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(54) **6,7-UNSATURATED-7-CARBAMOYL SUBSTITUTED MORPHINAN DERIVATIVE**

(71) Applicant: **SHIONOGI & CO., LTD.**, Osaka-shi, Osaka (JP)

(72) Inventors: **Masanao Inagaki**, Toyonaka (JP); **Shin-ichiro Hara**, Toyonaka (JP); **Nobuhiro Haga**, Osaka (JP); **Yoshinori Tamura**, Toyonaka (JP); **Yoshihisa Goto**, Amagasaki (JP); **Tsuyoshi Hasegawa**, Toyonaka (JP)

(73) Assignee: **Shionogi & Co., Ltd.**, Osaka (JP)

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CPC ***C07D 489/08*** (2013.01)

(58) **Field of Classification Search**
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USPC 514/282
See application file for complete search history.

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Primary Examiner — Alan Diamond

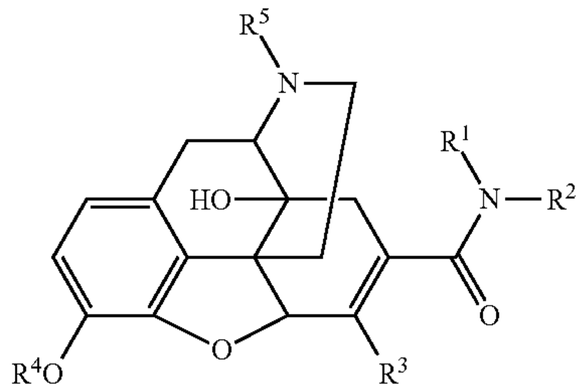
(74) *Attorney, Agent, or Firm* — Finnegan, Henderson, Farabow, Garrett & Dunner, LLP

(57) **ABSTRACT**

A novel compound which is useful as an agent for treating and/or preventing emesis, vomiting and/or constipation. 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 cycloalkyl, optionally substituted aryl etc., R^3 is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkoxy etc., R^4 is hydrogen or lower alkyl, R^5 is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl, or a pharmaceutically acceptably salt, or a solvate thereof is provided.

30 Claims, No Drawings

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6,7-UNSATURATED-7-CARBAMOYL SUBSTITUTED MORPHINAN DERIVATIVE

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

[This application is a 371 national phase filing of International Application No. PCT/JP2006/310454, filed May 25, 2006, now International Publication No. WO 2006/126637, which claims priority from Japanese Patent Application No. 2005-151864, filed May 25, 2005, Japanese Patent Application No. 2006-065762, filed Mar. 10, 2006, and International Application No. PCT/JP2006/310231, filed May 23, 2006, now International Publication No. WO 2006/126529, each of which are herein incorporated by reference for all purposes.]

This application is a reissue application of U.S. Pat. No. 8,084,460, issued on Dec. 27, 2011 from U.S. patent application Ser. No. 11/920,851, which is the National Stage Entry of International Application No. PCT/JP2006/310454, filed May 25, 2006, which claims the benefit of priority of Japan Application No. 2005-151864, filed on May 25, 2005, Japan Application No. 2006-065762, filed Mar. 10, 2006, and International Application No. PCT/JP2006/310231, filed May 23, 2006, all of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention relates to a 6,7-unsaturated-7-carbamoyl-substituted 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.

BACKGROUND ART

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.

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-substituted-morphinan derivatives 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)

DISCLOSURE OF INVENTION

Problems to be Solved by the Invention

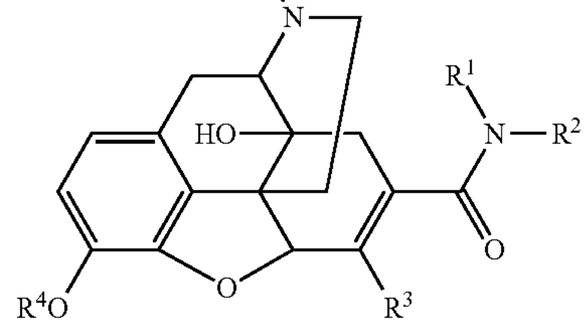
We found 6,7-unsaturated-7-carbamoyl-substituted morphinan derivatives useful as a composition for treating and/or preventing emesis, vomiting and/or constipation.

Means to Solve the Problems

The present invention provides:
(1) a compound represented by the formula (I):

[Chemical formula 1]

(I)

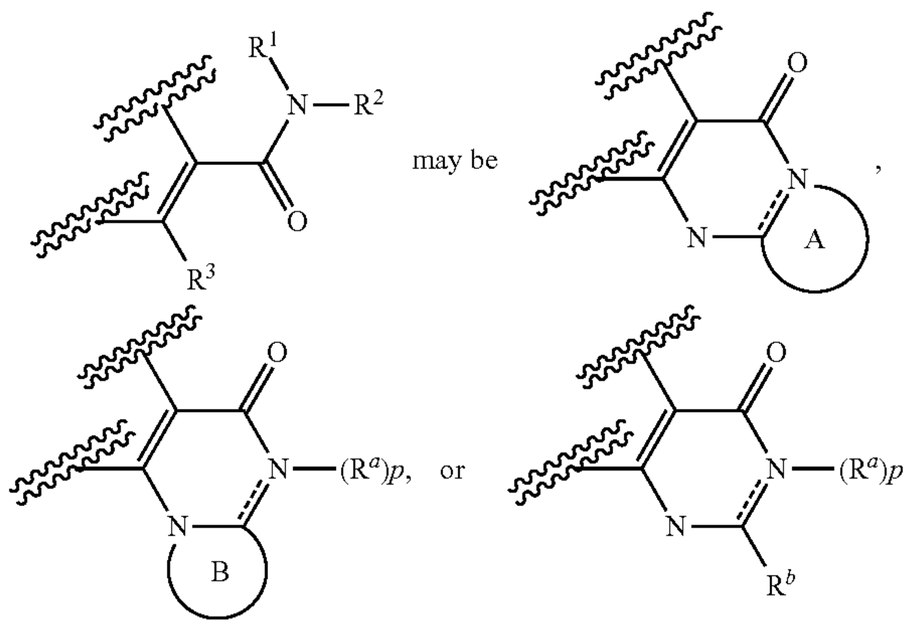


wherein R^1 and R^2 are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkylsulfonyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, 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 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]



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;

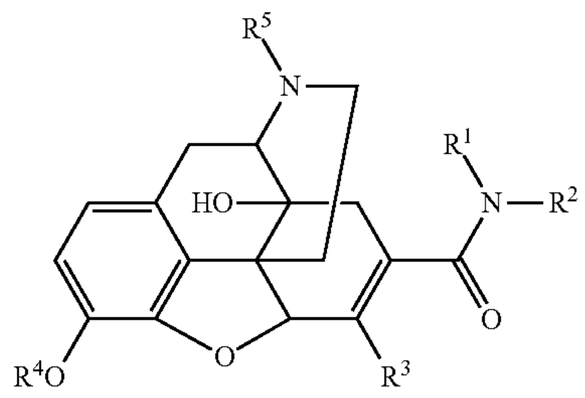
R^5 is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl,

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 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 with lower alkoxy, cycloalkyl substituted with lower alkylcarbonyl, or a heterocyclic group substituted with lower alkoxy or with 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.

EFFECT OF THE INVENTION

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 composition 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.

BEST MODE FOR CARRYING OUT THE INVENTION

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.

The "lower alkyl" includes 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.

Examples of a substituent of the "optionally substituted lower alkyl"include 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.

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".

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".

The "lower alkenyl" includes 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.

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

The "lower alkynyl" includes 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.

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

Examples of the substituent of the "optionally substituted amino"include 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.

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

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.

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

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

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

Examples of the substituent of the "optionally substituted cycloalkyl"include on 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.

The "cycloalkenyl" includes 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.

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

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

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

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

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".

Examples of the substituent of the "optionally substituted aryl", the "optionally substituted phenyl", and the "optionally substituted arylsulfonyl"include 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.

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.

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.

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.

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

Examples of the substituent of the "optionally substituted heterocyclic group" include 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.

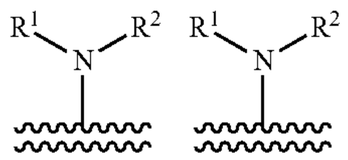
The "acyl" includes straight or branched chain-like aliphatic acyl of a carbon number of 1 to 10, preferably a carbon number of 1 to 6, further preferably a carbon number of 1 to 4, cyclic aliphatic acyl of a carbon number of 4 to 9, preferably a carbon number of 4 to 7, aroyl and heterocyclic carbonyl. Herein, the "chain-like aliphatic" includes the aforementioned "lower alkyl", the aforementioned "lower alkenyl", and the aforementioned "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, pyridine carbonyl, piperidinecarbonyl, piperazinecarbonyl, morpholinocarbonyl, and the like.

