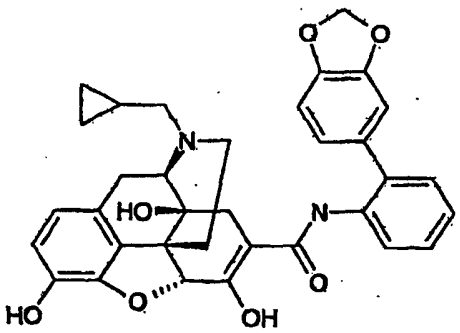
[Table 28]

Compound No.	chemical structure	LC/MS*1	NMR (1H-NMR(d6-DMSO) δ)
I-99		m/z 537 $[M+H]^+$ 1.17 min	
I-100		m/z 581 $[M+H]^+$ 1.15 min	
I-101		m/z 581 $[M+H]^+$ 1.03 min	
I-102		m/z 538 $[M+H]^+$ 0.85 min	

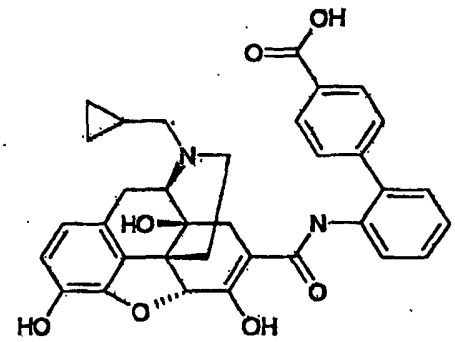
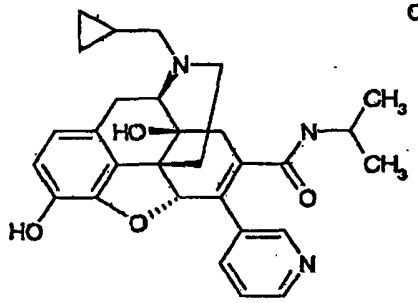
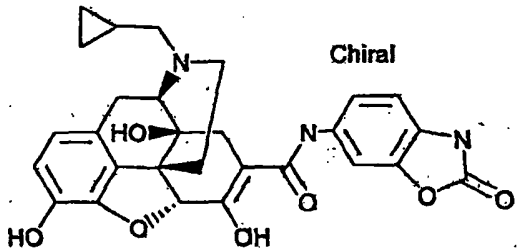
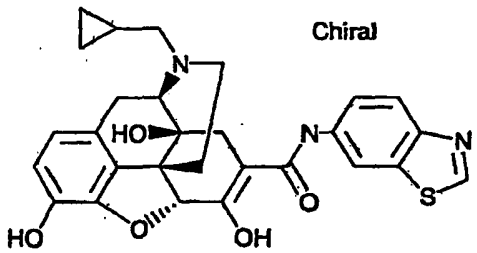
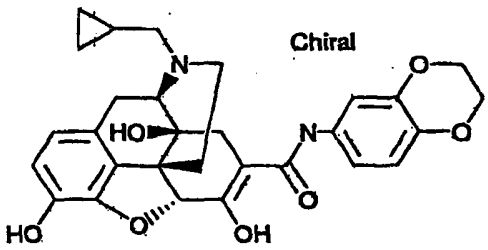
(continued)

Compound No.	chemical structure	LC/MS*1	NMR (1H-NMR(d6-DMSO) δ)
I-103	Chiral 	m/z 540 $[M+H]^+$ 1.05 min	

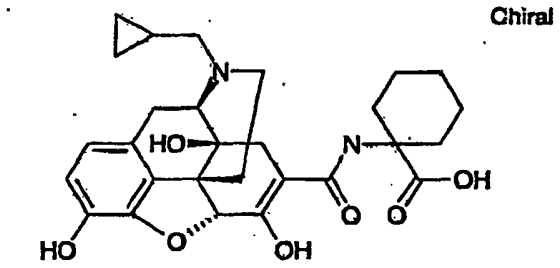
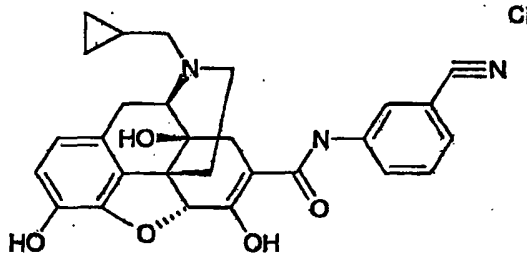
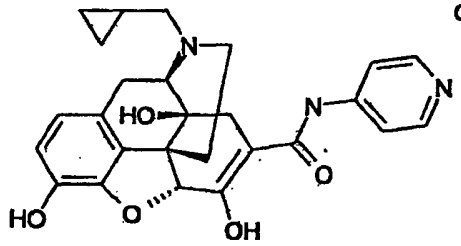
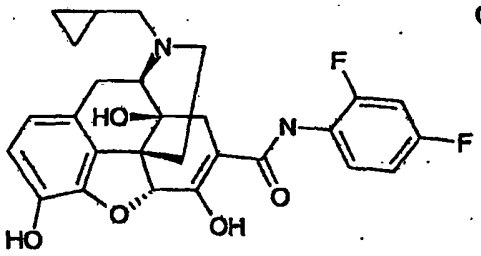
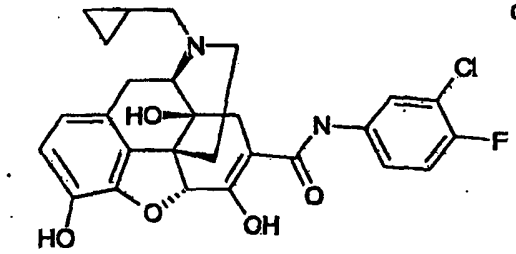
[Table 29]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-104		m/z 581 $[M+H]^+$ 1.12 min	
I-105		m/z 538 $[M+H]^+$ 0.90 min	
I-106		m/z 537 $[M+H]^+$ 1.05 min	
I-107		m/z 581 $[M+H]^+$ 1.09 min	

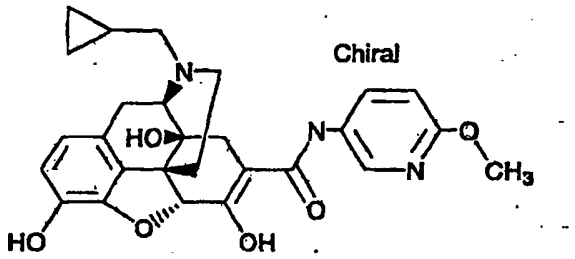
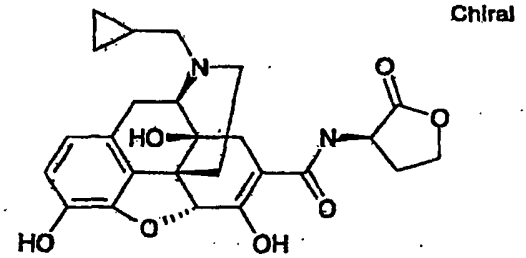
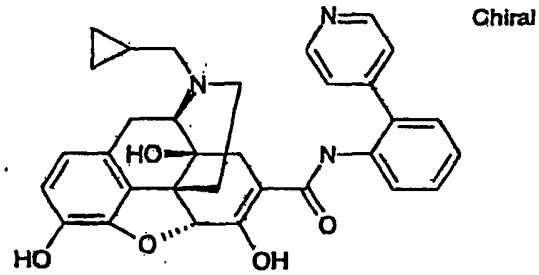
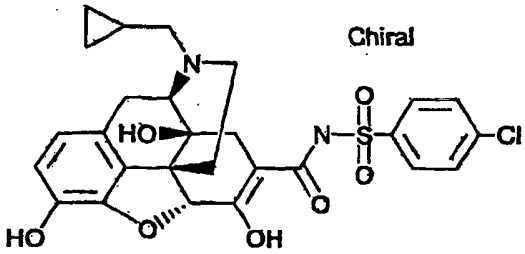
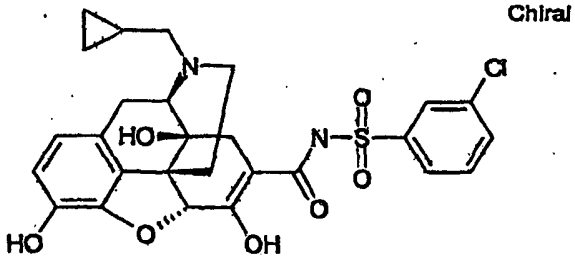
[Table 30]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-108		m/z 581 $[M+H]^+$ 1.03 min	
I-109		m/z 488 $[M+H]^+$ 0.50 min	
I-110		m/z 518 $[M+H]^+$ 0.50 min	
I-111		m/z 518 $[M+H]^+$ 0.56 min	
I-112		m/z 519 $[M+H]^+$ 0.50 min	

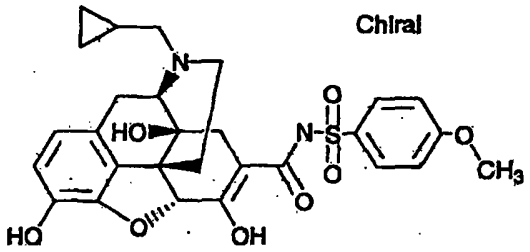
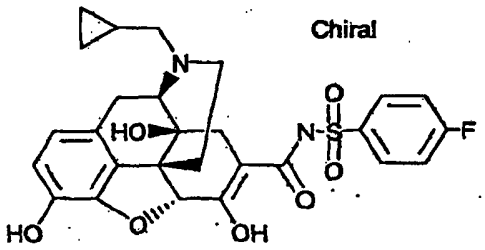
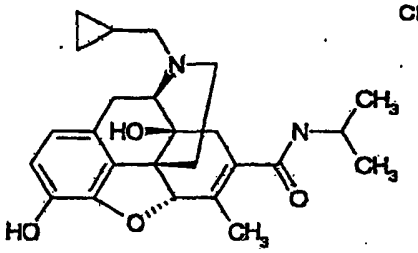
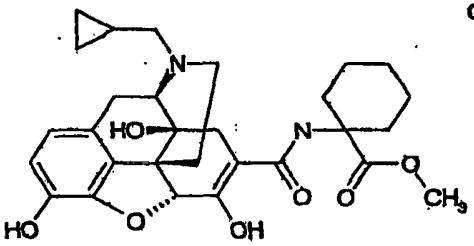
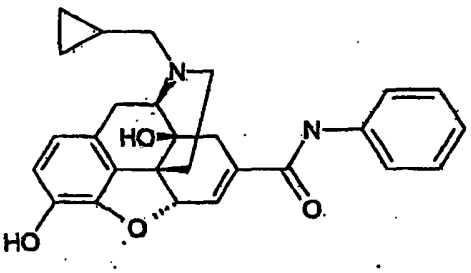
[Table 31]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-113		m/z 511 [M+H]+ 0.50 min	
I-114		m/z 486 [M+H]+ 0.57 min	
I-115		m/z 462 [M+H]+ 0.44 min	
I-116		m/z 497 [M+H]+ 0.63 min	
I-117		m/z 513 [M+H]+ 0.69 min	

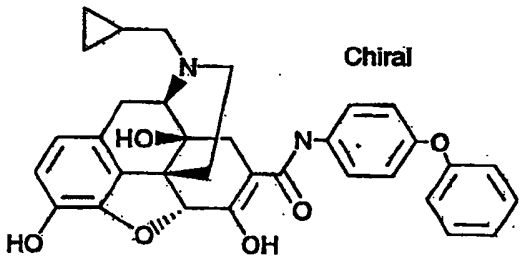
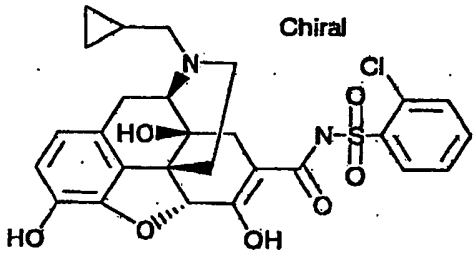
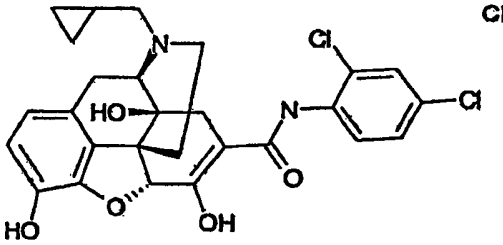
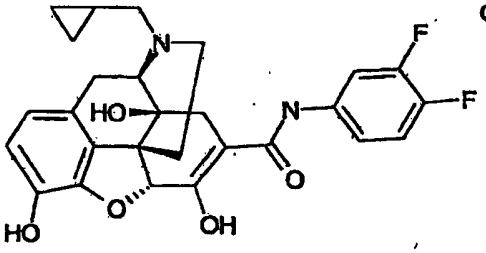
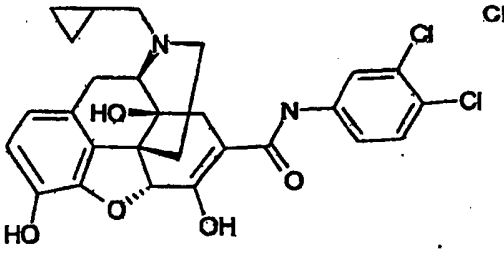
[Table 32]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-118		m/z 493 [M+H]+ 1.06 min	
I-119		m/z 469 [M+H]+ 0.44 min	
I-120		m/z 538 $[M+H]^+$ 0.94 min	
I-121		m/z 559 $[M+H]^+$ 0.69 min	
I-122		m/z 559 [M+H]+ 0.69 min	

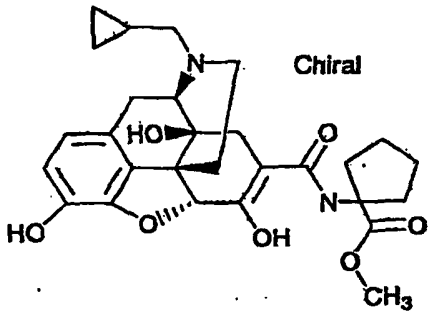
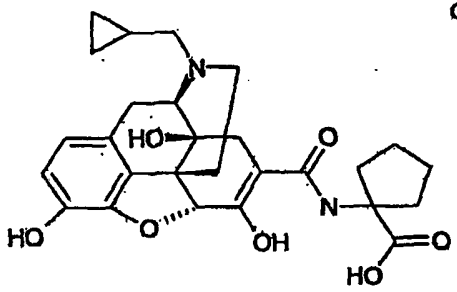
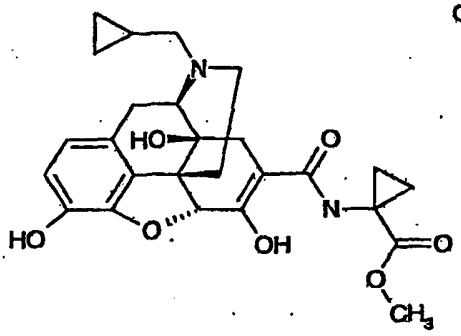
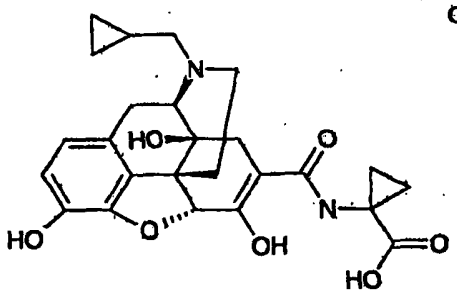
[Table 33]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-123		m/z 555 $[M+H]^+$ 0.56 min	
I-124		m/z 543 $(M+H]^+$ 0.63 min	
I-125		m/z 425 $[M+H]^+$ 0.50 min	
I-126		m/z 525 $[M+H]^+$ 0.56 min	
I-127			(CDCl3+CD3OD) d : 0.10-0.21 (m, 2H), 0.48-0.63 (m, 2H), 0.78-0.94 (m, 1H), 1.67 (d, J = 9.6 Hz, 1H), 2.10-2.50 (m, 6H), 2.57-2.80 (m, 2H), 3.08 (d, J = 18.6 Hz, 1H), 3.27 (brs. 1H), 5.10 (d, J = 1.7 Hz, 1H), 6.31-6.40 (m. 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H). 7.02-7.12 (m. 1H), 7.2-7.34 (m, 2H), 7.44-7.56 (m, 2H).