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

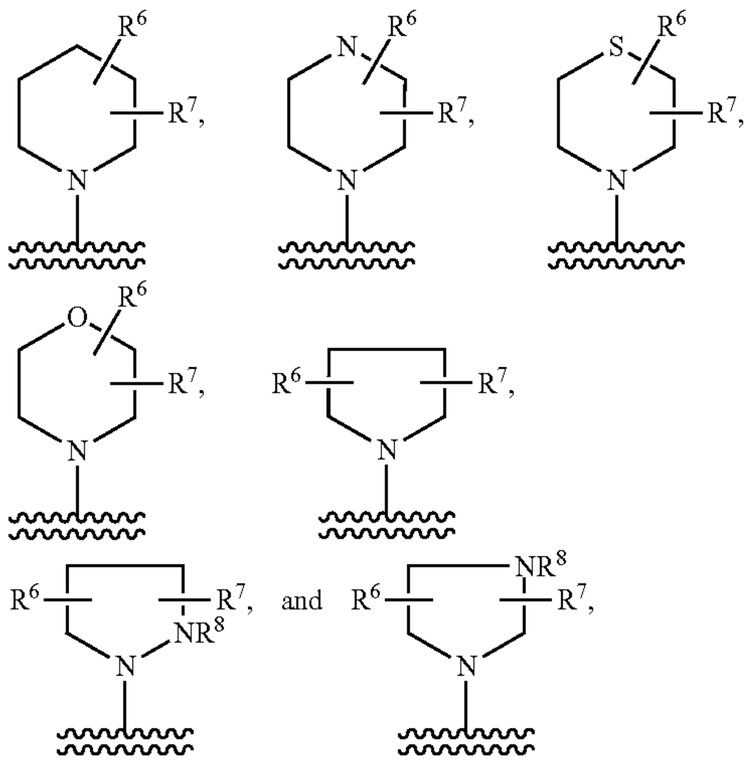
The substituent of the "optionally substituted acyl" or the "optionally substituted" is the same as the substituent of the aforementioned "optionally substituted lower alkyl" when the "acyl" is chain-like aliphatic acyl, and includes one or more groups selected from the Substituent group a when the "acyl"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

The "optionally substituted heterocycle" formed when R^1 and R^2 are taken together with the nitrogen atom to which they are attached, 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

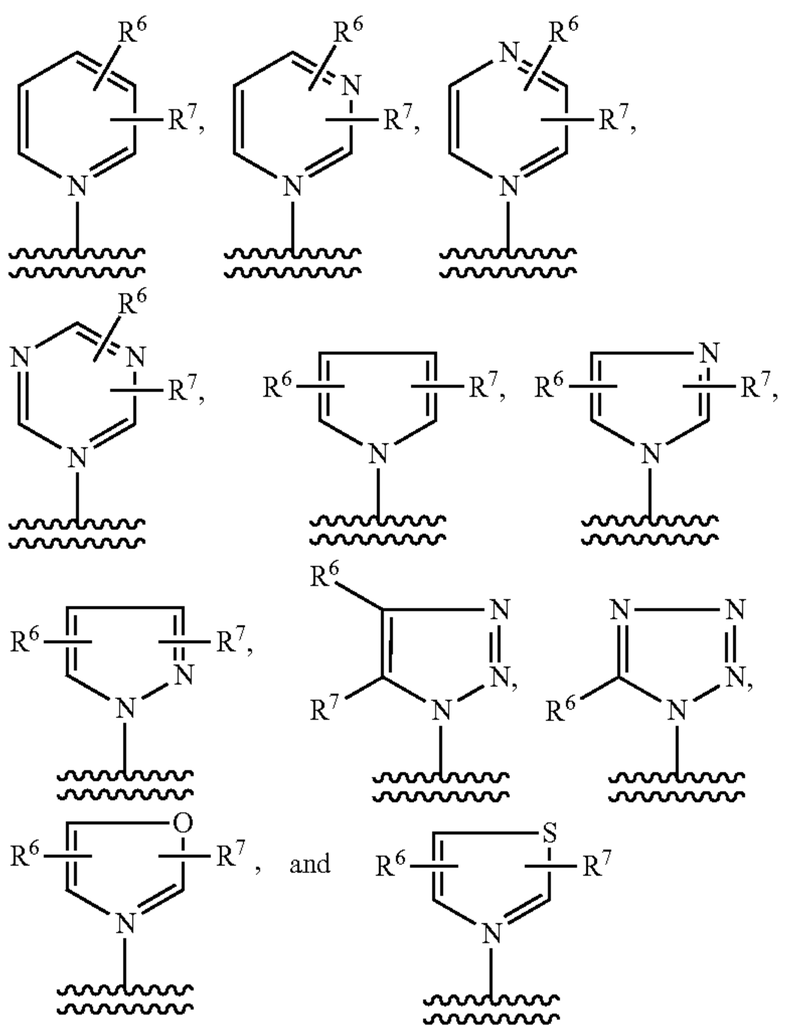
[Chemical formula 4]



is a saturated heterocycle group such as



, or an unsaturated heterocycle group such as

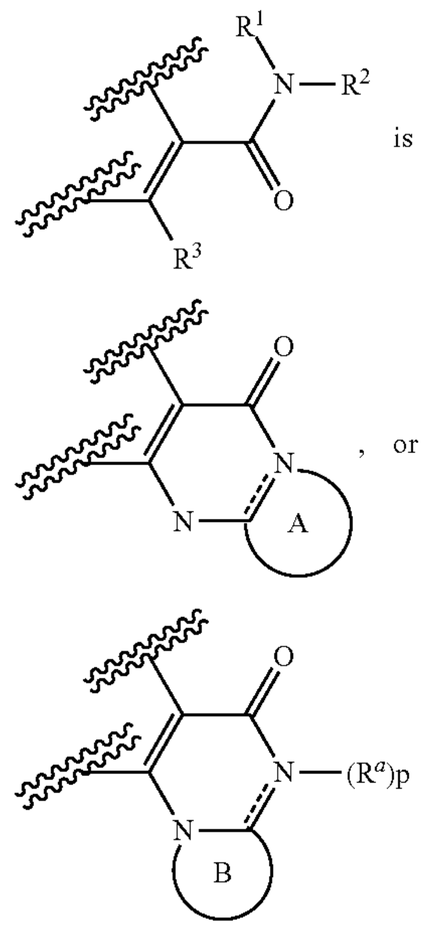


wherein R^6, R^7 and R^8 are each independently hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, lower alkylthio, acyl, acyloxy, amino, lower alkylamino, acylamino, lower alkoxycarbonylamino, carboxy or lower alkoxycarbonyl,

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.

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".

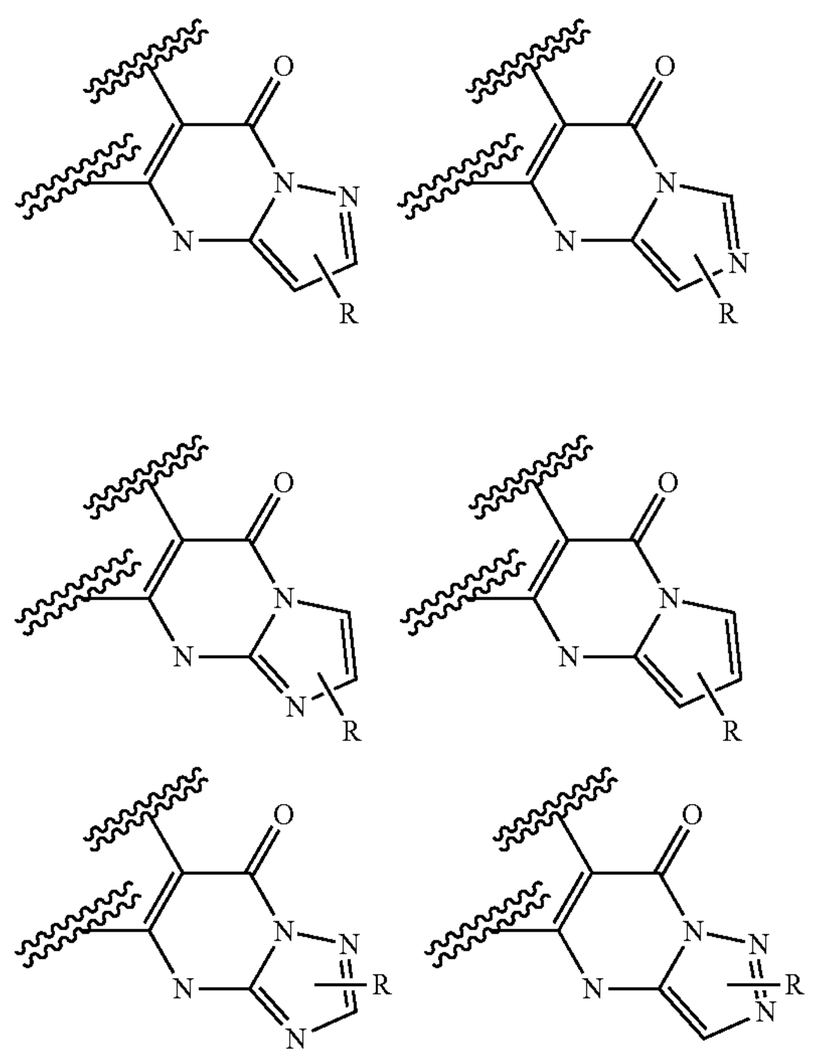
[Chemical formula 5]



is

includes, for example, the following:

[Chemical formula 6]



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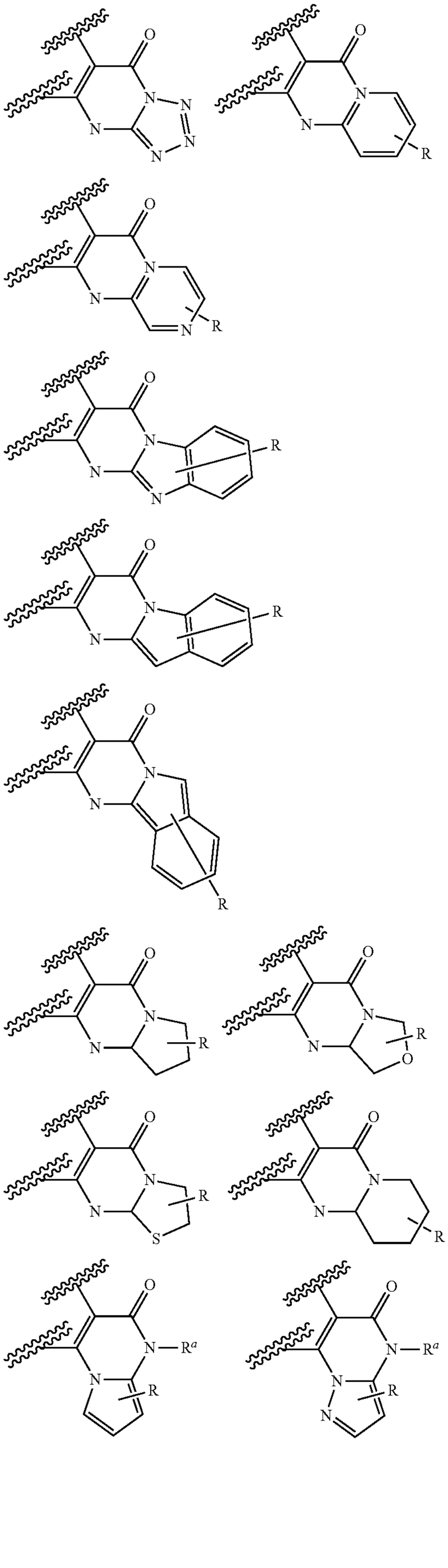

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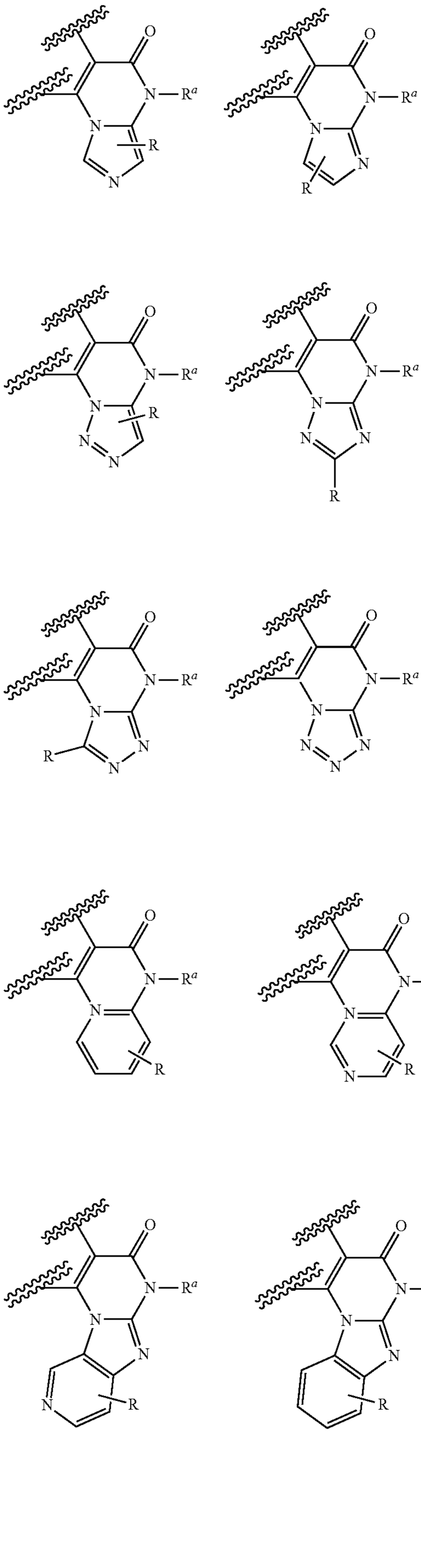

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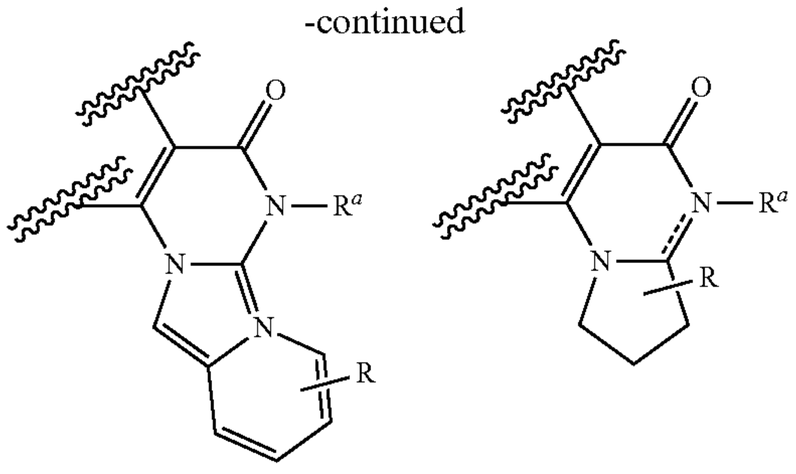
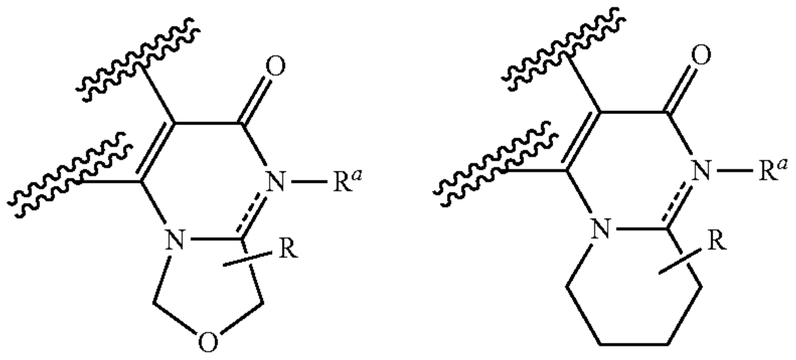




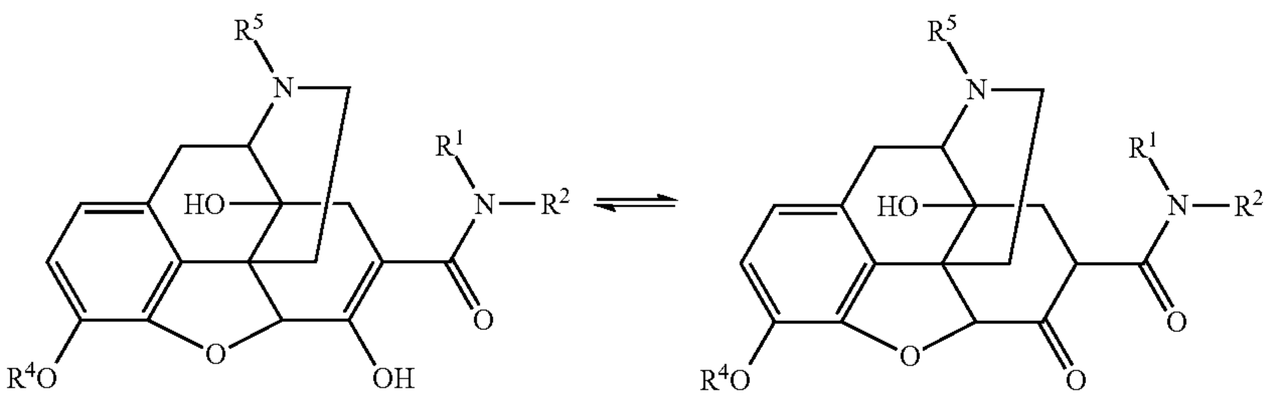
wherein R^a is as defined above, and R is hydrogen or a group selected from Substituent group α.