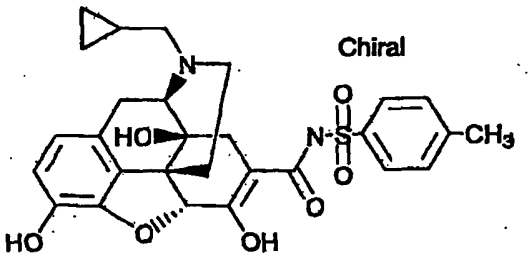
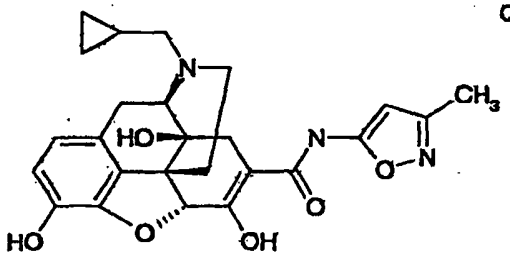
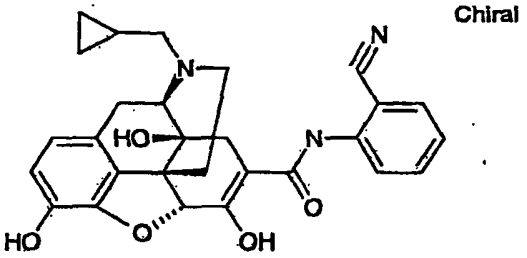
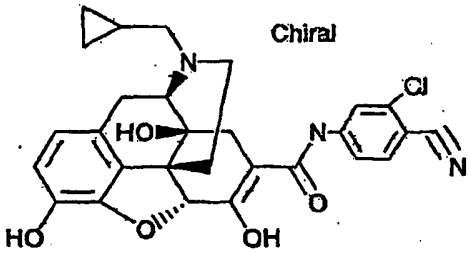
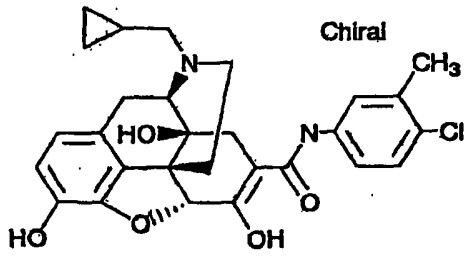
[Table 34]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-128		m/z 553 $[M+H]^+$ 0.94 min	
I-129		m/z 559 $[M+H]^+$ 0.63 min	
I-130		m/z 529 $[M+H]^*$ 0.75 min	
I-131		m/z 497 $[M+H]^+$ 0.63 min	
I-132		m/z 529 $[M+H]^+$ 0.88 min	

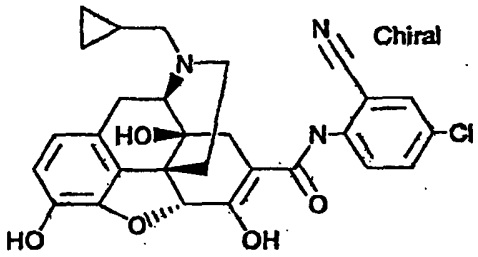
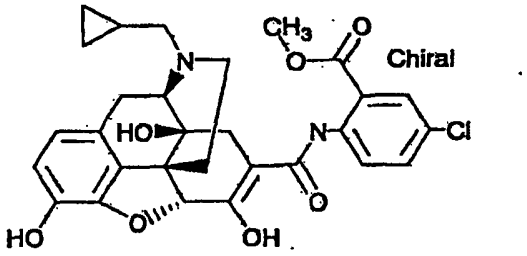
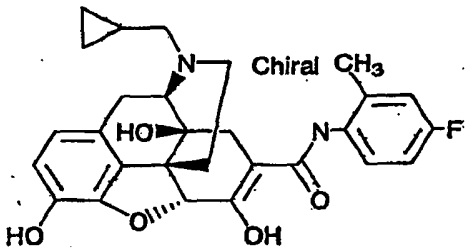
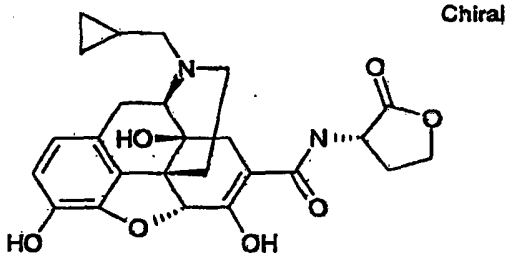
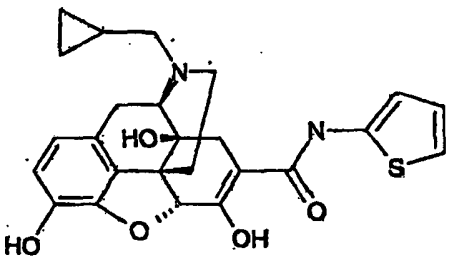
[Table 35]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-133		m/z 511 $[M+H]^+$ 0.97 min	0.12-0.10 (m, 2H), 0.46-0.52 (m, 2H). 0.86 (m, 1H), 1.42 (d, J = 10.5 Hz. 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06-2.65 (m, 15H), 3.05 (d, J = 18.3 Hz, 1H), 3.26 (d, J = 5.9 Hz, 1H), 3.55 (s, 3H), 4.73 (s 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.78 (brs, 1H), 9.31 (brs, 1H), 13.8 (brs, 1H)
I-134		m/z 498 $[M+H]^+$ 0.96 min	0.13-0.18 (m, 2H), 0.48-0.54 (m, 2H), 0.87 (m, 1H), 1.43 (d, (J =10.5 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06-2.67 (m, 15H), 3.08 (d, J = 18.8 Hz, 1H), 3.27 (d, J = 6.0 Hz, 1H), 4.73 (s 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.72 (brs, 1H), 9.20 (brs, 1H), 14.1 (brs, 1H)
I-135		m/z 483 $[M+H]^+$ 0.87 min	0.12-0.14 (m, 2H), 0.46-0.51 (m, 2H), 0.85 (m, 1H), 1.06-1.09 (m, 2H), 1.35-1.35 (m, 2H), 1.41 (d, J = 11.7 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.17-2.81 (m, 7H), 3.03 (d, J = 18.3 Hz 1H), 3.17 (d, J = 6.0 Hz, 1H), 3.56 (s, 3H), 4.74 (s, 1H), 4.77 (brs, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 9.17 (brs, 1H), 14.1 (brs, 1H)
I-136		m/z 469 $[M+H]^+$ 0.89 min	0.12-0.16 (m, 2H), 0.43-0.51 (m, 2H), 0.85 (m, 1H), 1.06-1.12 (m, 2H),1.35-1.38 (m, 2H), 1.42 (d, J =11.7 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06-2.63 (m, 7H), 3.02 (d, J = 18.3 Hz, 1H), 3.13 (d, J = 5.4 Hz, 1H), 4.76 (s 1H), 4.77 (brs, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 9.18 (brs, 1H), 14.1 (brs, 1H)

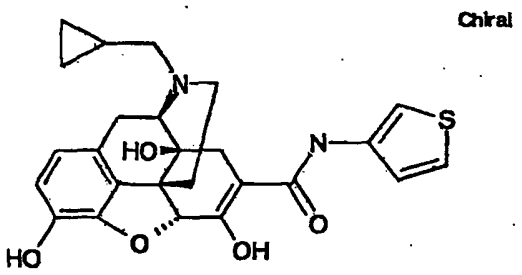
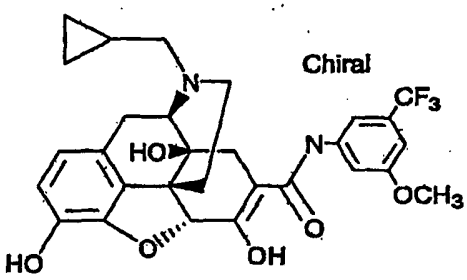
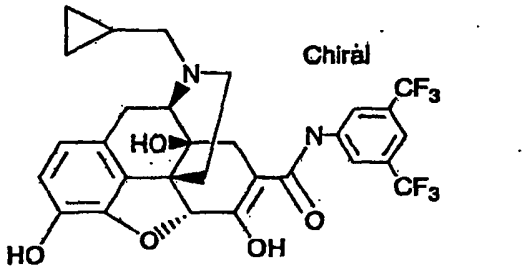
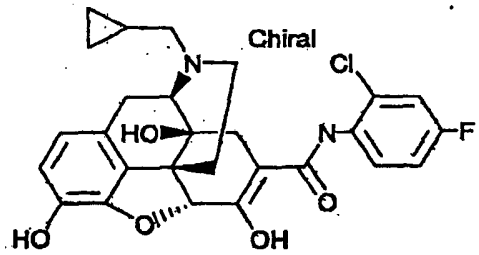
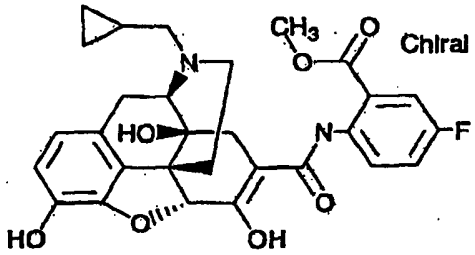
[Table 36]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-137		m/z 539 [M+H]+ 0.50 min	
I-138		m/z 466 [M+H]+ 0.57 min	
I-139		m/z 486 [M+H]+ 0.44 min	
I-140		m/z 520 [M+H]+ 0.56 min	
I-141		m/z 510 [M+H]+ 0.75 min	

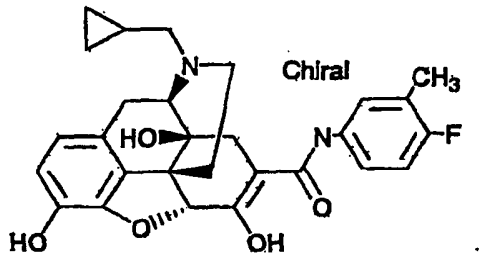
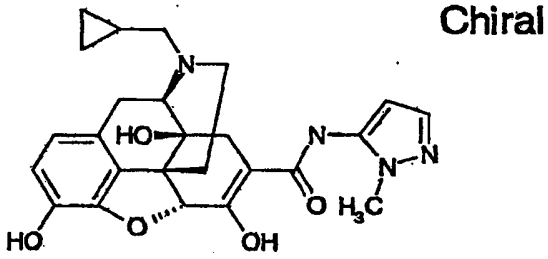
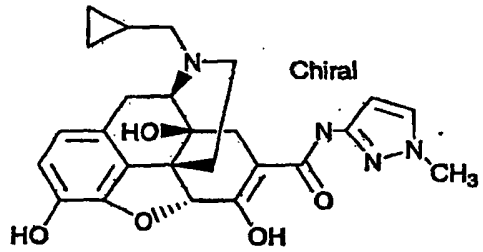
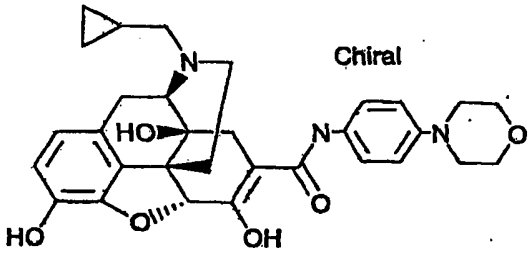
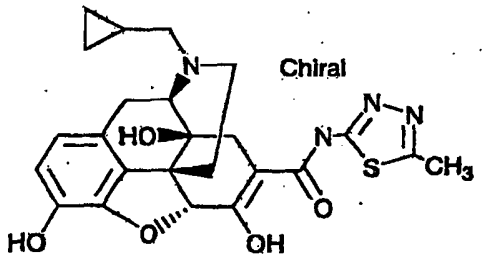
[Table 37]

Compound No.	Chemical structure	LC/M*1	NMR (1H-NMR (d6-DMSO) δ)
I-142		m/z 521 $[M+H]^+$ 0.50 min	
I-143		m/z 553 $[M+H]^+$ 0.88 min	
I-144		m/z 494 $[M+H]^+$ 0.57 min	
I-145		m/z 469 $[M+H]^+$ 0.83 min	
I-146		m/z 467 [M+H]+ 1.01 min	

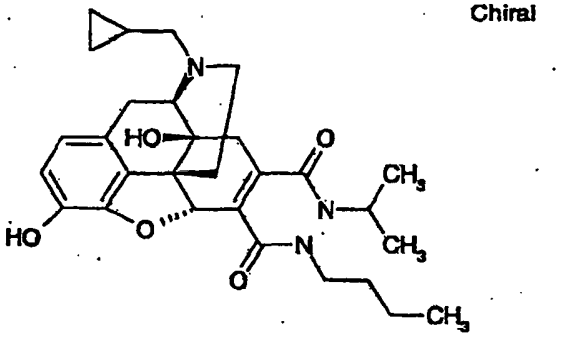
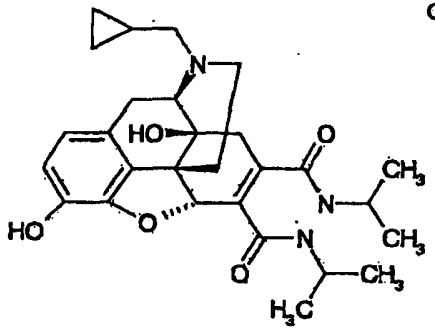
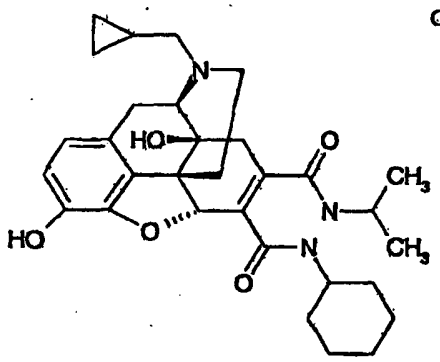
[Table 38]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-147		m/z 467 [M+H]+ 1.00 min	
I-148		m/z 559 [M+H]+ 1.16 min**	
I-149		m/z 598 [M+H]+ 1.34 min**	
I-150		m/z 514 [M+H]$^+$ 0.50 min	
I-151		m/z 538 [M+H]$^+$ 0.63 min	

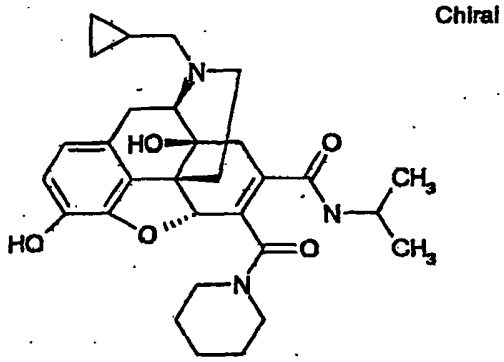
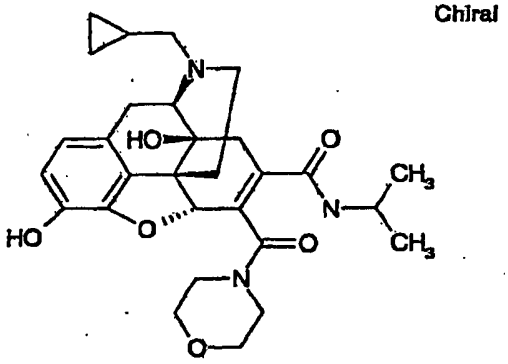
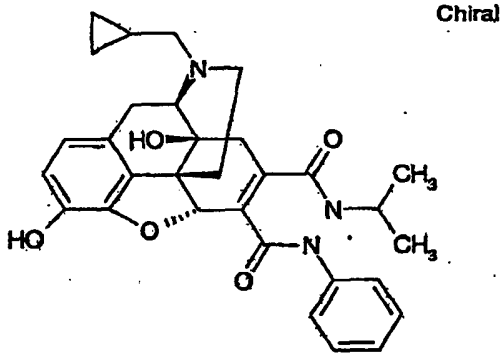
[Table 39]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-152		m/z 494 $[M+H]^+$ 0.56 min	
I-153		m/z 465 $[M+H]^+$ 0.90 min	
I-154		m/z 465 $[M+H]^+$ 0.96 min	
I-155		m/z 544 $[M+H]^+$ 1.00 min	
I-156		m/z 483 $[M+N]^+$ 0.35 min	

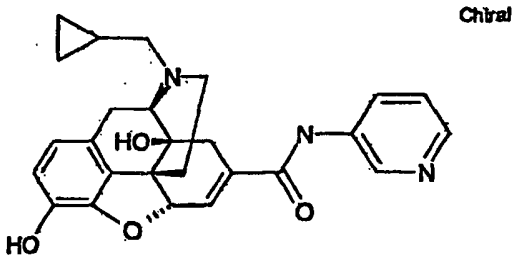
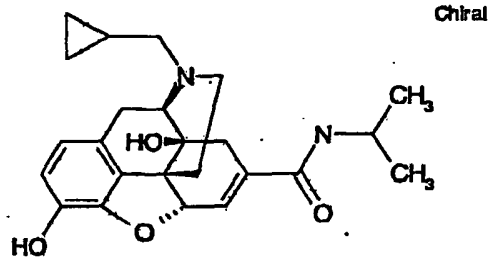
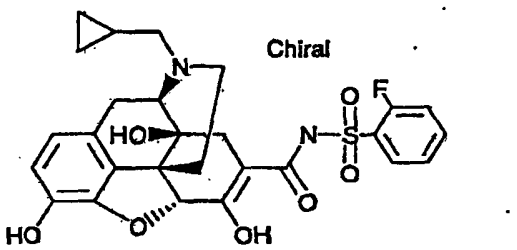
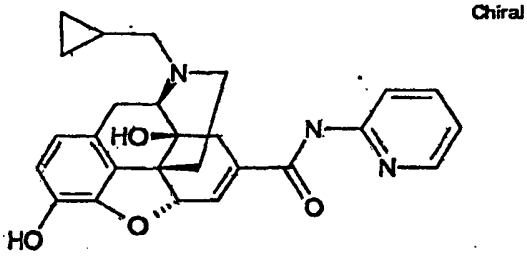
[Table 40]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-157		m/z 510 $[M+H]^+$ 0.96 min	0.11-0.14 (m, 2H), 0.46-0.50 (m, 2H), 0.83 (m, 1H), 0.87 (t, J = 7.2 Hz, 1H, 0.99 (d, J = 4.2 Hz, 3H), 1.01 (d, J = 42 Hz, 3H), 1.08-1.43 (m, 5H), 1.95 (d, J =17.1 Hz, 1H), 2.11-2.65 (m, 7H), 2.96-3.16 (m, 4H), 3.78 (q, J = 7.5 Hz, 1H), 4.78 (brs, 1H), 5.21 (s, 1H), 6.49 (d, J = 8.1 Hz, 1H), 8.55 (d, J = 8.1 Hz, 1H), 7.41 (t, J = 5.1 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 9.02 (brs, 1H)
I-168		m/z 496 $[M+H]^+$ 0.93 min	0.11-0.13 (m, 2H), 0.46-0.50 (m, 2H), 0.85 (m, 1H), 1.01 (d, J = 4.1 Hz, 3H), 1.02 (d, J = 4.2 Hz, 3H), 1.07 (d, J = 4.0 Hz, 3H), 1.09 (d, J = 4.0 Hz, 3H), 1.40 (d J = 11.1 Hz, 1H), 1.95 (d, J = 17.1 Hz, 1H), 2.09-2.63 (m. 7H), 2.98 (d J = 18.1 Hz, 1H), 3.13 (d, J = 5.4 Hz, 1H), 3.82 (q, J = 6.6 Hz, 1H), 3.88 (q, J = 6.9 Hz, 1H), 5.24 (brs, 1H), 5.76 (s, 1H), 6.50 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 6.9 Hz, 1H), 9.01 (brs, 1H)
I-159		m/z 536 $[M+H]^+$ 0.95 min	0.11-0.13 (m, 2H), 0.46-0.50 (m, 2H), 0.83 (m, 1H), 0.99 (d, J = 3.0 Hz, 3H), 1.01 (d, J = 3.0 Hz, 3H), 1.15-1.38 (m, 6H), 1.40 (d, J = 11.1 Hz, 1H), 1.52-1.80 (m, 4H), 1.97 (d, J = 17.1 Hz, 1H), 2.09-2.65 (m, 7H), 2.98 (d, J = 18.6 Hz, 1H), 3.13 (d, J = 5.7 Hz, 1H), 3.58 (m, 1H), 3.79 (q, J = 6.9 Hz, 1 H), 5.23 (s, 1H), 6.50 (d, J = 7.8, Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 9.00 (brs, 1H)

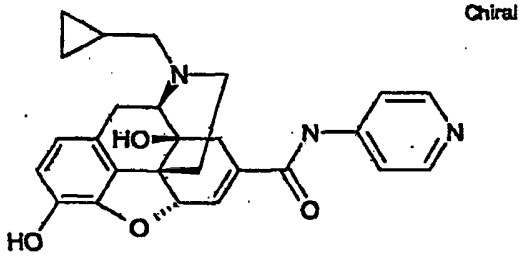
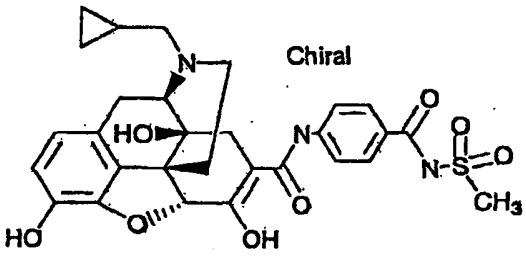
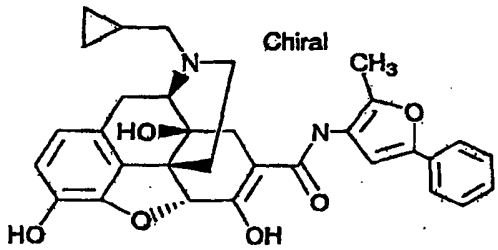
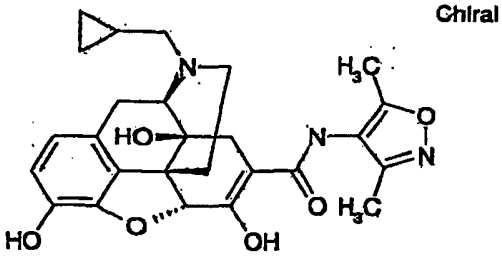
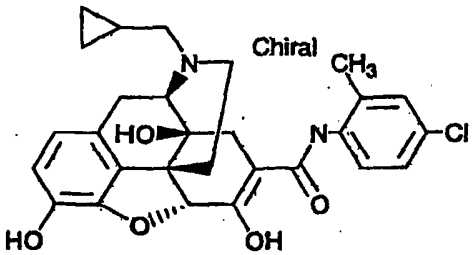
[Table 41]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-160		m/z 522 $[M+H]^+$ 1.04 min	0.12-0.13 (m, 2H), 0.46-0.51 (m, 2H), 0.85 (m, 1 HX 0.99 (d, J = 3.3 Hz, 3H), 1.01 ,(d, J = 3.3 Hz, 3H), 1.15-1.49 (m, 7H), 1.91 (d, J = 16.5 Hz, 1H), 2.08-2.65 (m, 7H), 2.98 (d, J = 17.5 Hz, 1H), 3.12 (d, J = 5.7 Hz, 1H), 3.16-3.34 (m, 4H), 3.79 (q, J = 6.9 Hz, 1H), 4.76 (brs, 1H), 5.01 (s, 1H), 6.54 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 9.01 (brs, 1H)
I-161		m/z 524 $[M+H]^+$ 0.92 min	0.12-0.14 (m, 2H), 0.46-0.51 (m, 2H), 0.86 (m, 1H), 0.99 (d, J = 3.3 Hz, 3H), 1.01 (d, J = 3.3 Hz, 3H), 1.41 (d, J = 11.1 Hz, 1H), 1.95 (d, J = 17.1 Hz, 1H), 2.08-2.67 (m, 11H), 2.98 (d, J = 17.5 Hz, 1H), 3.12 (d, J = 5.7 Hz, 1H), 3.49-3.60 (m, 4H), 3.82 (q, J = 6.9 Hz, 1H), 4.78 (brs, 1H), 5.01 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 9.13 (brs, 1H)
I-162		m/z 530 $[M+H]^+$ 0.94 min	0.13-0.14 (m, 2H), 0.47-0.51 (m, 2H), 0.83 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.44 (d, J = 10.5 Hz, 1H), 2.02 (d, J = 16.8 Hz, 1H), 2.11-2.65 (m, 7H), 3.03 (d, J = 18.6 Hz, 1H), 3.17 (d, J = 5.7 Hz, 1H), 3.58 (m, 1H), 3.74 (q, J = 6.3 Hz, 1H), 4.86 (brs, 1H), 5.39 (s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.1 Hz, 2H), 9.01 (brs, 1H), 9.70 (brs, 1H)

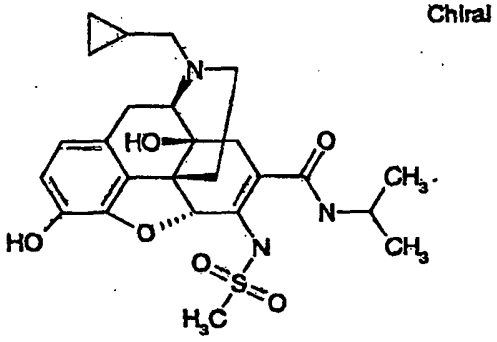
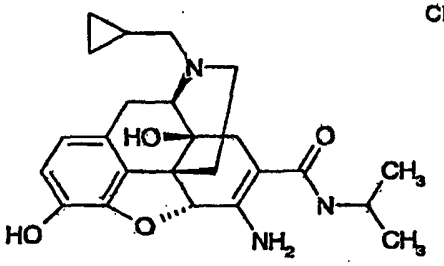
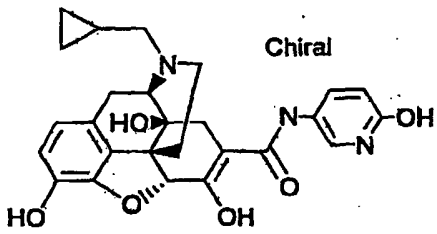
[Table 42]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-163		m/z 445 $[M+H]^+$ 0.83 min	
I-164			0.14-0.22 (m, 2H), 0.48-0.61 (m, 2H), 0.91 (m, 1H), 1.12 (d, J = 6.6 Hz, 6H), 1.53-1.66 (m, 1H), 2.15-2.22 (m, 2H), 2.23-2.30 (m, 2H), 2.35-2.49 (m, 2H), 2.70 (d.d, J = 18.9 & 6.6 Hz, 2H), 3.13 (d, J= 18.9 Hz, 1H), 3.27 (d, J = 6.6Hz, 1H), 3.98 (quintet, J = 6.8 Hz, 1H), 4.99-5.04 (m, 1H), 6.32-6.36 (m, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H).
I-165		m/z 543 $[M+H]^+$ 0.63 min	
I-166		m/z 446 $[M+H]^+$ 0.94 min	

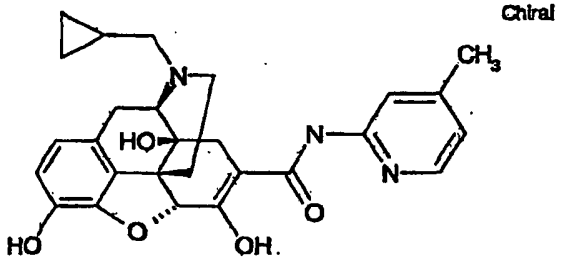
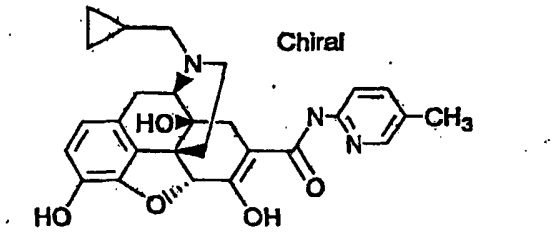
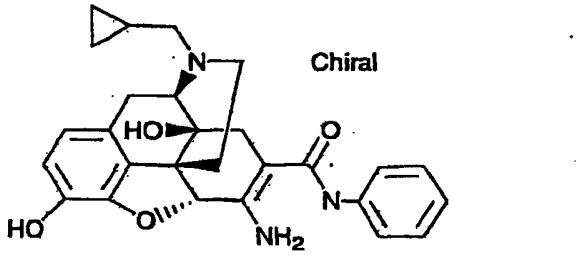
[Table 43]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-167			(CD3OD) d: 0.12-0.22 (m, 2H), 0.48-0.63 (m, 2H), 0.82-1.00 (m, 1H), 1.83 (d, J = 8.1 Hz, 1H), 2.10-2.50 (m, 7H), 2.72 (d.d, J=18.6 & 6.6Hz, 2H), 3.15 (d, J = 18.6 Hz, 1H), 5.10 (brs, 1H), 6.50-6.65 (m, 3H), 7.67 (d.d, J=4.8&1.5Hz, 1H), 8.36 (d.d, J = 4.8 & 1.5Hz, 1H).
I-168		m/z 582 $[M+H]^+$ 0.90 min	
I-169		m/z 541 $[M+H]^+$ 1.15 min	
I-170		m/z 480 $[M+H]^+$ 0.37 min	
I-171		m/z 509 $[M+H]^+$ 0.75 min	

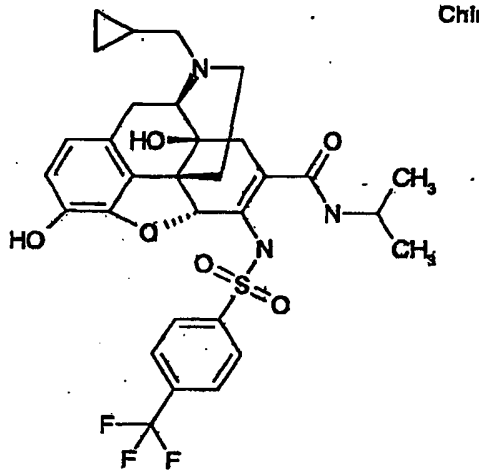
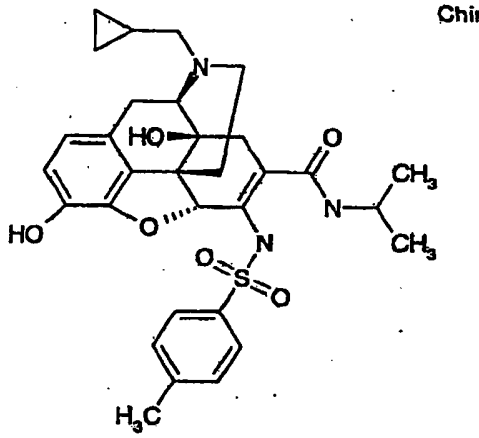
[Table 44]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-172		m/z 505 $[M+H]^+$ 0.97 min	0.11-0.13 (m, 2H), 0.46-0.50 (m, 2H), 0.84 (m, 1H), 0.98 (d, J = 3.1 Hz, 3H), 1.01 (d, J = 3.1 Hz, 3H), 1.37 (d, J = 10.8 Hz, 1H), 2.08 (d, J = 17.4 Hz, 1H). 2.11-2.24 (m, 2H), 2.35 (d, J = 6.6 Hz, 1H), 2.51-2.63 (m, 2H), 3.01 (d, J = 18.3 Hz, 1H), 3.13 (d, J = 5.7 Hz, 1H), 3.54 (s, 3H), 3.86 (q, J = 7.2 Hz, 1H), 4.79 (brs, 1H), 4.98 (brs, 1H), 5.76 (s, 1H), 6.54 (d, J = 7.8 Hz, 1H), 8.59 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 9.16 (brs, 1H)
I-173		m/z 426 $[M+H]^+$ 0.90 min	0.12-0.14 (m, 2H), 0.46-0.52 (m, 2H), 0.85 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 8.6 Hz, 3H), 1.38 (d, J = 10.2 Hz, 1H), 1.86 (d, J = 15.0 Hz, 1H), 2.02 (d, J = 15.0 Hz, 1H), 2.10-2.17 (m, 2H), 2.28 (dd, J = 6.9, 6.9 Hz, 1H), 2.43 (dd, J = 6.9. 8.4 Hz, 1H), 2.54-2.62 (m, 2H), 3.01 (d, J = 18.3 Hz, 1H), 3.17 (d, J = 5.7 Hz, 1H), 3.58 (m, 1H), 3.88 (q, J = 7.2 Hz, 1H), 4.62 (brs, 1H), 4.68 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 8.55 (d, J = 8.1 Hz, 1H), 6.94 (brs, 1H), 9.06 (brs, 1H)
I-174			(CD3OD) d : 0.10-0.25 (m, 2H), 0.48-0.63 (m, 2H), 0.83-1.00 (m, 1H), 1.55 (d, J = 8.1 Hz, 1H), 2.01 (d, J=15.6Hz, 1H), 2.22-2.57 (m, 6H), 2.70 (d.d, J=18.3 & 7.2Hz, 2H), 3.12 (d, J = 18.3 Hz, 1H), 4.67 (s, 1H), 6.44-6.62 (m, 3H). 7.54 (d.d, J = 9.6 & 3.6Hz, 1H), 8.00 (d, J = 3.6Hz, 1H).

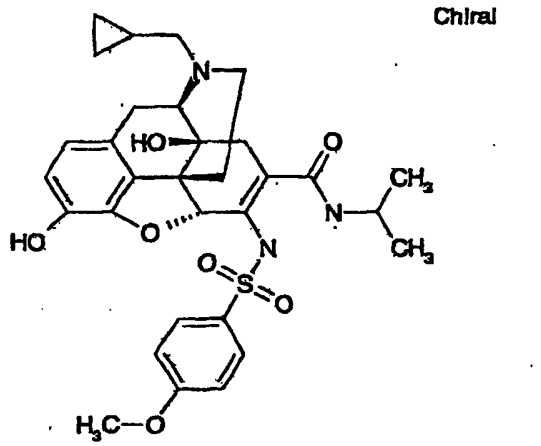
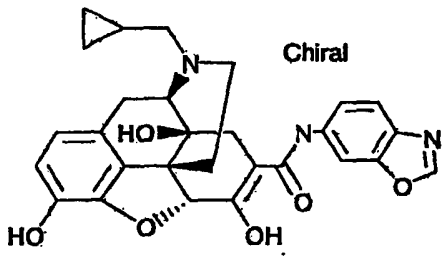
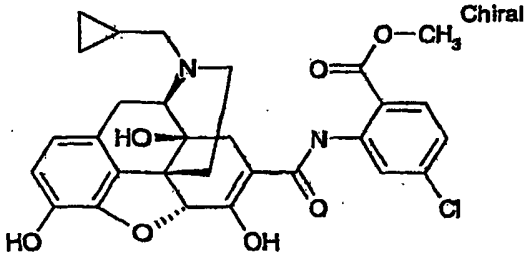
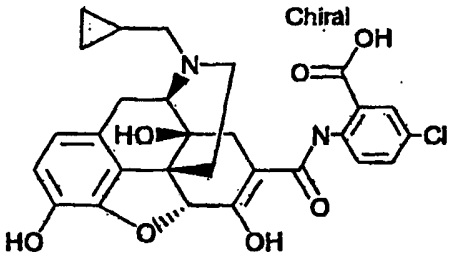
[Table 45]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-175		m/z 458 $[M+H]^+$ 0.86 min	
I-176		ESI : m/z 458 [M+H]+	
I-177		m/z 460 $[M+H]^+$ - 1.20 min	0.13-0.17 (m. 2H), 0.47-0.50 (m, 2H), 0.87 (m, 1H), 1.41 (d, J =10.5 Hz, 1H), 2.07 (d, J = 15.0 Hz, 1H), 2.10-2.25 (m, 2H), 2.32 (dd, J = 5.7, 6.9 Hz, 1H), 2.45 (dd, J = 5.7, 6.0 Hz, 1H). 2.63 (dt, J = 6.3, 11.7, 2H), 3.05 (d, J = 18.3 Hz, 1H), 3.19 (d, J = 6.0 Hz, 1H), 4.67 (brs, 1H), 4.75 (s, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 3.8 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H). 8.38 (brs, 1H), 9.07 (brs, 1H)