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.

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-toluene-sulfonic 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.

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').

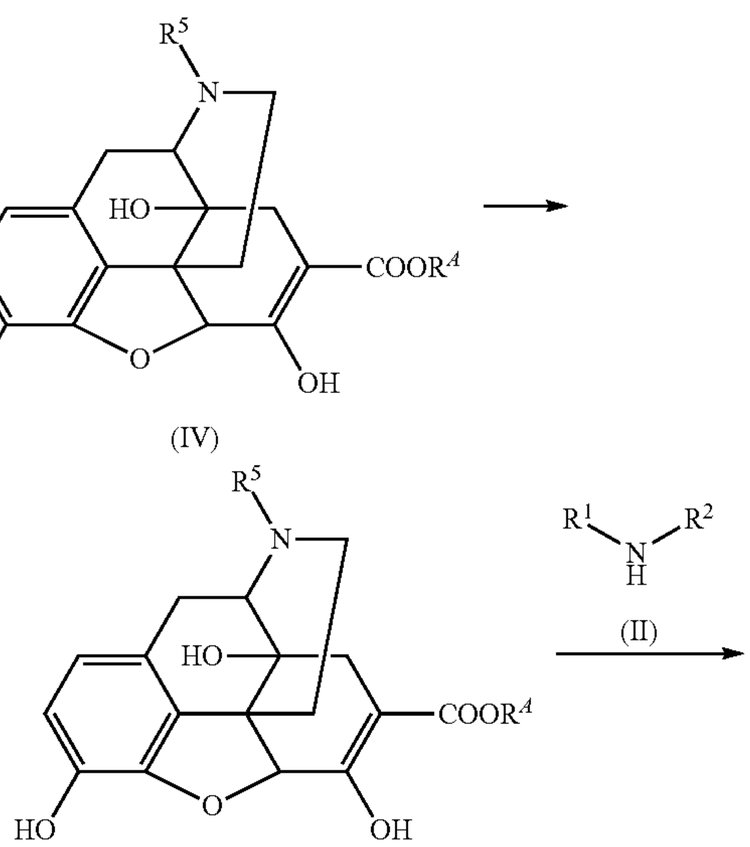
[Chemical formula 7]



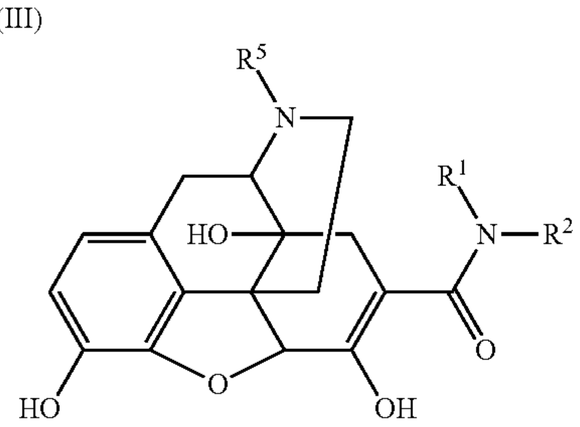
(I) (I')

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

[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.

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.

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.), tri-aryl lower alkylsilyl(tribenzylsilyl etc.), lower

alkoxy lower alkyl (methoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxy-ethyl etc.), lower alkoxy lower alkoxy lower alkyl(methoxy-ethoxymethyl 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)

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

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)

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

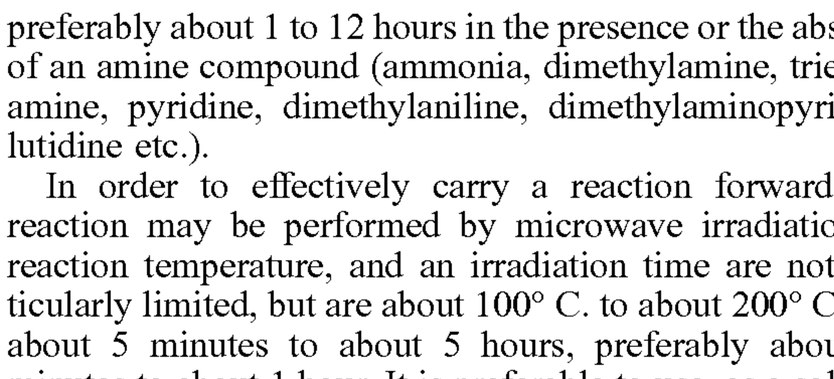
For example, compound (III) and compound (II) may be reacted by heating in a suitable solvent (methanol, ethanol, tetrahydrofuran, dimethylformamide, diethyl ether, dichloromethane, dichloroethane, toluene, xylene, chlorobenzene, orthodichlorobenzene, 2-methoxyethanol or diethylene glycol dimethyl ether 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.).

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.

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)

[Chemical formula 9]



(VII)

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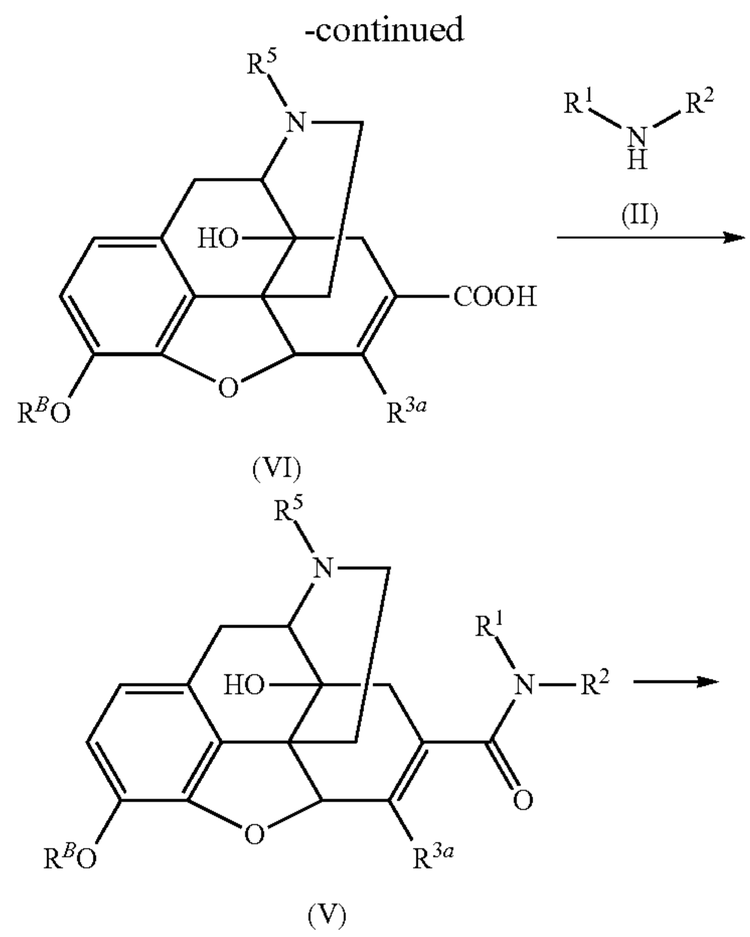
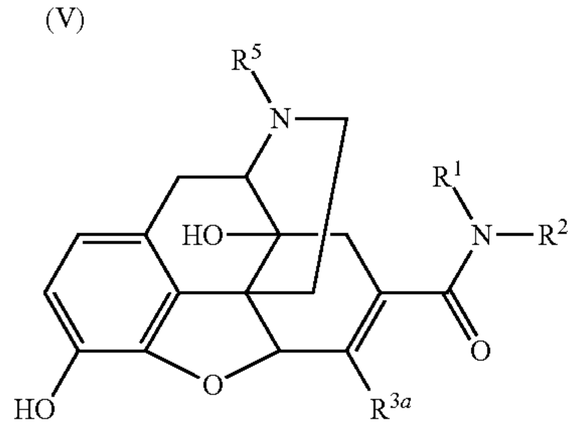


(VI)

(V)



(Ib)

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

(First Step)

When R^3 of objective compound (I) is optionally substituted lower alkoxy, first, the known compound (IV) is etherized by a conventional method.

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)

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).

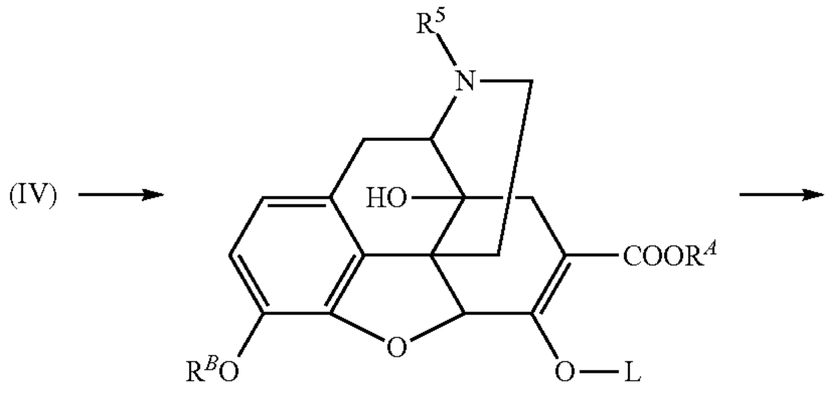
(Third Step and Fourth Step)

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.).

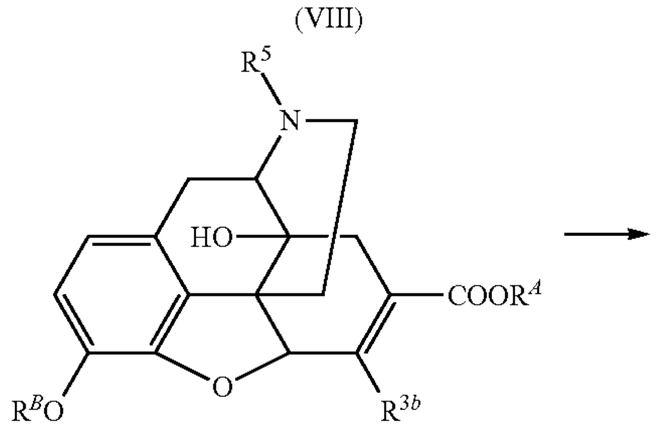
In addition, when R^4 of objective compound (I) is lower alkyl, an etherization reaction may be performed at an arbitrary stage as described above.

(C Process)

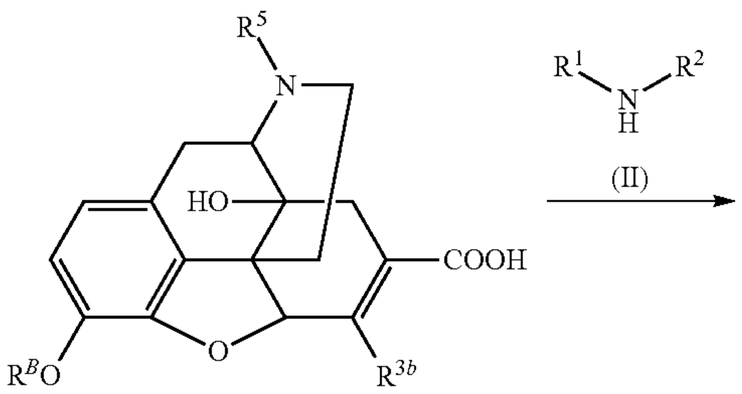
[Chemical formula 10]



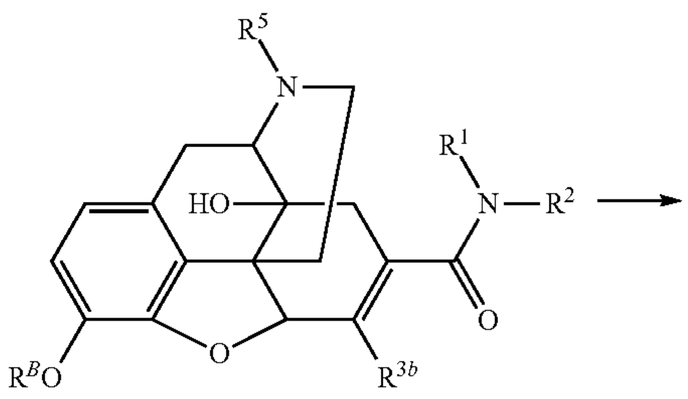
(VIII)



(IX)



(X)



(XI)

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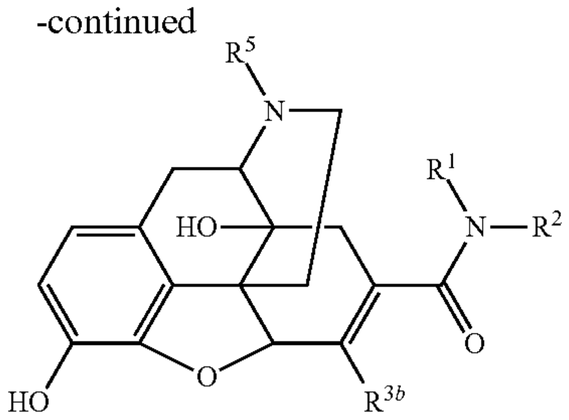


(Ic)

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)

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)

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

(Third Step, Fourth Step and Fifth Step)

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).

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)

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.

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, 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-yl), 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-yl), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,

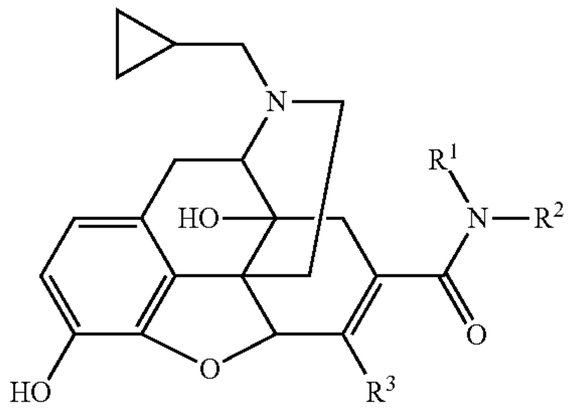
ab) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle, R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl group or lower alkenyl,

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.

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



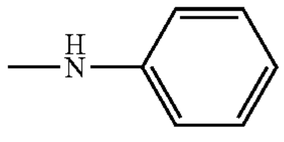
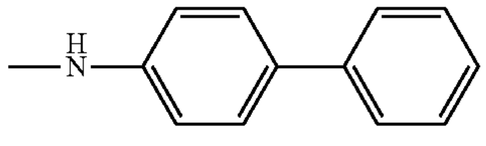
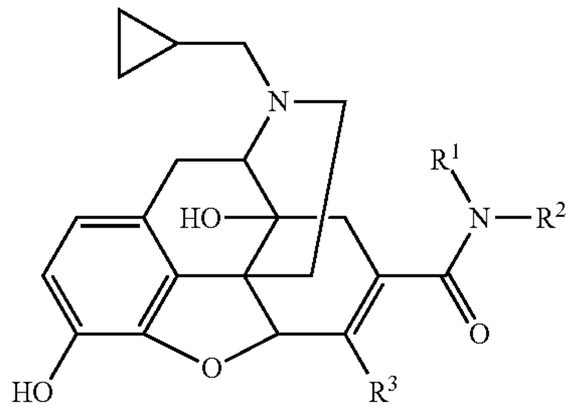
	NR1R2	CR9R10
AA	—NHiPr	—
AB		—
AC		—

TABLE 1-continued



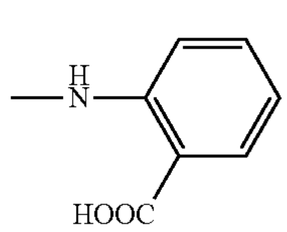
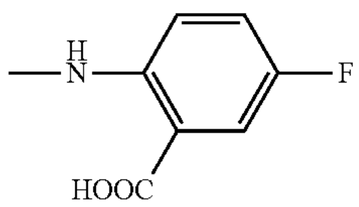
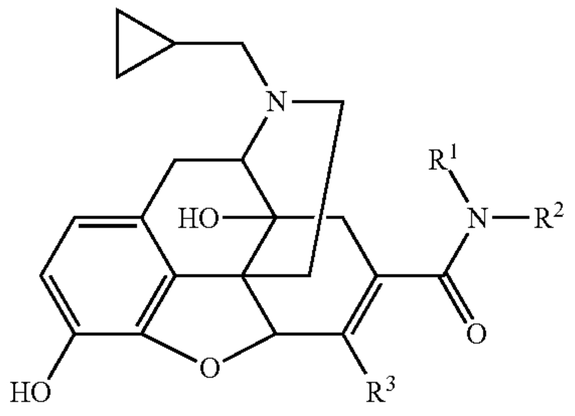
	NR1R2	CR9R10
AD		—
AE		—
AF		—
AG	—NHCR9R10CONH2	Ra
AH	—NHCR9R10CONH2	Rb
AI	—NHCR9R10CONH2	Rc
AJ	—NHCR9R10CONH2	Rd
AK	—NHCR9R10CONH2	Re
AL	—NHCR9R10CONH2	Rf
AM	—NHCR9R10CONH2	Rg
AN	—NHCR9R10CONH2	Rh
AO	—NHCR9R10CONH2	Ri
AP	—NHCR9R10CONH2	Rj
AQ	—NHCR9R10CONH2	Rk
AR	—NHCR9R10CONH2	Rl
AS	—NHCR9R10CONH2	Rm
AT	—NHCR9R10CONH2	Rn
AU	—NHCR9R10CONH2	Ro
AV	—NHCR9R10CONH2	Rp
AW	—NHCR9R10CONH2	Rq
AX	—NHCR9R10CONH2	Rr
AY	—NHCR9R10CONH2	Rs
AZ	—NHCR9R10CONH2	Rt
BA	—NHCR9R10CONMe2	Ra
BB	—NHCR9R10CONMe2	Rb
BC	—NHCR9R10CONMe2	Rc
BD	—NHCR9R10CONMe2	Rd
BE	—NHCR9R10CONMe2	Re
BF	—NHCR9R10CONMe2	Rf
BG	—NHCR9R10CONMe2	Rg
BH	—NHCR9R10CONMe2	Rh
BI	—NHCR9R10CONMe2	Ri
BJ	—NHCR9R10CONMe2	Rj
BK	—NHCR9R10CONMe2	Rk
BL	—NHCR9R10CONMe2	Rl
BM	—NHCR9R10CONMe2	Rm
BN	—NHCR9R10CONMe2	Rn
BO	—NHCR9R10CONMe2	Ro
BP	—NHCR9R10CONMe2	Rp
BQ	—NHCR9R10CONMe2	Rq
BR	—NHCR9R10CONMe2	Rr
BS	—NHCR9R10CONMe2	Rs
BT	—NHCR9R10CONMe2	Rt
BU	—NHCR9R10COOH	Ra
BV	—NHCR9R10COOH	Rb
BW	—NHCR9R10COOH	Rc
BX	—NHCR9R10COOH	Rd
BY	—NHCR9R10COOH	Re