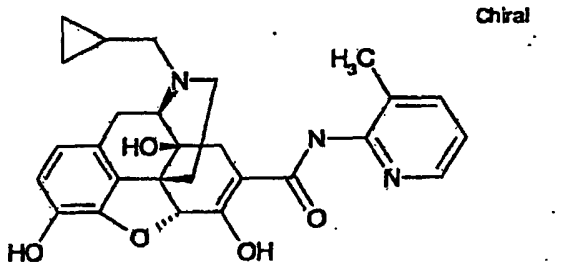
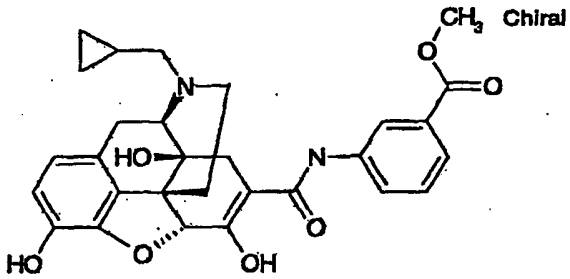
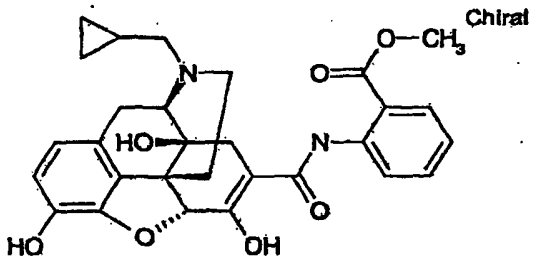
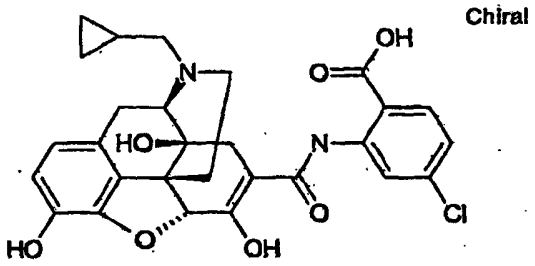
[Table 46]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-178	 Chiral	m/z 636 $[M+H]^+$ 1.11 min	0.11-0.13 (m, 2H), 0.46-0.51 (m, 2H), 0.86 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H), 1.46 (d, J = 11.1 Hz, 1H), 1.87 (d, J = 18.0 Hz, 1H), 2.11-2.63 (m, 7H), 2.25 (s, 3H) 3.03 (d, J = 17.4 Hz, 1H), 3.18 (brs, 1H), 3.84 (q, J = 7.2 Hz, 1H), 4.71 (brs, 1H), 5.45 (brs, 1H), 6.50 (brs, 1H), 6.57 (brs, 1H), 7.81-8.19 (m, 4H), 9.03 (brs, 1H), 10.7 (brs, 1H), 12.7 (brs, 1H)
I-179	 Chiral	m/z 581 $[M+H]^+$ 1.06 min	0.11-0.13 (m, 2H). 0.46-0.51 (m, 2H), 0.86 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H), 1.46 (d, J = 11.1 Hz, 1H), 1.87 (d, J = 18.0 Hz, 1H), 2.09 (s, 3H), 2.11-2.63 (m, 7H), 3.03 (d, J = 17.4 Hz, 1H), 3,18 (brs, 1H), 3.84 (q, J = 7.2 Hz, 1H), 4.69 (brs, 1H), 5.45 (brs, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.55 (d, J = 72 Hz, 1H), 7.33 (brs, J = 5.4 Hz, 2H), 7.54 (brs, 1H), 7.74 (d, J = 7.5 Hz, 2H), 9.11 (brs, 1H), 12.3 (brs, 1H)

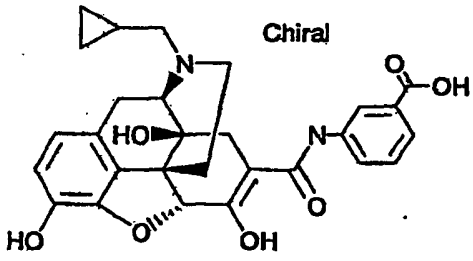
[Table 471

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-180		m/z 597 $[M+H]^+$ 1.03 min	0.11-0.13 (m, 2H), 0.46-0.51 (m, 2H), 0.85 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H), 1.46 (d, J = 9.9 Hz, 1H), 1.87 (d, J = 17.4 Hz, 1H), 2.11-2.62 (m, 7H), 3.01 (d, J = 17.7 Hz, 1H), 3.15 (d, J = 4.8 Hz, 1H), 3.82 (s, 3H), 3.83 (q, J = 5.4 Hz, 1H); 4.67 (brs, 1H), 5.44 (s, 1H), 6.49 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.52 (brs, J = 9.3 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 9.12 (brs, 1H), 12.2 (brs, 1H)
I-181		m/z 502 $[M+H]^+$ 0.35 min	
I-182		m/z 553 $[M+H]^+$ 0.68 min	
I-183		m/z 539 $[M+H]^+$ FAB-MS	

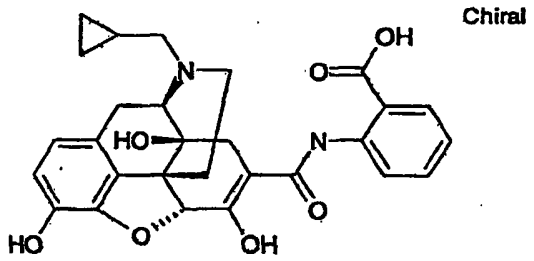
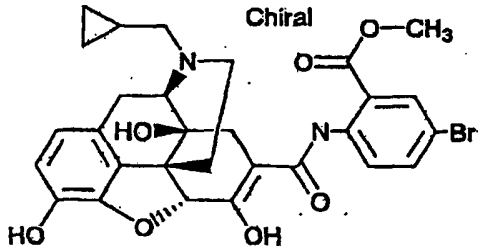
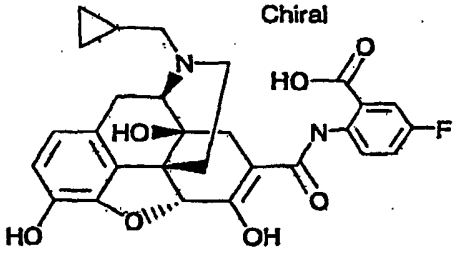
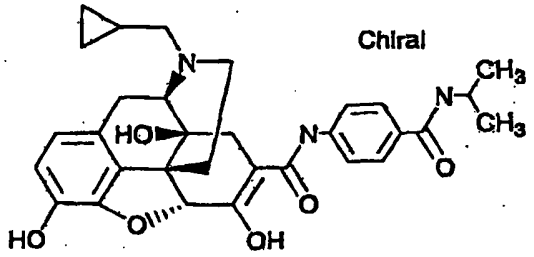
[Table 48]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-184		m/z 458 $[M+H]^+$ 0.97 min	
I-185		m/z 519 $[M+H]^+$ 0.43 min	
I-186		m/z 519 $[M+H]^+$ 1.67 min**	
I-187		m/z 539 $[M+H]^+$ 0.50 min	

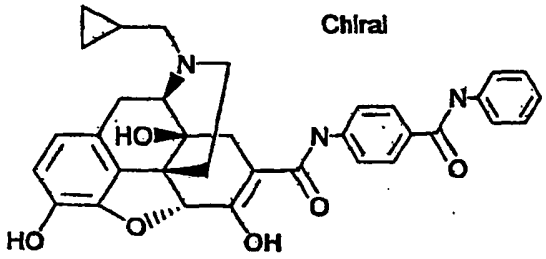
[Table 49]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-188		m/z 505 $[M+H]^+$ 0.35 min	

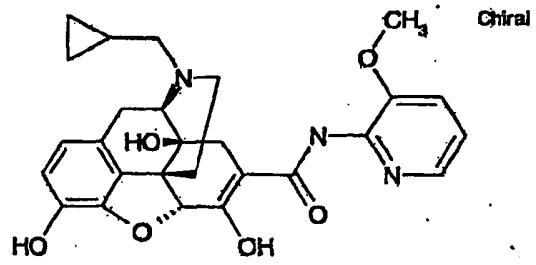
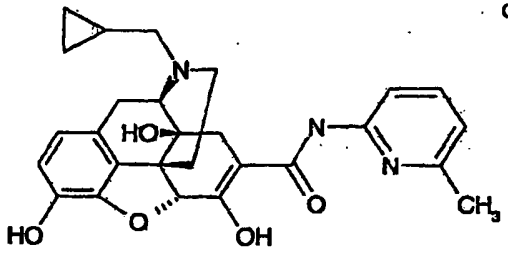
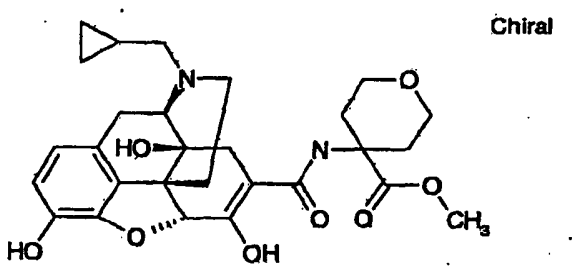
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-189		m/z 505 $[M+H]^+$ 0.42 min	
I-190		m/z 597 $[M+H]^+$ 0.77 min	
I-191		m/z 523 $[M+H]^+$ 1.20 min	
I-192		m/z 546 $[M+H]^+$ 1.00 min	

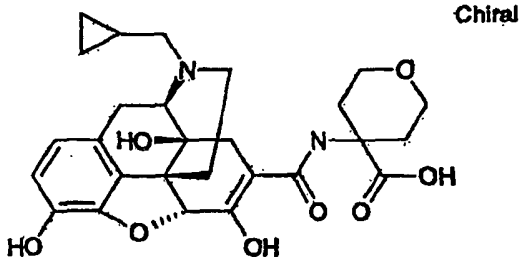
[Table 50]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-193		m/z 580 $[M+H]^+$ 1.09 min	

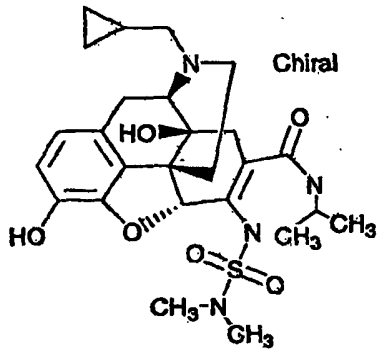
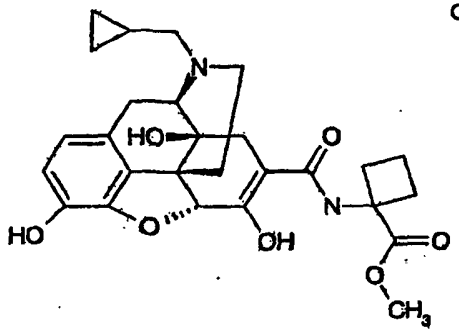
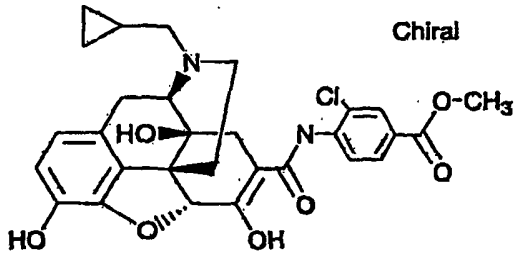
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-194		m/z 474 [M+H]+ 0.88 min	
I-195		m/z 458 [M+H]+ 1.08 min	
I-196			0.12-0.16 (m, 2H), 0.46-0.55 (m, 2H), 0.88 (m, 1H), 1.43 (d, J = 12.4 Hz, 1H), 1.65-2.65 (m, 12H), 2.97-3.70 (m, 6H), 3.59 (s, 3H), 4.74 (s 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 7.68 (brs, 1H), 9.16 (brs, 1H), 13.6 (brs, 1H)

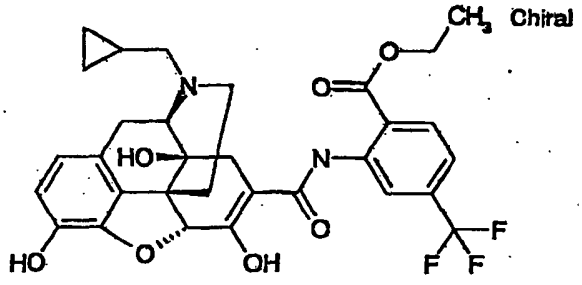
[Table 51]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-197			0.20-0.40 (m, 2H). 0.46-0.65 (m, 2H), 0.97 (m, 1H), 1.54 (d, J = 6.8 Hz, 1H), 1.80-2.10 (m, 3H), 2.31-3.69 (m, 15H), 4.83 (s 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 7.56 (brs, 1H), 9.29 (brs, 1H), 13.6 (brs, 1H)

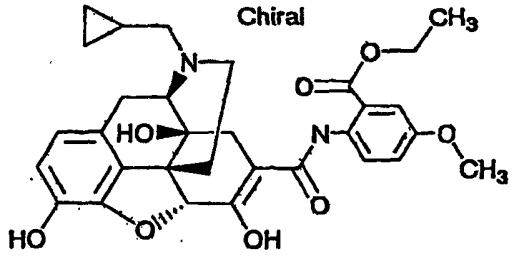
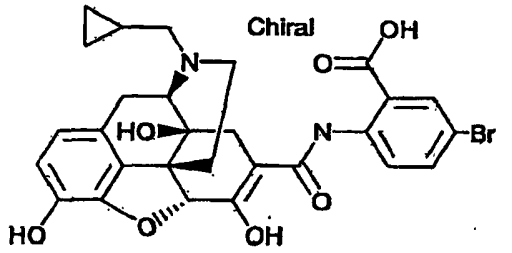
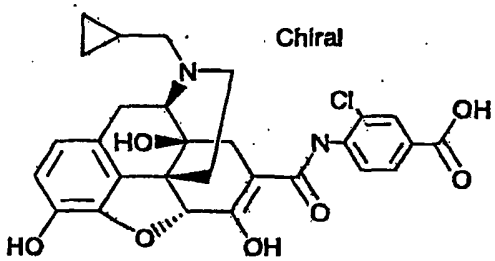
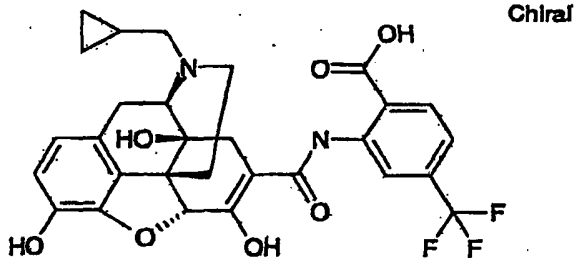
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-198		m/z 533 $[M+H]^+$ 0.95 min	0.11-0.13 (m, 2H), 0.46-0.52 (m, 2H), 0.86 (m, 1H), 1.03 (d, 6.3 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 1.46 (brd, J = 8.4 Hz, 1 H), 1.94 (d, J = 17.7 Hz, 1H), 2.71-2.80 (m, 7H), 2.81 (s, 6H), 3.04 (d, J = 17.1 Hz, 1H), 3.18 (brs, 1H), 3.95 (q, J = 5.4 Hz, 1H), 4.77 (brs, 1H), 5.45 (s, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 7.5 Hz, 1H), 7.64 (brs, 1H), 9.14 (brs, 1H), 12.2 (brs, 1H)
I-199		m/z 497 $[M+H]^+$ 0.97 min	0.13-0.15 (m, 2H), 0.48-0.52 (m, 2H), 0.88 (m, 1H), 1.41 (d, J = 11,4 Hz, 1H), 1.85 (t, J = 7.8 Hz, 2H), 1.93 (d, J = 16.5 Hz, 1H), 2.07-2.62 (m, 11H), 3.05 (d, J = 18.3 Hz, 1H), 3.21 (d, J = 8.0 Hz, 1H), 3.59 (s, 3H), 4.72 (s, 1H), 4.77 (brs, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 8.26 (brs, 1H), 9.15 (brs, 1H), 14.1 (brs, 1H)
I-200		m/z 553 $[M+H]^+$ 0.47 min	

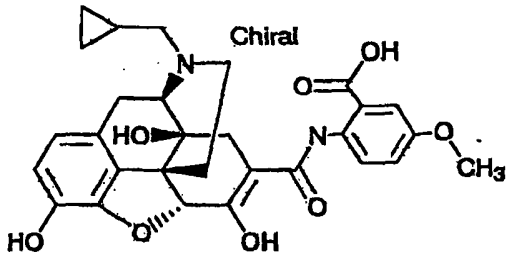
[Table 52]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-201		m/z 601 $[M+H]^+$ 1.01 min	

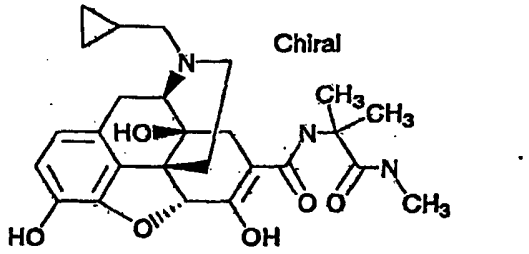
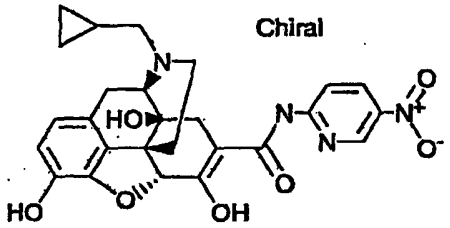
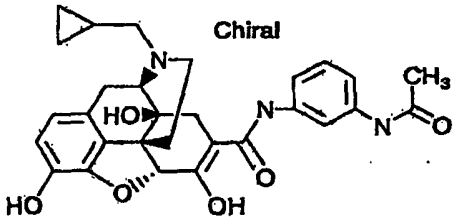
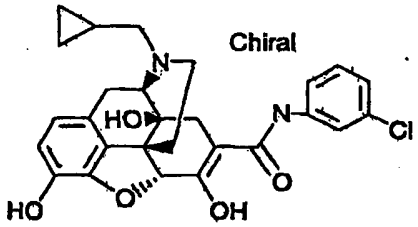
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-202		m/z 563 $[M+H]^+$ 0.58 min	
I-203		m/z 583 $[M+H]^+$ 0.54 min	
I-204		m/z 539 $[M+H]^+$ 0.33 min	
I-205		m/z 573 $[M+H]^+$ 0.62 min	

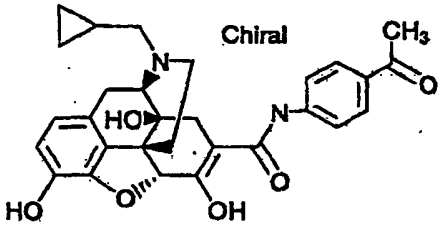
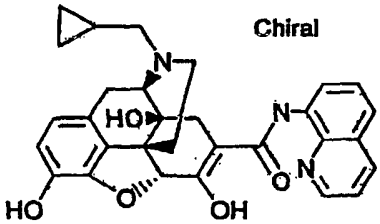
[Table 53]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-206		m/z 535 $[M+H]^+$ 0.41 min	

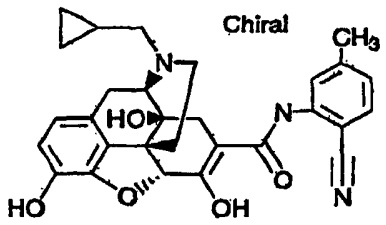
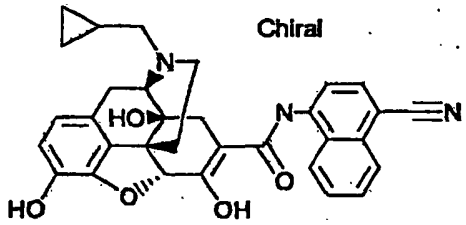
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-207		m/z 484 [M+H]+ 0.32 min	
I-208		m/z 507 [M+H]+ 1.05 min	
I-209		m/z 518 [M+H]+ 1.14 min**	
I-210		m/z 495 [M+H]+ 1.64 min**	

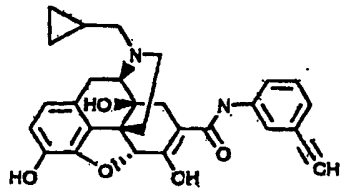
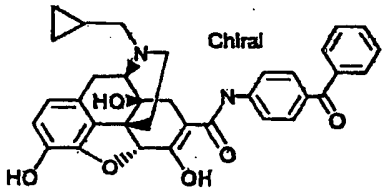
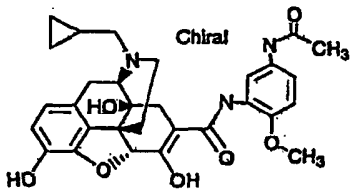
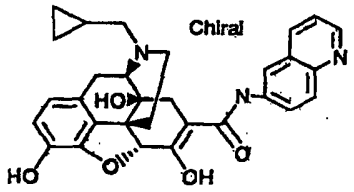
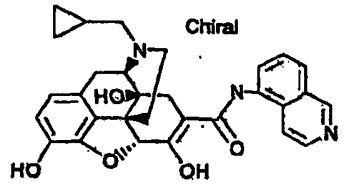
[Table 54]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-271		m/z 503 [M+H]+ 1.33 min**	
I-212		m/z 512 [M+H]+ 1.67 min**	

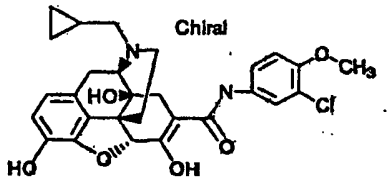
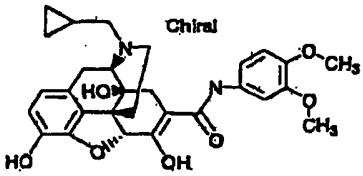
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-213		m/z 500 [M+H]+ 1.41 min**	
I-214		m/z 536 [M+H]+ 1.69 min**	

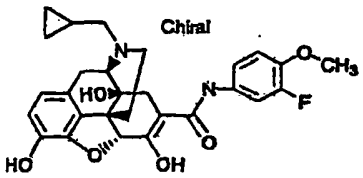
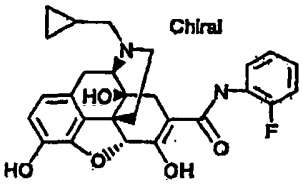
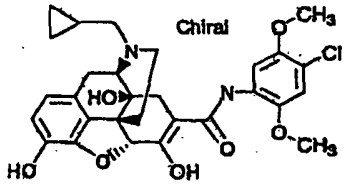
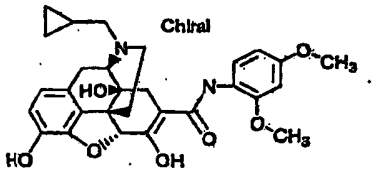
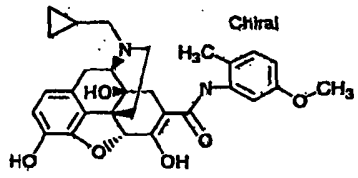
[Table 55]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-215		m/z 485 [M+H]+ 1.60 min**	
I-216		m/z 565 [M+H]+ 1.82 min**	
I-217		m/z 548 [M+H]+ 1.17 min**	
I-218		m/z 512 [M+H]+ 0.95 min**	
I-219		m/z 512 [M+H]+ 1.66 min**	

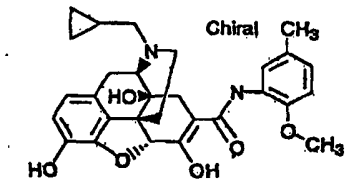
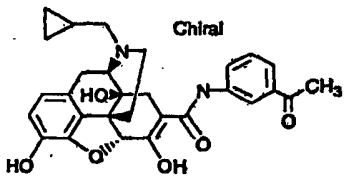
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-220		m/z 525 [M+H]+ 1.60 min**	
I-221		m/z 521 [M+H]+ 1.35 min**	

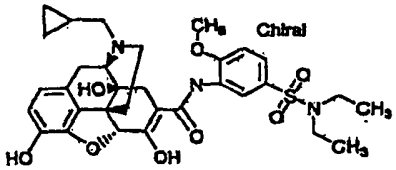
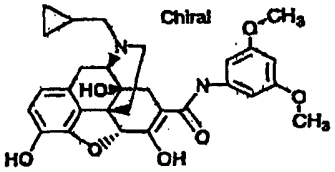
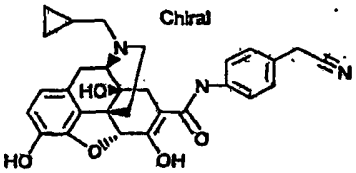
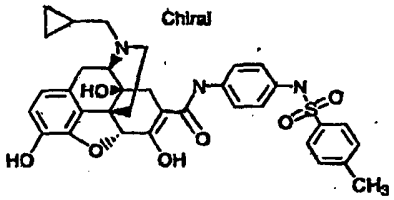
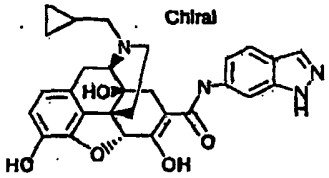
[Table 56]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-222		m/z 508 [M+H]+ 1.57 min**	
I-223		m/z 479 [M+H]+ 1.50 min**	
I-224		m/z 555 [M+H]+ 1.76 min**	
I-225		m/z 519 [M+H]+ 1.67 min**	
I-226		m/z 505 [M+H]+ 1.53 min**	

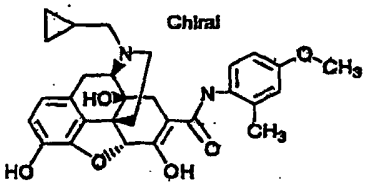
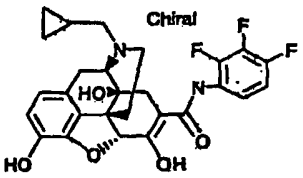
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-227		m/z 505 [M+H]+ 1.64 min**	
I-228		m/z 503 [M+H]+ 1.38 min **	

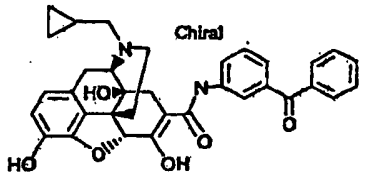
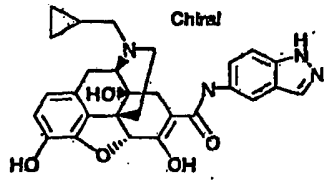
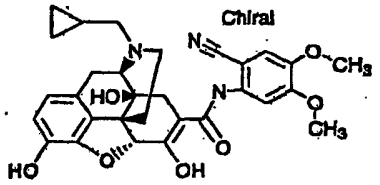
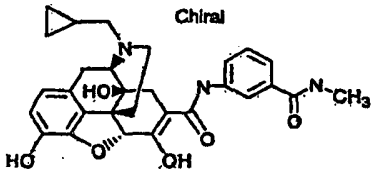
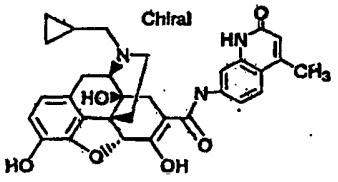
[Table 57]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-229		m/z 826 [M+H]+ 1.74 min**	
I-230		m/z 521 [M+H] 1.56 min**	
I-231		m/z 500 [M+H]+ 1.40 min**	
I-232		m/z 630 [M+H]+ 1.72 min**	
I-233		m/z 501 [M+H]+ 1.25 min**	

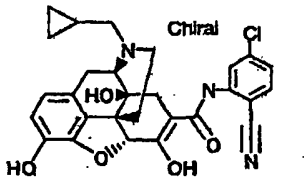
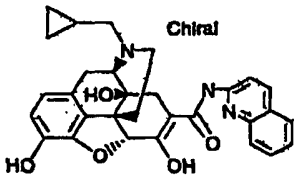
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-234		m/z 505 [M+H]+ 1.46 min**	
I-235		m/z 515 [M+H]+ 1.56 min**	

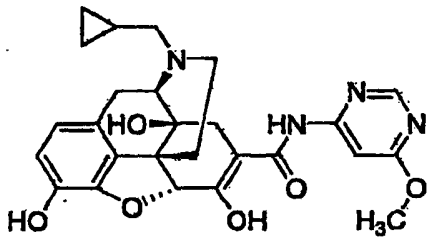
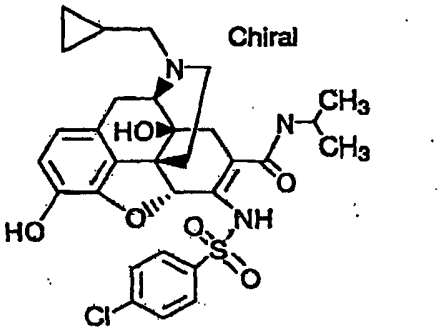
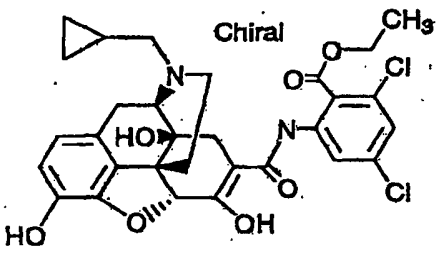
[Table 58]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-236		m/z 565 [M+H]+ 1.77 min**	
I-237		m/z 501 [M+H]+ 1.17 min**	
I-238		m/z 548 [M+H]+ 1.29 min**	
I-239		m/z 518 [M+H]+ 1.21 min**	
I-240		m/z 542 [M+H]+ 1.31 min**	

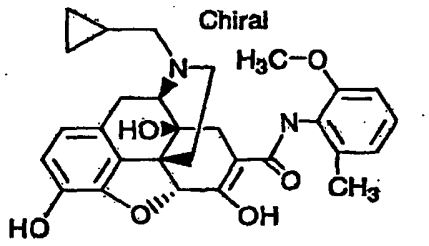
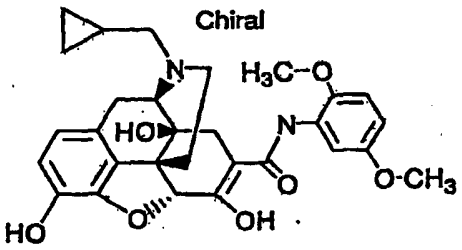
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-241		m/z 520 [M+H]+ 1.50 min**	
I-242			

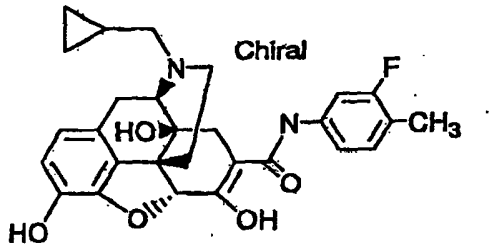
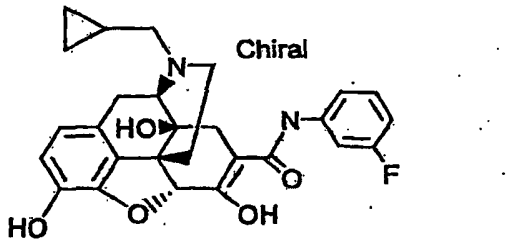
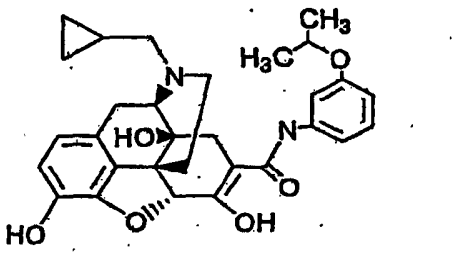
[Table 59]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR(d6-DMSO) δ)
I-243		m/z 493 [M+H]+ 1.05 min	
I-244		m/z 601 [M+H]+ 1.02 min	(m, 2H), 0.48-0.51 (m, 2H), 0.87 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H), 1.48 (d, J = 11.1 Hz, 1H), 1.88 (d, J = 18.0 Hz, 1H), 2.10 (s, 3H), 2.18-2.57 (m, 7H), 3.04 (d, J = 16.8 Hz, 1H), 3.19 (brs, 1H), 3.78 (q, J = 6.9 Hz, 1H), 4.68 (brs, 1H), 5.43 (brs, 1H), 6.49 (d, J = 6.6 Hz, 1H), 6.51 (d, J = 6.6 Hz, 1H), 7.35-7.37 (m, 2H), 7.54 (brs, 1H), 7.85 (d, J = 6.9 Hz, 2H), 9.09 (brs, 1H), 12.4 (brs, 1H)
I-245		m/z 601 [M+H]+ 0.76 min	

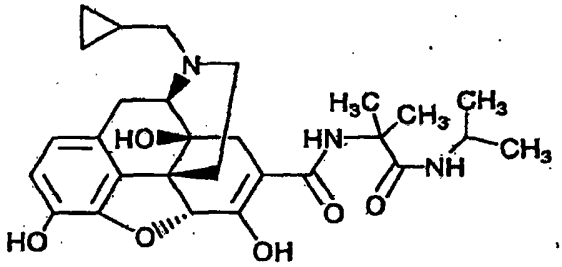
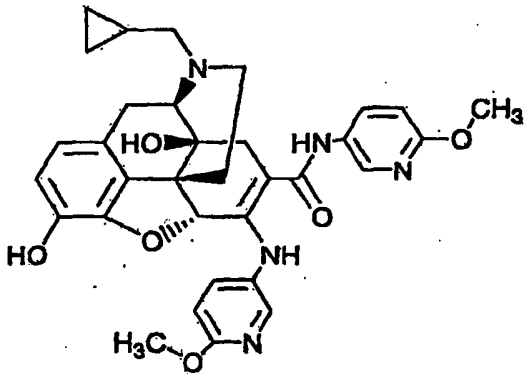
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR(d6-DMSO) δ)
I-246		m/z 505 [M+H]+ 1.38 min **	
I-247		m/z 521 [M+H]+ 1.58 min**	

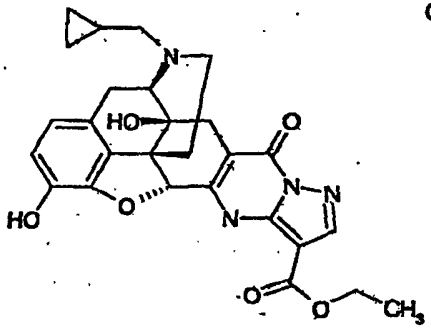
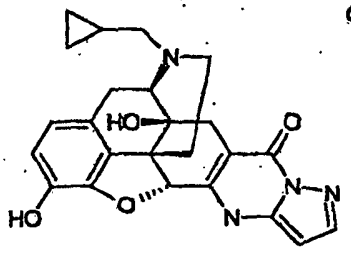
[Table 60]