TABLE 1-continued



	NR1R2	CR9R10
BZ	—NHCR9R10COOH	Rf
CA	—NHCR9R10COOH	Rg
CB	—NHCR9R10COOH	Rh
CC	—NHCR9R10COOH	Ri
CD	—NHCR9R10COOH	Rj
CE	—NHCR9R10COOH	Rk
CF	—NHCR9R10COOH	Rl
CG	—NHCR9R10COOH	Rm
CH	—NHCR9R10COOH	Rn
CI	—NHCR9R10COOH	Ro
CJ	—NHCR9R10COOH	Rp
CK	—NHCR9R10COOH	Rq
CL	—NHCR9R10COOH	Rr
CM	—NHCR9R10COOH	Rs
CN	—NHCR9R10COOH	Rt
CO	—NHCR9R10COOMe	Ra
CP	—NHCR9R10COOMe	Rb
CQ	—NHCR9R10COOMe	Rc
CR	—NHCR9R10COOMe	Rd

TABLE 2

	NR1R2	CR9R10
CS	—NHCR9R10COOMe	Re
CT	—NHCR9R10COOMe	Rf
CU	—NHCR9R10COOMe	Rg
CV	—NHCR9R10COOMe	Rh
CW	—NHCR9R10COOMe	Ri
CX	—NHCR9R10COOMe	Rj
CY	—NHCR9R10COOMe	Rk
CZ	—NHCR9R10COOMe	Rl
DA	—NHCR9R10COOMe	Rm
DB	—NHCR9R10COOMe	Rn
DC	—NHCR9R10COOMe	Ro
DD	—NHCR9R10COOMe	Rp
DE	—NHCR9R10COOMe	Rq
DF	—NHCR9R10COOMe	Rr
DG	—NHCR9R10COOMe	Rs
DH	—NHCR9R10COOMe	Rt
DI	—NHCR9R10COOEt	Ra
DJ	—NHCR9R10COOEt	Rb
DK	—NHCR9R10COOEt	Rc
DL	—NHCR9R10COOEt	Rd
DM	—NHCR9R10COOEt	Re
DN	—NHCR9R10COOEt	Rf
DO	—NHCR9R10COOEt	Rg
DP	—NHCR9R10COOEt	Rh
DQ	—NHCR9R10COOEt	Ri
DR	—NHCR9R10COOEt	Rj
DS	—NHCR9R10COOEt	Rk
DT	—NHCR9R10COOEt	Rl
DU	—NHCR9R10COOEt	Rm
DV	—NHCR9R10COOEt	Rn
DW	—NHCR9R10COOEt	Ro
DX	—NHCR9R10COOEt	Rp
DY	—NHCR9R10COOEt	Rq
DZ	—NHCR9R10COOEt	Rr
EA	—NHCR9R10COOEt	Rs
EB	—NHCR9R10COOEt	Rt
EC	—NHCR9R10COOiPr	Ra
ED	—NHCR9R10COOiPr	Rb

TABLE 2-continued

	NR1R2	CR9R10
EE	—NHCR9R10COOiPr	Rc
EF	—NHCR9R10COOiPr	Rd
EG	—NHCR9R10COOiPr	Re
EH	—NHCR9R10COOiPr	Rf
EI	—NHCR9R10COOiPr	Rg
EJ	—NHCR9R10COOiPr	Rh
EK	—NHCR9R10COOiPr	Ri
EL	—NHCR9R10COOiPr	Rj
EM	—NHCR9R10COOiPr	Rk
EN	—NHCR9R10COOiPr	Rl
EO	—NHCR9R10COOiPr	Rm
EP	—NHCR9R10COOiPr	Rn
EQ	—NHCR9R10COOiPr	Ro
ER	—NHCR9R10COOiPr	Rp
ES	—NHCR9R10COOiPr	Rq
ET	—NHCR9R10COOiPr	Rr
EU	—NHCR9R10COOiPr	Rs
EV	—NHCR9R10COOiPr	Rt
EW	—NHCR9R10CONHMe	Ra
EX	—NHCR9R10CONHMe	Rb
EY	—NHCR9R10CONHMe	Rc
EZ	—NHCR9R10CONHMe	Rd
FA	—NHCR9R10CONHMe	Re
FB	—NHCR9R10CONHMe	Rf
FC	—NHCR9R10CONHMe	Rg
FD	—NHCR9R10CONHMe	Rh
FE	—NHCR9R10CONHMe	Ri
FF	—NHCR9R10CONHMe	Rj
FG	—NHCR9R10CONHMe	Rk
FH	—NHCR9R10CONHMe	Rl
FI	—NHCR9R10CONHMe	Rm
FJ	—NHCR9R10CONHMe	Rn
FK	—NHCR9R10CONHMe	Ro
FL	—NHCR9R10CONHMe	Rp
FM	—NHCR9R10CONHMe	Rq
FN	—NHCR9R10CONHMe	Rr
FO	—NHCR9R10CONHMe	Rs
FP	—NHCR9R10CONHMe	Rt
FQ	—NHCR9R10CONHiPr	Ra
FR	—NHCR9R10CONHiPr	Rb
FS	—NHCR9R10CONHiPr	Rc
FT	—NHCR9R10CONHiPr	Rd
FU	—NHCR9R10CONHiPr	Re
FV	—NHCR9R10CONHiPr	Rf
FW	—NHCR9R10CONHiPr	Rg
FX	—NHCR9R10CONHiPr	Rh
FY	—NHCR9R10CONHiPr	Ri
FZ	—NHCR9R10CONHiPr	Rj
GA	—NHCR9R10CONHiPr	Rk
GB	—NHCR9R10CONHiPr	Rl
GC	—NHCR9R10CONHiPr	Rm
GD	—NHCR9R10CONHiPr	Rn
GE	—NHCR9R10CONHiPr	Ro
GF	—NHCR9R10CONHiPr	Rp
GG	—NHCR9R10CONHiPr	Rq
GH	—NHCR9R10CONHiPr	Rr
GI	—NHCR9R10CONHiPr	Rs
GJ	—NHCR9R10CONHiPr	Rt
GK	—NHCR9R10CONHPh	Ra
GL	—NHCR9R10CONHPh	Rb
GM	—NHCR9R10CONHPh	Rc
GN	—NHCR9R10CONHPh	Rd
GO	—NHCR9R10CONHPh	Re
GP	—NHCR9R10CONHPh	Rf
GQ	—NHCR9R10CONHPh	Rg
GR	—NHCR9R10CONHPh	Rh
GS	—NHCR9R10CONHPh	Ri
GT	—NHCR9R10CONHPh	Rj
GU	—NHCR9R10CONHPh	Rk
GV	—NHCR9R10CONHPh	Rl
GW	—NHCR9R10CONHPh	Rm
GX	—NHCR9R10CONHPh	Rn
GY	—NHCR9R10CONHPh	Ro
GZ	—NHCR9R10CONHPh	Rp
HA	—NHCR9R10CONHPh	Rq