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-248		m/z 493 [M+H]+ 1.69 min**	
I-249		m/z 479 [M+H]+ 1.55 min**	
I-250		m/z 519 [M+H]+ 1.74 min **	

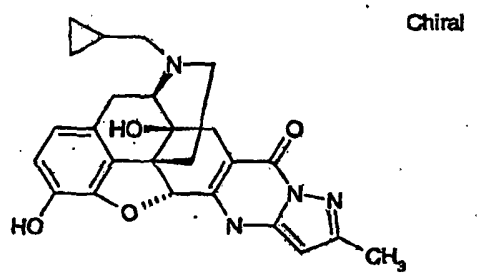
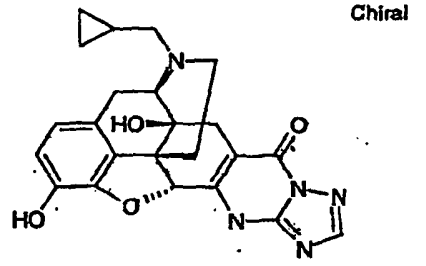
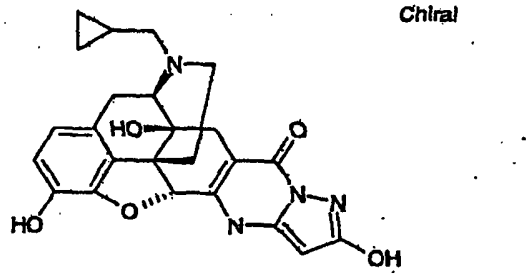
(continued)

Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-251		m/z 512 [M+H]+ 0.38 min	
I-252			0.10-0.15 (m, 2H), 0.34-0.38 (m, 2H), 0.73 (m, 1H), 1.26 (d, J = 9.6 Hz, 1 H), 1.93-2.54 (m, 10H), 2.94 (d, J = 18.4 Hz, 1H), 3.10 (d, J = 6.0 Hz, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 4.58 (s, 1H), 4.84 (s, 1H), 6.42 (d, J = 8.0 Hz, 2H), 6.48 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 9.3 Hz, 2H), 6.69 (d. J = 9.2 Hz, 2H), 7.56 (dd, J = 2.8, 8.8 Hz, 1H), 7.66 (dd, J = 2.8, 8.8 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 20 Hz, 1H), 8.76 (s, 1H), 8.97 (s, 1H), 10.78 (s, 1H).

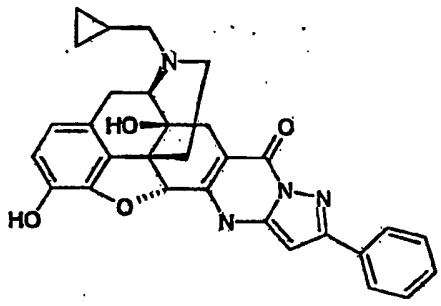
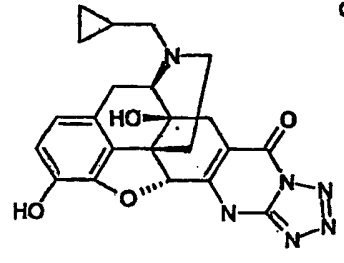
[Table 61]

Compound No.	Chemical structure
I-253	 Chiral
I-254	 Chiral

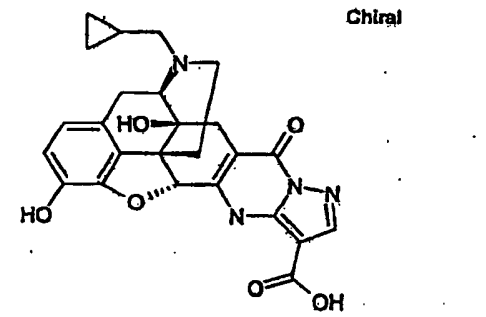
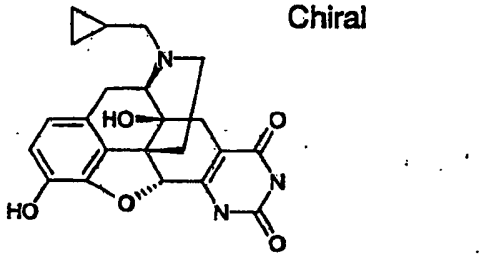
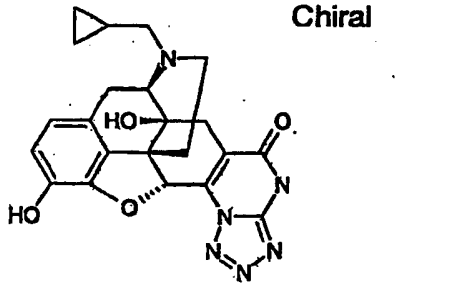
(continued)

Compound No.	Chemical structure
I-255	
I-256	
I-257	

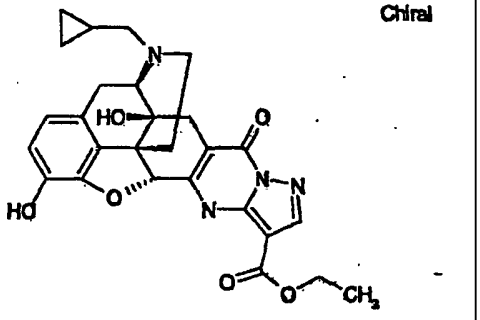
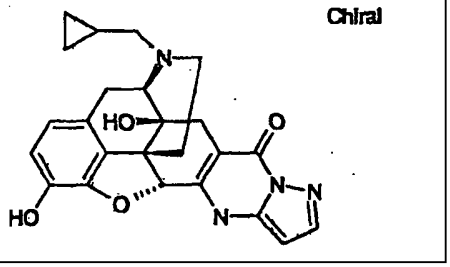
[Table 62]

Compound No.	Chemical structure
I-258	
I-259	

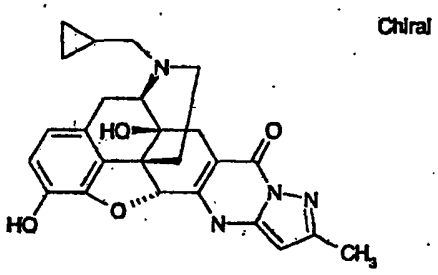
(continued)

Compound No.	Chemical structure
I-260	
I-261	
I-262	

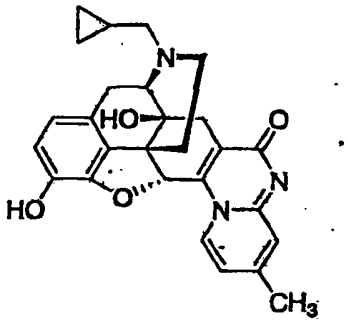
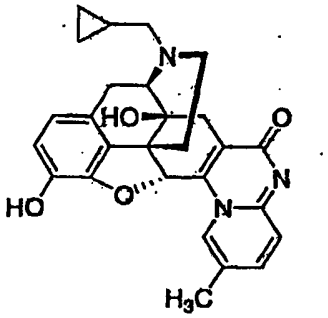
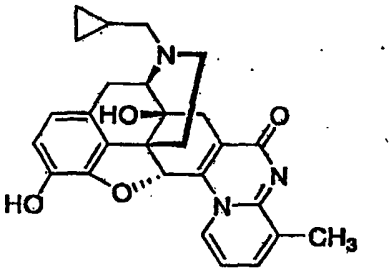
[Table 63]

Compound No.	Chemical structure
I-253	
I-254	

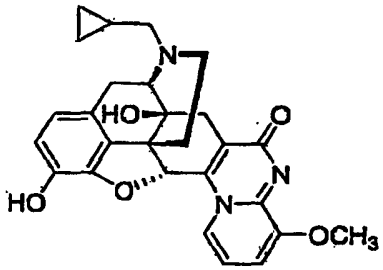
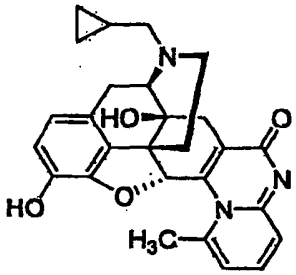
(continued)

Compound No.	Chemical structure
I-255	

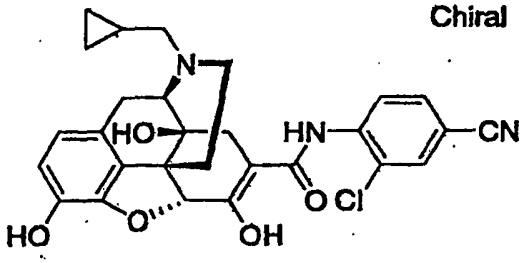
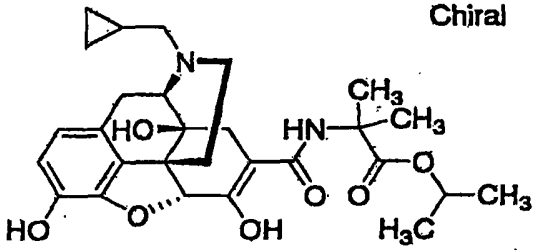
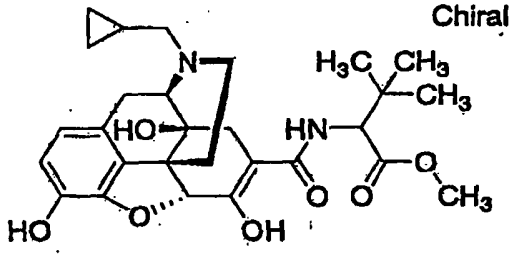
[Table 64]

Compound No.	Chemical structure	
I-266		m/z 457.91 [M+H]+0.97min
I-267		m/z 457.91 [M+H]+0.62min
I-268		m/z 457.91 [M+H]+0.87min

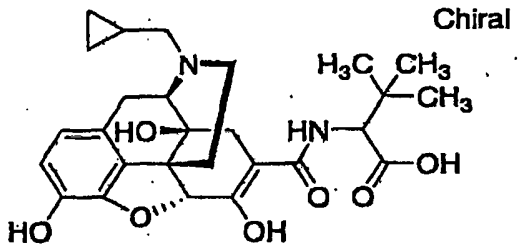
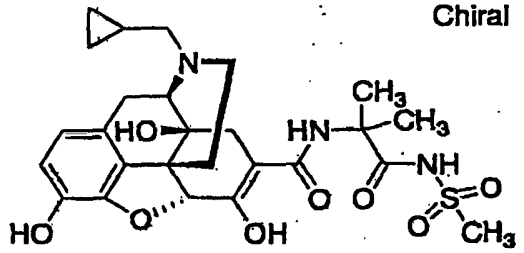
(continued)

Compound No.	Chemical structure	
I-269		m/z 473.91 [M+H]+0.69
I-270		m/z 457.91 [M+H]+0.97min

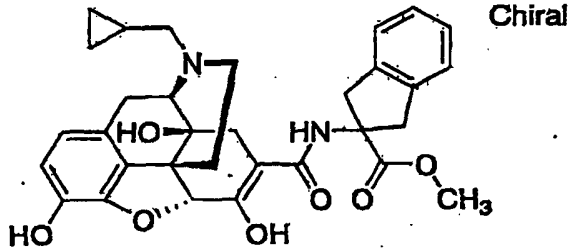
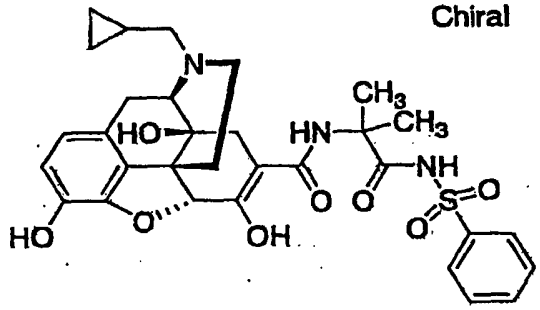
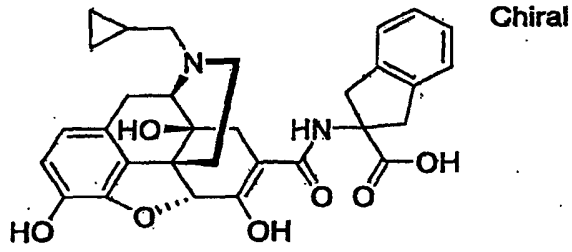
[Table 65]

Compound No.	Chemical structure	LC/MS*1
I-271		m/z 520 [M+H]+ 1.63 min**
I-272		m/z 513 [M+H]+ 0.45 min
I-273		m/z 513 [M+H]+ 0.38 min

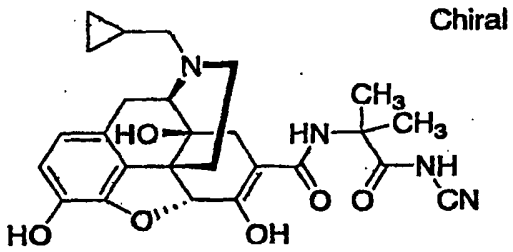
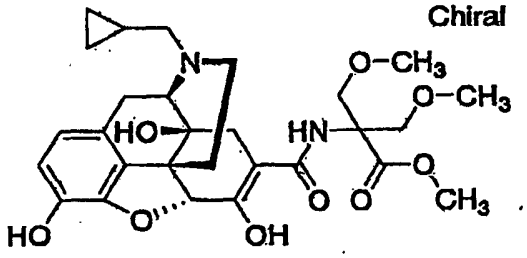
(continued)

Compound No.	Chemical structure	LC/MS*1
I-274		m/z 499 [M+H]+ 0.38 min
I-275		m/z 548 [M+H]+0.38 min

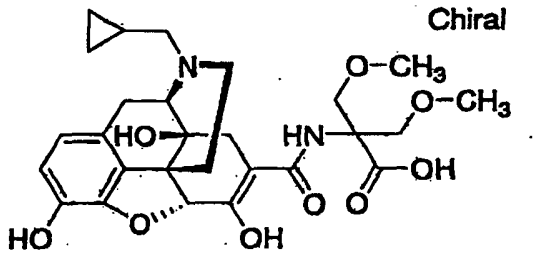
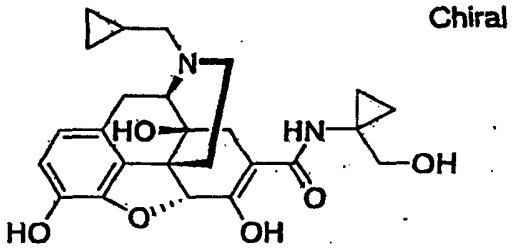
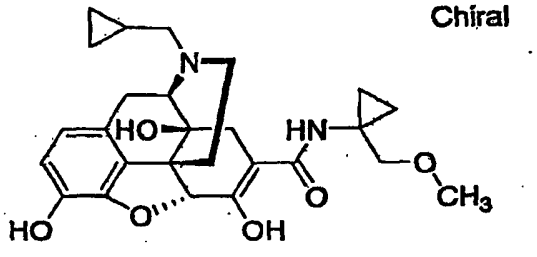
[Table 66]

Compound No.	Chemical structure	LC/MS*1
I-276		m/z 559 [M+H]+ 0.53 min
I-277		m/z 610 [M+H]+ 0.46 min
I-278		m/z 545 [M+H]+ 0.38 min

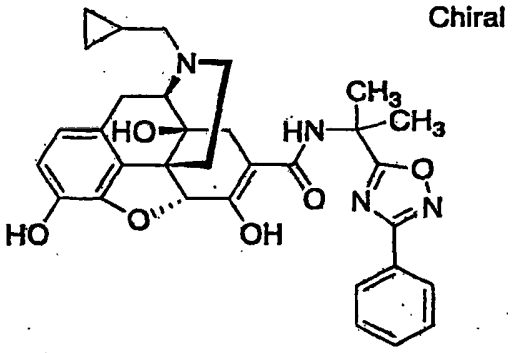
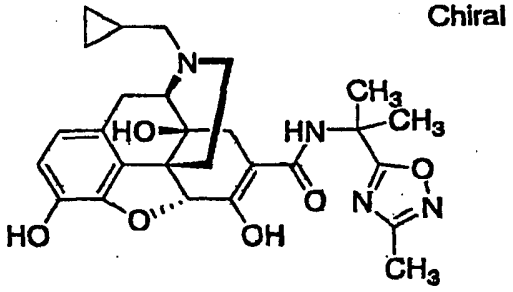
(continued)

Compound No.	Chemical structure	LC/MS*1
I-279		m/z 495 [M+H]+ 0.31 min
I-280		m/z 545 [M+H]+ 0.97min

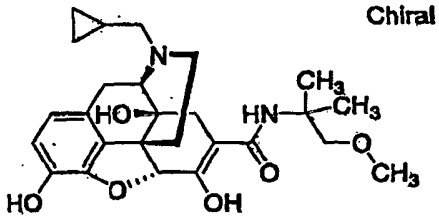
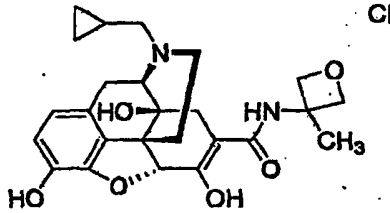
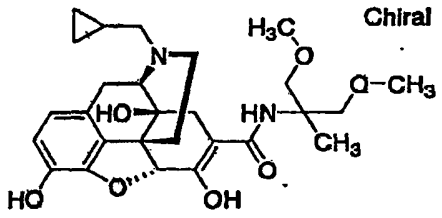
[Table 67]

Compound No.	Chemical structure	LC/MS*1
I-281		m/z 531 [M+H]+ 0.92min
I-282		m/z 455 [M+H]+ 0.87min
I-283		m/z 469 [M+H]+ 0.94min

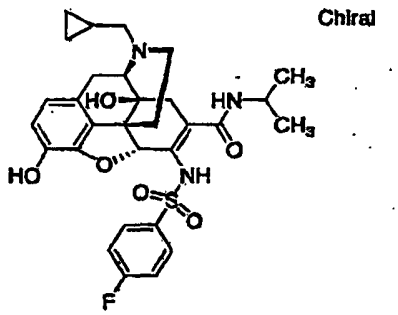
(continued)

Compound No.	Chemical structure	LC/MS*1
I-284		m/z 571 [M+H]+ 0.68 min
I-285		m/z 509 [M+H]+ 0.32 min

[Table 68]

Compound No.	Chemical structure	LC/MS*1
I-286		m/z 471 [M+H]+ 0.32 min
I-287		m/z 455 [M+H]+ 0.90min
I-288		m/z 501 [M+H]+ 0.32 min

(continued)

Compound No.	Chemical structure	LC/MS*1
I-289		m/z 584 [M+H]+ 0.46 min

(LC/MS conditions of measurement)*1:
Column: Chromolith Flash ROD RP-18e, 25X4.6mmLD.
Flow Rate: 2ml/min
UV Detector: 280nm
Solvent System: [A]=H20_0.05%HCOOH
[B]=MeOH_0.05%HCOOH
Gradient: 0min: 90%[A]_10%[B]
0.2min; 90%[A]_10%[B]
1.0min; 10%[A]_90%[B]
1.80min: 10%[A]_90%[B]
Proviso, values with symbol ** follow below conditions of measurement
Column: Phenomenex Luna 5μ C18(2) 100A, size 50 x 4.60mm
Gradient: 10% - 100% Acetnitrile linear during 3.0min at 3.0mL/min

Test Example 1 Binding assay of opioid δ receptor

1) Method of preparing membrane specimen for binding assay

[0120] A rat cerebrum (Slc: SD) which had been stored at -80°C was used. To a cerebrum which had been weighed was added a 20-fold amount of ice-cooled 10 mM Tris-HCl buffer (pH 7.0), and the mixture was homogenized (25000 rpm, 30 seconds) with Histocolon (NITI-ON), and centrifuged at 36600 x g for 20 minutes. To the resulting pellet was added 15ml of the same buffer, and the mixture was treated with Histocolon similarly, and centrifuged. This washing work was performed two times. After centrifugation, to the resulting pellet was added 15 mL of a 50 mM Tris-HCl buffer (pH 7.4), and this was treated with Histocolon, and finally resuspended in a 10-fold amount of the same buffer, which was used as a crude membrane fraction (Life Sci. 48, 111-116, 1991). The prepared membrane specimen was frozen and stored at -80°C, and at an assay, the specimen was rapidly thawed, and diluted to about 900 μg/mL with a 50 mM Tris-HCl butter (pH 7.4) after the centrifugation and Histocolon treatment, and was used in an experiment. For measuring a protein concentration of the membrane specimen, Micro BCA Protein Assay Kit (PIERCE) was used.

2) Method of δ receptor biding assay and data analysis

[0121] To a solution of 10 μl of the test compound diluted at 10-fold stage was added 10 μl of final 3nM [^{3}H]-DADLE (51.5 Ci/mmol: PerkinElmer) as a ligand. Into a tube was placed 480 μl of a rat cerebrum membrane fraction to which 100 mM choline chloride, 3 mM $MnCl_2$ and 100 nM DAMGO had been added, and this was incubated at 25°C for 2 hours. After incubation, this was suction-filtered with a Whatman GF/C filter which had been pre-treated with 0.5% polyethyleneimine, and washed with 2.5 mL of an ice-cooled 10mM Tris-HCl buffer (pH7.4) four times. After washing, the filter was transferred to a mini vial for liquid scintillation counter, 5 mL of a scintillator (Cleasol I) was added, this was allowed to stand overnight, and the radioactivity was measured for 3 minutes with a liquid scintillation counter Tri-Carb 2200CA (PACKARD). DMSO was used for total binding (Total bound: TB) for data analysis, and 20 μM levallorphan was used for non-specific binding (Non-specific bound: NB), and a Ki value of the test compound was calculated using a KD value (2.93 nM) obtained in advance by Scatchard plot analysis.

[0122] Results are shown in Table 69.

[Table 69]

test compound	Ki (nM)
I-3	8.76
I-4	7.38
I-7	7.4
I-10	19.92
I-13	5.02
I-30	5.34
I-39	41.8
I-49	3.99
I-92	5.23
I-118	27.65
I-133	9.85
I-135	9.76
I-145	13.87
I-188	3.01
I-199	12.77
I-208	13.28
I-229	5.9
I-240	11.5
I-243	5.2
I-244	0.56
I-267	41.46
I-283	3.73
I-284	0.91
I-285	5.77
I-286	2.46
I-288	5.36
I-289	0.47

[0123] From the above results, it is seen that compound (I) has an affnity for an opioid δ receptor.

Test Example 2 Bindind assay to opioid μ receptor

1) Method of preparing membrane specimen for binding assay

[0124] A rat cerebrum (Slc: SD) which had been stored at -80°C was used. To a cerebrum which had been weighed was added a 20-fold amount of ice-cooled 10 mM Tris-HCl buffer (pH 7.0), the mixture was homogenized (25000 rpm, 30 seconds) with Histocolon (NITI-ON), and centrifuged at 36600 x g for 20 minutes. To the resulting pellet was added 15ml of the same buffer, and the mixture was treated with Histocolon similarly, and centrifuged. This washing work was performed two times. After centrifugation, to the resulting pellet was added 15 mL of a 50 mM Tris-HCl buffer (pH 7.4), this was treated with Histocolon, and this was finally resuspended in a 10-fold amount of the same buffer, which was used as a crude membrane fraction (Life Sci. 48, 111-116, 1991). The prepared membrane specimen was frozen and stored at =80°C, and at a test, the specimen was rapidly thawed, and diluted to about 900 μg/mL with a 50 mM Tris-

HCl bluffer (pH 7.4) after the centrifugation and Histocolon treatment, and was used in an experiment. For measuring a protein concentration of the membrane specimen, Micro BCA Protein Assay Kit (PIERCE) was used.

2) Method of μ preceptor binding assay and data analysis.

[0125] To a solution of 10 μl of the test compound diluted at 10-fold stage diluted test compound was added 10 μl of final 2nM [^{3}H]-DAMGO (51.6 Ci/mmol: PerkinElmer) as a ligand, further, 480 μl of a rat cerebrum membrane fraction was placed into a tube, and this was incubated at 25°C for 2 hours. After incubation, this was suction-filtered with a Whatman GF/C filter which had beenpre-treated with 0.5% polyethyleneimine, and washed with 2.5mL of an ice-cooled 10mM Tris-HCl buffer (pH 7.4) four times. After washing, the filter was transferred to a mini vial for liquid scintillation counter, 5mL of a scintillator (Cleasol 1) was added, and this was allowed to stand overnight, and the radioactivity was measured for 3 minutes with a liquid scintillation counter Tri-Carb 2200CA (PACKARD). DMSO was used for total binding (Total bound: TB) for data analysis, and 20 μM levallorphan was used for non-specific binding (Non-specific bound: NB), and a Ki value of the test compound was calculated using a KD value (1.72nM) obtained in advance by Scatchard plot analysis (Anal.Biochem. 107(1), 220-239, 1980).

[0126] Results are shown in Table 70.

[Table 70]

test compound	Ki (nM)
I-4	5.18
I-10	4.05
I-39	0.33
I-49	16.49
I-118	2.29
I-122	2.7
I-123	1.68
I-124	3.9
I-133	4.99
I-135	1.58
I-138	15.53
I-145	28.09
I-188	17.27
I-199	9.45
I-208	5.89
I-229	1.3
I-240	6.85
I-243	5.28
I-244	11.02
I-267	0.84
I-283	20.14
I-284	1.13
I-285	7.29
I-286	13.98
I-288	14.38
I-289	12.95

Test Example 3 Mouse carbon powder transport assay

1) Preparation of test diet (carbon powder)

[0127] Using a 10 w/v% arabic gum aqueous solution, a 5 w/v% active carbon solution was prepared, which was used as a test diet.

2) Animal

[0128] A ddY line male mouse (5 to 6 weeks old) was used. The mouse was fasted from about 20 or more hours before assay initiation, and water was given ad lib.

3) Test compound and medium

[0129] The test compound was dissolved in a solvent (DMAA/Solutol/5% meglumine= 15/15/70).
DMAA: N,N-dimethylacetamide
Solutol: Solutol (registered trademark) HS15
Meglumine: D(-)-N-methylglucamine

[0130] Morphine hydrochloride was dissolved in a physiological saline. The test compound, the above solvent and morphine were all administered at a liquid amount of 10 mL/kg.

4) Assay method

[0131] The test comppund 3 mg/kg (test compound administration group) or the solvent (solvent administration group) were subcutaneously administered and, after 15 minutes, amount of 3 mg/kg of morphine was administered to all groups. As a control group, the solvent was subcutaneously administered and, after 15 minutes, a physiological saline was administered.

[0132] The test diet 10 mL/kg was orally administered at 15 minutes after administration of morphine. At thirty minutes after administration of the test diet (60 minutes after administration of the test substance), all mice were isolated from esophagus to an ileocecal part near a stomach cardia part. A distance from pyloric part of the stomach to an ileocecal part (full length of small intestine) and a distance until a carbon powder reaching front part (carbon powder movement distance) were measured. The antagonistic activity on the carbon powder transport of inhibitory activity by morphine was calculated as MPE (%) using the following equation. Results are shown in Table 71.

$$\text{Transport rate (\%)} = (\text{carbon powder movement distance}) / \text{full length of small intestine (cm)} \times 100$$

$$\text{M.P.E.(\%)} = \{(\text{small intestine transport rate (\%) of each individual of test compound administration group} - \text{average small intestine transport rate (\%) of solvent administration group}) / (\text{average small intestine transport rate (\%) of control group} - \text{average small intestine transport rate (\%) of solvent administration group})\} \times 100$$

[Table 71]

test compound	M.P.E. (%)
I-39	52

(continued)

test compound	M.P.E. (%)
I-49	80
I-118	55.6
I-122	31.5
I-123	44.1
I-124	46.6
I-133	106.9
I-135	59.7
I-138	55.8
I-145	60.2
I-188	74.6
I-199	62.8
I-208	81.2
I-229	39.7
I-240	36.3
I-243	52.6
I-244	71.6
I-267	60
I-283	63.7
I-284	79.6.
I-285	82.5
I-286	70.6
I-288	101.3
I-289	67

Formulation Example 1

[0133] A granule containing the following ingredients is prepared.

Ingredient	Compound represented by formula (I)	10 mg
	Lactose	700 mg
	Corn starch	274 mg
	HPC-L	16 mg
		1000 mg

[0134] The compound represented by the formula (I) and lactose are passed through a 60 mesh sieve. Corn starch is passed through a 120 mesh sieve. These are mixed with a V-type mixer. To a mixed powder is added a HPC-L (lower viscosity hydroxypropylcellulose) aqueous solution, the materials are kneaded, granulated (extrusion granulation, pore diameter 0.5 to 1 mm), and dried. The resulting dry granule is passed through a sieve using a vibration sieve (12/60 mesh) to obtain a granule.

Formulation Example 2

[0135] A granule for filling into a capsule containing the following ingredients is prepared.

Ingredient	Compound represented by formula (I)	15 mg
	Lactose	90 mg
	Corn starch	42 mg
	HPC-L	3 mg
		150 mg

[0136] The compound represented by the formula (I) and lactose are passed through a 60 mesh sieve. Corn starch is passed through a 120 mesh sieve. These are mixed, to a mixed powder is added a HPC-L solution, the materials are kneaded, granulated, and dried. The resulting dry granule is size-adjusted, 150 mg of which is filled into a No.4 hard gelatin capsule.

Formulation Example 3

[0137] A tablet containing the following ingredients is prepared.

Ingredient	Compound represented by the formula (I)	10 mg
	Lactose	90 mg
	Microcrystalline cellulose	30 mg
	CMC-Na	15 mg
	Magnesium stearate	5 mg
		150 mg

[0138] The compound represented by the formula (I), lactose, microcrystallinecellulose, CMC-NA (carboxymethylcellulose sodium salt) are passed through a 60 mesh sieve, and mixed. Into a mixed powder is mixed magnesium stearate to obtain a mixed powder for tabletting. The present mixed powder is compressed to obtain 150 mg of a tablet.

Formulation Example 4

[0139] The following ingredients are warmed, mixed, and sterilized to obtain an injectable.

Ingredient	Compound represented by the formula (I)	3 mg
	Noniouic surfactant	15 mg
	Purified water for injection	1 ml

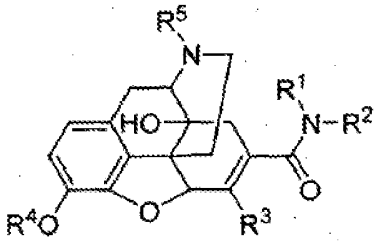
[Industrial applicability]

[0140] The present invention is useful as an agent for alleviating a side effect such as emesis, vomiting and/or constipation.

Patentkrav

1. Forbindelse som vist med formlen (I):

[kemisk formel 1]

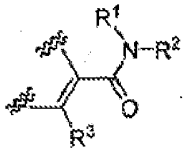


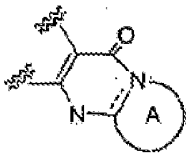
(I)

hvor R^1 og R^2 er hver uafhængigt hydrogen, eventuelt substitueret C1-C10-alkyl, eventuelt substitueret C2-C10-alkenyl, hvor C2-C10-alkenyl er en lige eller forgrenet alkenyl med et carbonantal på 2 til 10 med én eller flere dobbeltbindinger ved en arbitrær position, eventuelt substitueret C2-C10 alkynyl, hvor C2-C10-alkynyl er en lige eller forgrenet alkynyl med et carbonantal på 2 til 10 med én eller flere tredobbelt-bindinger ved en arbitrær position, eventuelt substitueret C1-C10-alkylsulfonyl, eventuelt substitueret acyl, eventuelt substitueret cycloalkyl, hvor cycloalkyl er en carbocyklisk gruppe med et carbonantal på 3 til 10, eventuelt substitueret cycloalkenyl, hvor cycloalkenyl er cycloalkenyl med én eller flere dobbeltbindinger ved en arbitrær position i en ring af cycloalkyl, eventuelt substitueret aryl, en eventuelt substitueret heterocyklisk gruppe, eventuelt substitueret arylsulfonyl, eller R^1 og R^2 er taget sammen med det nitrogenatom til hvilket de er bundet danner en eventuelt substitueret heterocykel;

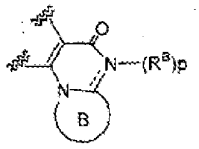
R^3 er hydrogen, hydroxy, eventuelt substitueret C1-C10-alkyl, eventuelt substitueret C2-C10-alkenyl, hvor C2-C10-alkenyl er en lige eller forgrenet-alkenyl med et carbonantal på 2 til 10 med én eller flere dobbeltbindinger ved en arbitrær position, eventuelt substitueret C2-C10 alkynyl, hvor C2-C10-alkynyl er en lige eller forgrenet alkynyl med et carbonantal på 2 til 10 med én eller flere tredobbelt-bindinger ved en arbitrær position, eventuelt substitueret C1-C10 alkoxy, mercapto, eventuelt substitueret C1-C10-alkylthio, eventuelt substitueret amino, eventuelt substitueret carbamoyl, eventuelt substitueret acyl, eventuelt substitueret acyloxy, eventuelt substitueret aryl, eller en eventuelt substitueret heterocyklisk gruppe;

en gruppe som vist med formlen:

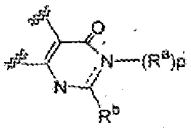




kan være



eller



hvor Ring A og Ring B er hver uafhængigt eventuelt substitueret nitrogen-indeholdende heterocykel eventuelt indeholdende et yderligere nitrogenatom, oxygenatom, og/eller svovlatom i ringen;

stiplet linje indikerer tilstedeværelsen eller fraværet af en binding;

når en stiplet linje indikerer tilstedeværelsen af en binding, p er 0;

når en stiplet linje indikerer fraværet af en binding, p er 1;

R^a er hydrogen, eventuelt substitueret C1-C10-alkyl, eventuelt substitueret C2-C10-alkenyl, hvor C2-C10-alkenyl er en lige eller forgrenet-alkenyl med et carbonantal på 2 til 10 med én eller flere dobbeltbindinger ved en arbitrær position, eller eventuelt substitueret C2-C 10 alkynyl, hvor C2-C10-alkynyl er en lige eller forgrenet alkynyl med et carbonantal på 2 til 10 med én eller flere tredobbelt-bindinger ved en arbitrær position;

og R^b er hydrogen eller oxo;

R^4 er hydrogen eller C1-C10-alkyl;