TABLE 2-continued

	NR1R2	CR9R10
HB	—NHCR9R10CONHPh	Rr
HC	—NHCR9R10CONHPh	Rs
HD	—NHCR9R10CONHPh	Rt

TABLE 3

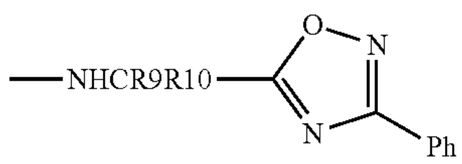
	NR1R2	CR9R10
HE	—NHCR9R10CONHCN	Ra
HF	—NHCR9R10CONHCN	Rb
HG	—NHCR9R10CONHCN	Rc
HH	—NHCR9R10CONHCN	Rd
HI	—NHCR9R10CONHCN	Re
HJ	—NHCR9R10CONHCN	Rf
HK	—NHCR9R10CONHCN	Rg
HL	—NHCR9R10CONHCN	Rh
HM	—NHCR9R10CONHCN	Ri
HN	—NHCR9R10CONHCN	Rj
HO	—NHCR9R10CONHCN	Rk
HP	—NHCR9R10CONHCN	Rl
HQ	—NHCR9R10CONHCN	Rm
HR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

TABLE 3-continued

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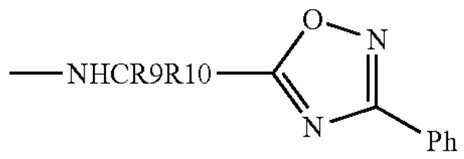
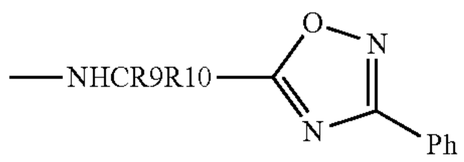
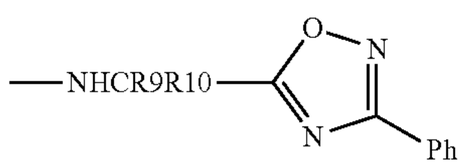
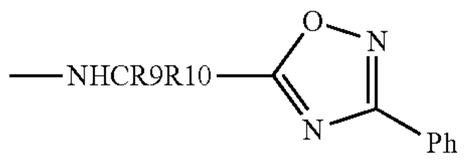
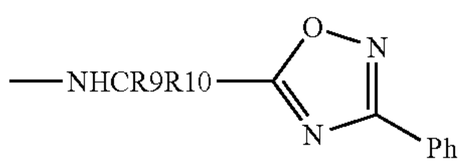
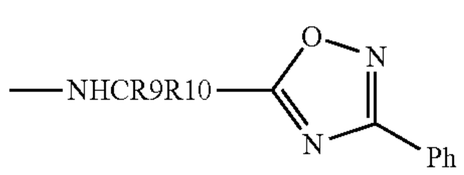
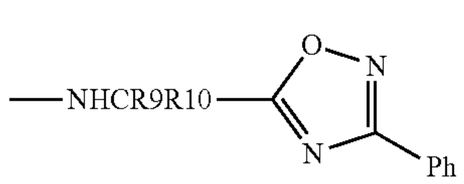
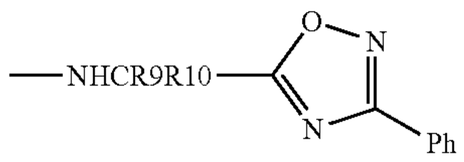
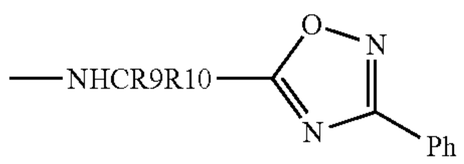
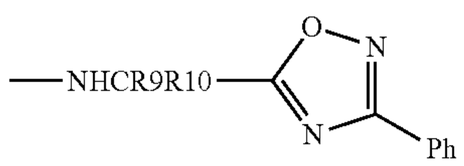
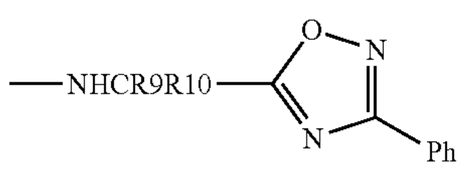
JN		Rb
JO		Rc
JP		Rd
JQ		Re
JR		Rf
JS		Rg
JT		Rh
JU		Ri
JV		Rj
JW		Rk
JX		Rl
JY		Rm

TABLE 4

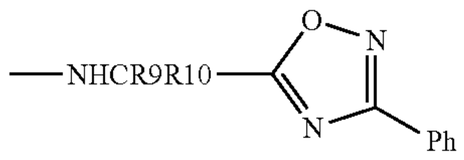
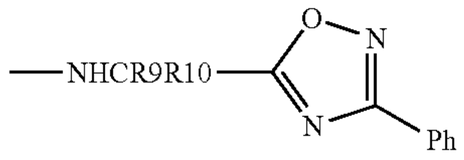
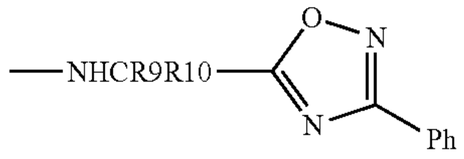
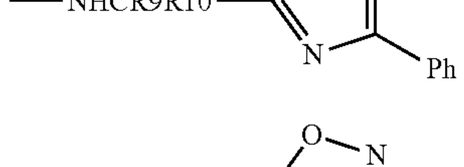
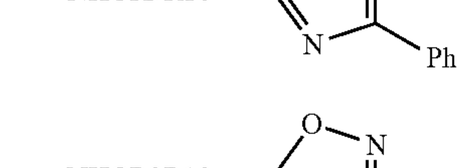
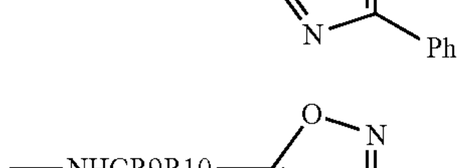
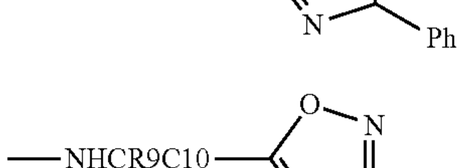
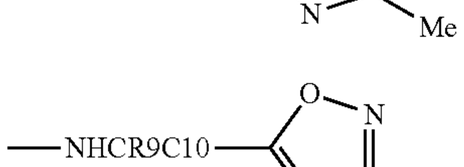
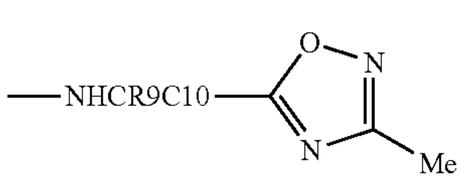
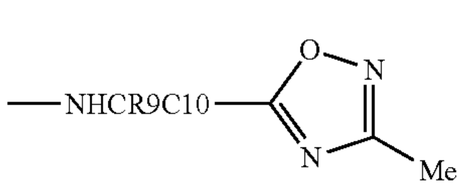
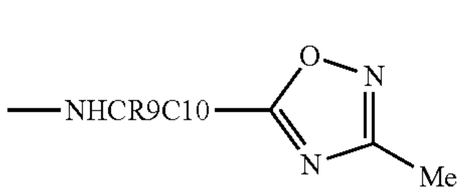
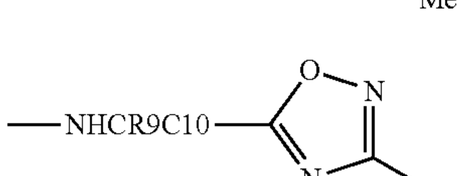
	NR1R2	CR9R10
JZ		Rn
KA		Ro
KB		Rp
KC		Rq
KD		Rr
KE		Rs
KF		Rt
KG		Ra
KH		Rb
KI		Rc
KJ		Rd
KK		Re
KL		Rf
KM		Rg

TABLE 4-continued

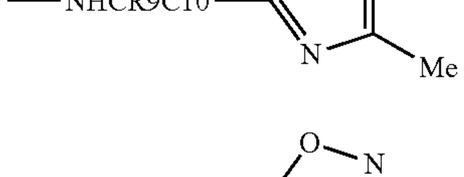
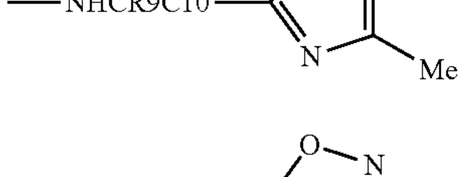
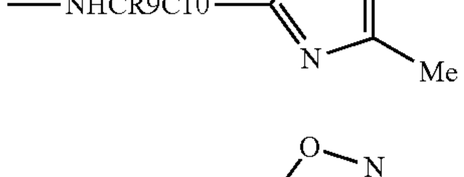
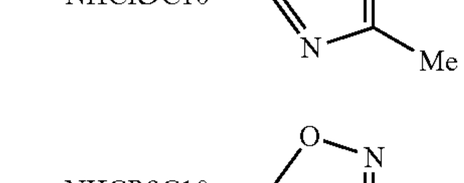
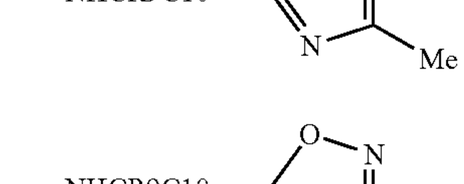
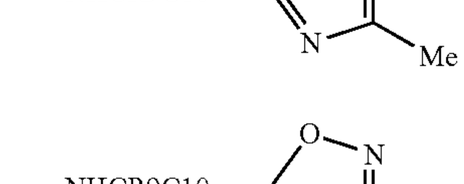
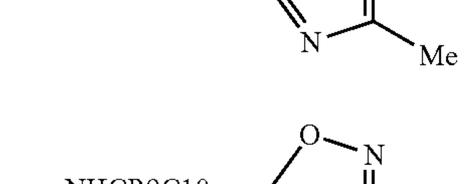
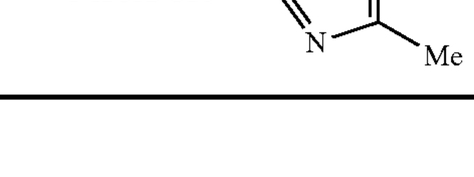
	NR1R2	CR9R10
KN		Rh
KO		Ri
KP		Rj
KQ		Rk
KR		Rl
KS		Rm
KT		Rn
KU		Ro
KV		Rp
KW		Rq
KX		Rr
KY		Rs
KZ		Rt