R^5 er hydrogen, C1-C10-alkyl, cycloalkyl C1-C10-alkyl, hvor cycloalkyl er en carbocyklisk gruppe med et carbonantal på 3 til 10, eller C2-C10-alkenyl, hvor C2-C10-alkenyl er en lige eller forgrenet-alkenyl med et carbonantal på 2 til 10 med én eller flere dobbeltbindinger ved en arbitrær position,

eller et farmaceutisk acceptabelt salt, eller et solvat deraf,

hvor den eventuelt substituerede C1-C10-alkyl, C2-C10-alkenyl, C2-C10 alkynyl, C1-C10-alkylsulfonyl, C1-C10 alkoxy, C1-C10-alkylthio, acyl, acyloxy, hvor acyl og acyloxy er kæde-lignende alifatisk acyl og acyloxy, eventuelt kan være substitueret med halogen, hydroxy, C1-C10 alkoxy, halogeno C1-C10 alkoxy, hydroxy C1-C10 alkoxy, C1-C10 akylthio, C1-C10-alkylamino, acylamino, acyl, acyloxy, cyano, carboxy, C1-C10 alkoxycarbonyl, carbamoyl, C1-C10-alkylcarbamoyl, cyanocarbamoyl, C1-C10-alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, sulfamoyl, C1-C10-alkylsulfamoyl, C1-C10-alkylsulfonyl, cycloalkyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, cycloalkenyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, aryl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, aryloxy eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, arylthio eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, en heterocyklisk gruppe eventuelt

substitueret med én eller flere substituenter valgt fra substituentgruppen α, og heterocyklisk oxy eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, eventuelt substitueret cycloalkyl, cycloalkenyl kan eventuelt være substitueret med én eller flere substituenter valgt fra substituentgruppen α, eventuelt substitueret acyl, hvor acyl er cyklisk alifatisk acyl, aroyl eller heterocyklisk carbonyl, eventuelt kan være substitueret med én eller flere substituenter valgt fra substituentgruppen α,

eventuelt substitueret acyloxy, hvor acyloxy er cyklisk alifatisk acyloxy, aroyloxy eller heterocyklisk carbonyloxy, eventuelt kan være substitueret med én eller flere substituenter valgt fra substituentgruppen α,

eventuelt substitueret aryl, arylsulfonyl kan eventuelt være substitueret med én eller flere substituenter valgt fra substituentgruppen α, phenyl-substitueret med én eller flere grupper valgt fra substituentgruppen α, phenoxy-substitueret med én eller flere grupper valgt fra substituentgruppen α, og C1-C10-alkylendioxy,

eventuelt substituet heterocyklisk gruppe, heterocyklen kan eventuelt være substitueret med én eller flere substituenter valgt fra gruppen bestående af substituentgruppen α og oxo, eventuelt substitueret amino, carbamoyl kan eventuelt være substitueret med C1-C10-alkyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, cycloalkyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, acyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, amino eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, aryl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, sulfamoyl, C1-C10-alkylsulfamoyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, arylsulfamoyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, C1-C10-alkylsulfonyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, arylsulfonyl eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, arylamino eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α, og en heterocyklisk gruppe eventuelt substitueret med én eller flere substituenter valgt fra substituentgruppen α,

hvor substituentgruppen α er gruppen bestående af halogen, hydroxy, C1-C10-alkyl, halogeno C1-C10-alkyl, hydroxy C1-C10-alkyl, C1-C10 alkoxy C1-C10-alkyl, carboxy C1-C10-alkyl, C1-C10 alkoxycarbonyl C1-C10-alkyl, amino C1-C10-alkyl, C1-C10-alkylamino C1-C10-alkyl, acylamino C1-C10-alkyl, cyano C1-C10-alkyl, C1-C10 alkoxy, halogeno C1-C10 alkoxy, hydroxy C1-C10 alkoxy, C1-C10-alkylthio, halogeno C1-C10-alkylthio, acyl, acyloxy, amino, C1-C10-alkylamino, acylamino, cyano, carboxy, C1-C10 alkoxycarbonyl, carbamoyl, C1-C10-alkylcarbamoyl, arylcarbamoyl, cyanocarbamoyl, C1-C10-alkylsulfonylcarbamoyl, sulfamoyl, C1-C10-alkylsulfamoyl, C1-C10-alkylsulfonyl, aryl

eventuelt substitueret med C1-C10-alkylendioxy, og en heterocyklisk gruppe.

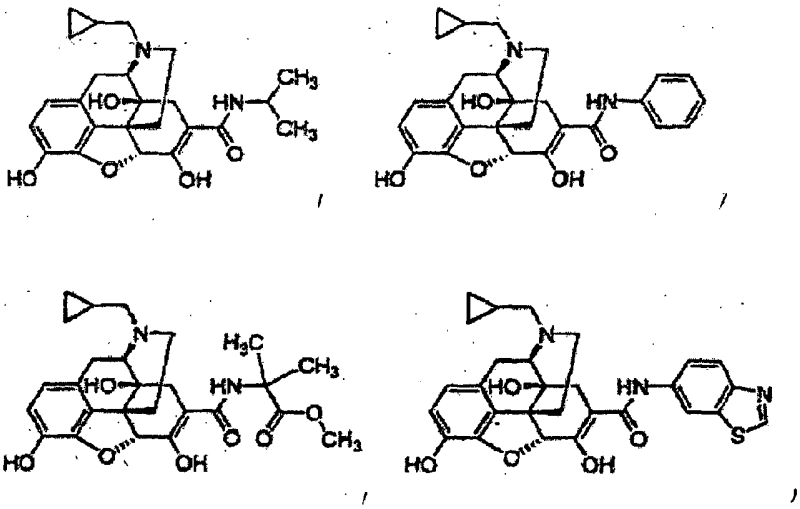
2. Forbindelsen ifølge krav 1, hvor R^3 er hydroxy,
eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

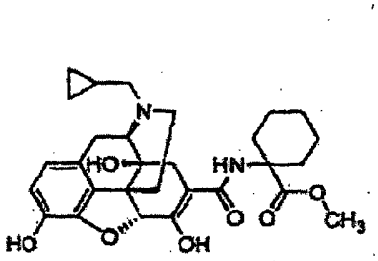
3. Forbindelsen ifølge krav 1, hvor R^3 eventuelt er substitueret amino ifølge krav 1, eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

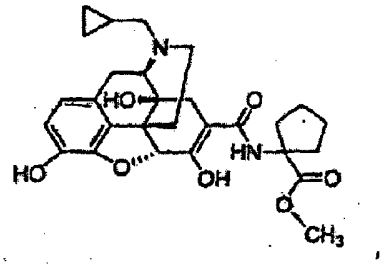
4. Forbindelsen ifølge et hvilket som helst af kravene 1 til 3, hvor R^1 er hydrogen eller C1-C10-alkyl, R^2 er eventuelt substitueret C1-C10-alkyl, eventuelt substitueret phenyl, eventuelt substitueret cycloalkyl som defineret i krav 1, eller en eventuelt substitueret heterocyklisk gruppe som defineret i krav 1, og R^5 er cyclopropylmethyl,
eller et farmaceutisk acceptabelt salt, eller et solvat deraf,
hvor eventuelt substitueret phenyl eventuelt kan være substitueret med én eller flere substituenter valgt fra substituentgruppen α, phenyl-substitueret med én eller flere grupper valgt fra substituentgruppen α, phenoxy-substitueret med én eller flere grupper valgt fra substituentgruppen α, og C1-C10-alkylendioxy.

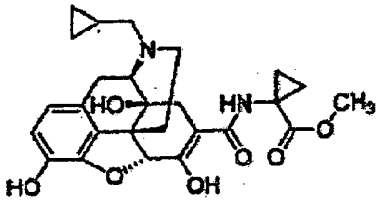
5. Forbindelsen ifølge et hvilket som helst af kravene 1, 2 og 4, hvor R^1 er hydrogen, R^2 er C1-C10-alkyl eventuelt substitueret med C1-C10 alkoxy eller med en heterocyklisk gruppe der eventuelt er substitueret med aryl, phenyl eventuelt substitueret med C1-C10,-alkyl eller med C1-C10 alkoxy, cycloalkyl som defineret i krav 1-substitueret med C1-C10-alkylcarbonyl, eller en heterocyklisk gruppe-substitueret med C1-C10 alkoxy eller med aryl, R^3 er hydroxy, R^4 er hydrogen, og R^5 er cyclopropylmethyl,
eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

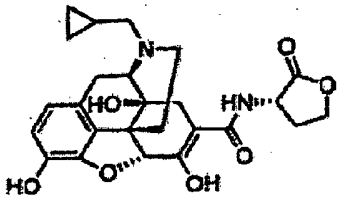
6. Forbindelsen ifølge et hvilket som helst af kravene 1, 2 og 4, hvor forbindelsen er

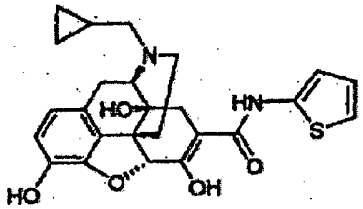


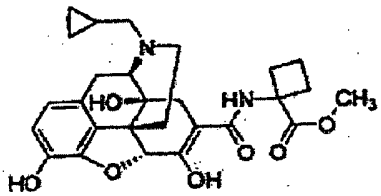


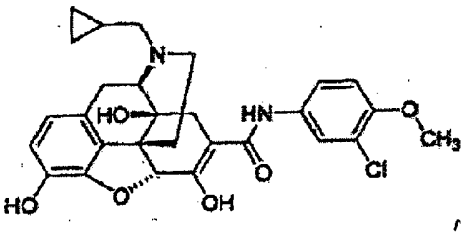


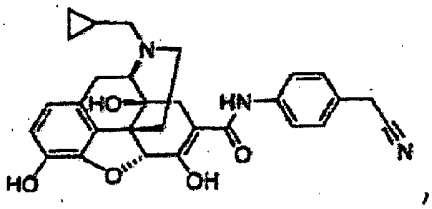


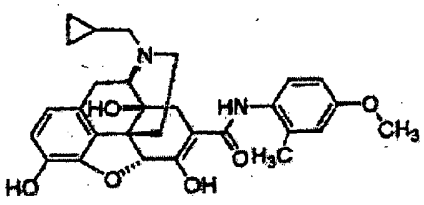


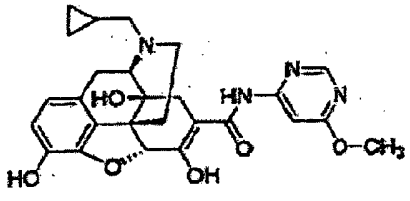


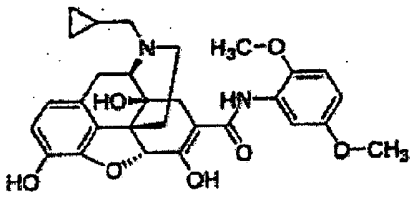


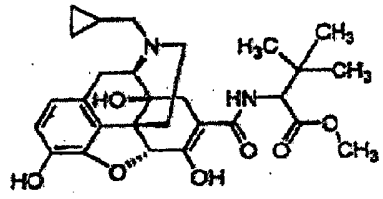


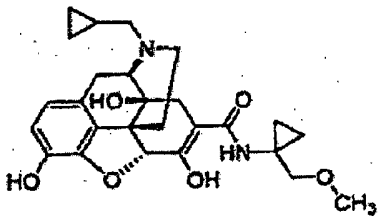


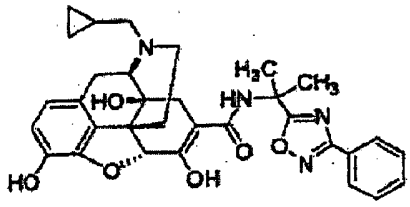


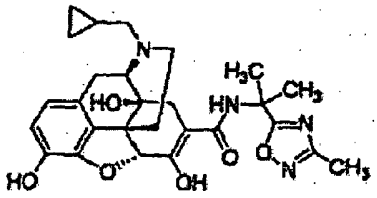


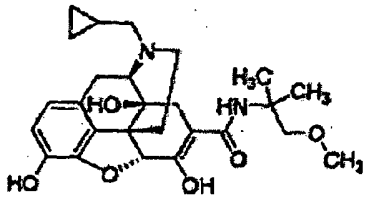


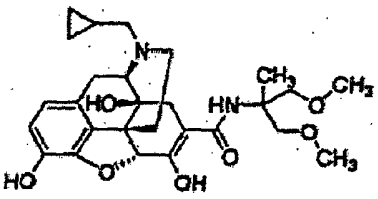






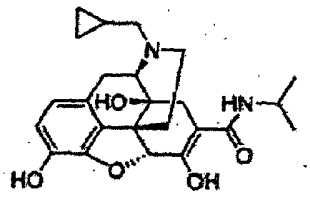


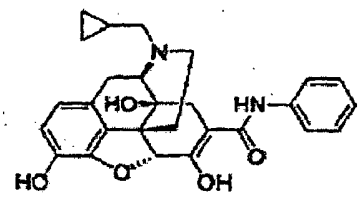


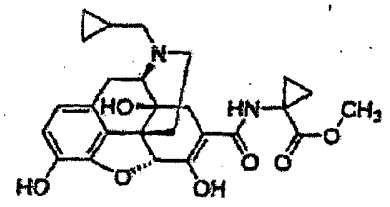


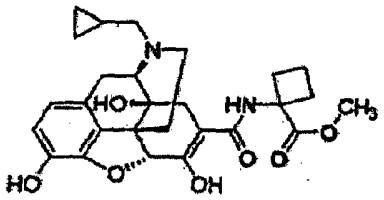
eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

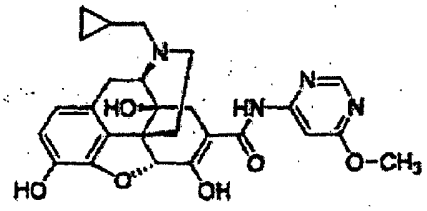
7. Forbindelsen ifølge et hvilket som helst af kravene 1, 2 og 4, hvor forbindelsen er

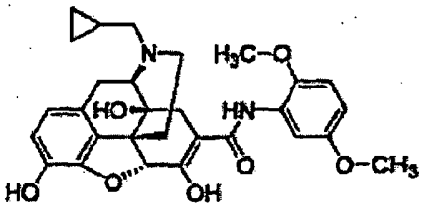


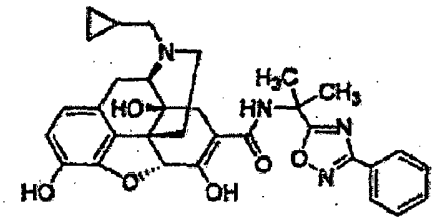


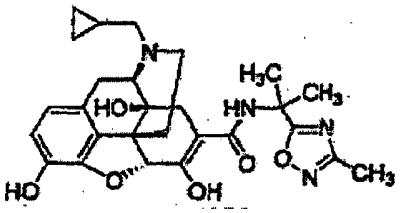


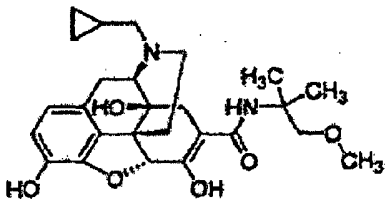


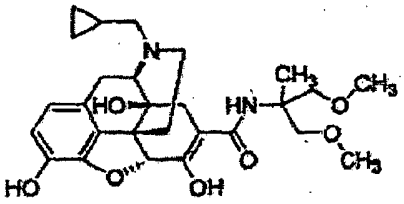












eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

8. Farmaceutisk sammensætning indeholdende en forbindelse ifølge et hvilket som helst af kravene 1 til 7, eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

9. Sammensætning med en opioid receptor-antagonistisk aktivitet indeholdende en forbindelse ifølge et hvilket som helst af kravene 1 til 7, eller et farmaceutisk acceptabelt salt eller et solvat deraf.

10. Sammensætning til behandling og/eller forebyggelse af emesis, opkastning og/eller forstoppelse indeholdende en forbindelse ifølge et hvilket som helst af kravene 1 til 7, eller

et farmaceutisk acceptabelt salt, eller et solvat deraf.

11. Sammensætning til lindring og/eller forebyggelse af en bivirkning induceret af en forbindelse med opioid receptoragonistisk aktivitet indeholdende en forbindelse ifølge et hvilket som helst af kravene 1 til 7, eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

12. Middel til behandling og/eller forebyggelse af en bivirkning ifølge krav 11, hvor bivirkningen er emesis, opkastning og/eller forstoppelse.

13. Sammensætning til behandling og/eller forebyggelse ifølge krav 11 eller 12, hvor forbindelsen med den opioid-receptoragonistiske aktivitet er morfin, oxycodon, eller et farmaceutisk acceptabelt salt, eller et solvat deraf.

14. Forbindelsen ifølge et hvilket som helst af kravene 1 til 7, eller et farmaceutisk acceptabelt salt, eller et solvat deraf, til anvendelse i en fremgangsmåde til behandling og/eller forebyggelse af emesis, opkastning og/eller forstoppelse.

15. Analgetisk sammensætning indeholdende
en forbindelse med en opioid receptor-agonistisk aktivitet,
og en effektiv mængde af forbindelsen ifølge et hvilket som helst af kravene 1 til 7, eller et farmaceutisk acceptabelt salt, eller et solvat deraf, til lindring og/eller forebyggelse af en bivirkning induceret ved administration af forbindelsen med en opioid receptor-agonistisk aktivitet.