TABLE 5

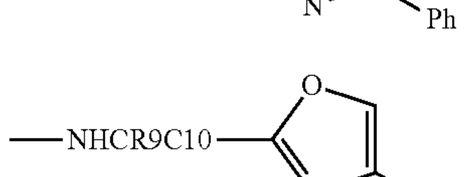
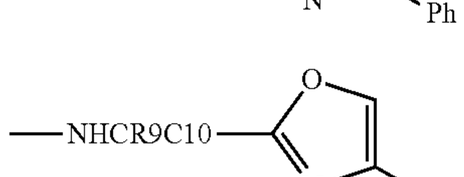
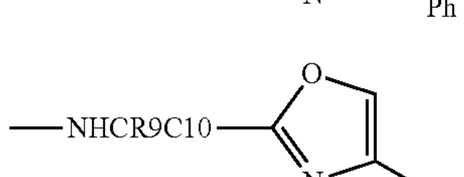
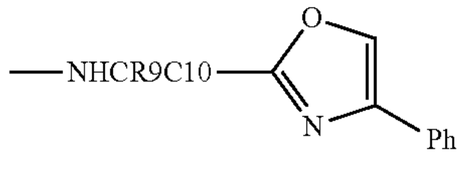
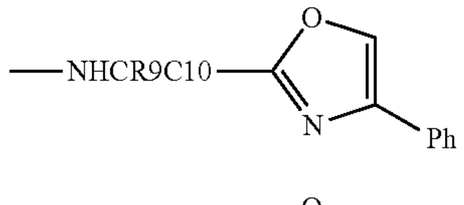
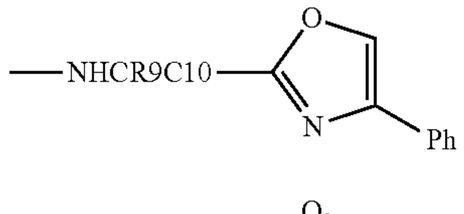
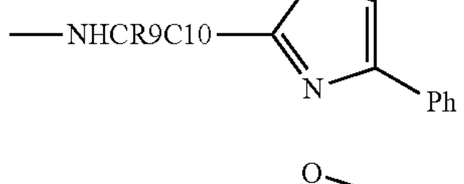
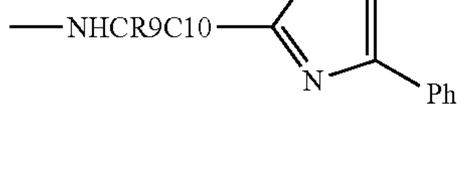
	NR1R2	CR9R10
LA		Ra
LB		Rb
LC		Rc
LD		Rd
LE		Re
LF		Rf
LG		Rg
LH		Rh
LI		Ri
LJ		Rj
LK		Rh
LL		Rl
LM		Rm
LN		Rn

TABLE 5-continued

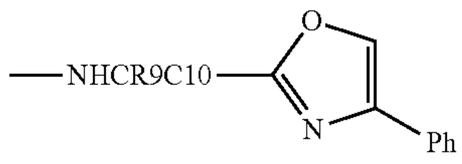
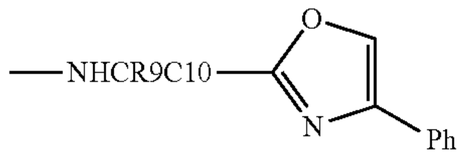
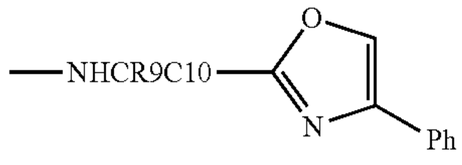
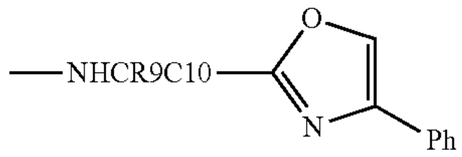
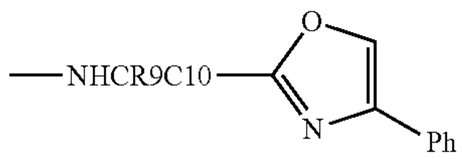
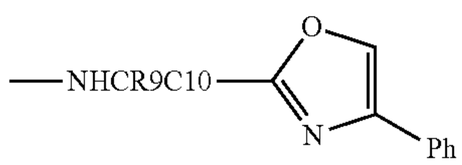
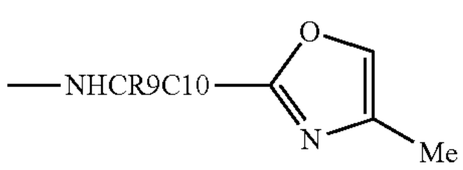
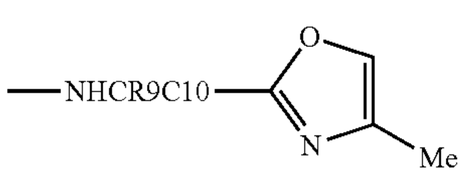
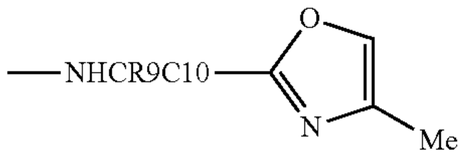
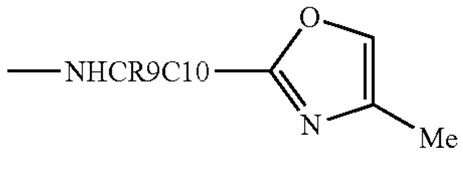
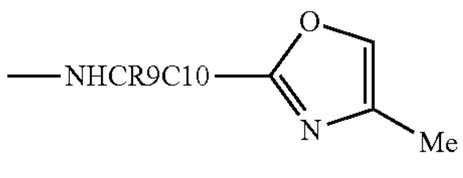
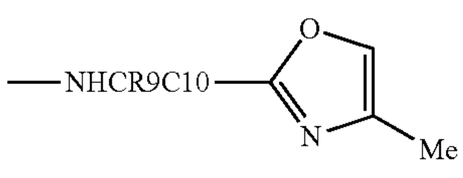
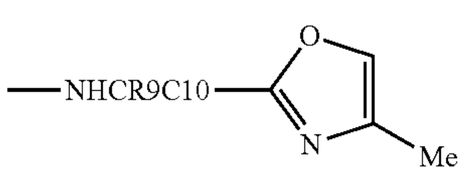
	NR1R2	CR9R10
LO		Ro
LP		Rp0
LQ		Rq
LR		Rr
LS		Rs
LT		Rt
LU		Ra
LV		Rb
LW		Rc
LX		Rd
LY		Re
LZ		Rf
MA		Rg

TABLE 5-continued

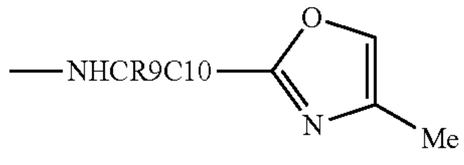
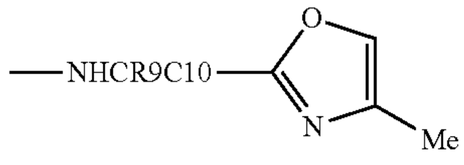
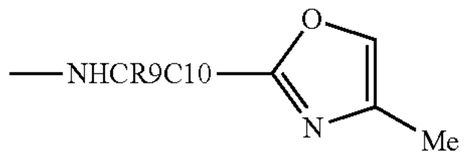
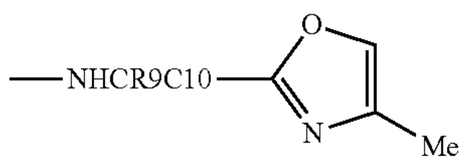
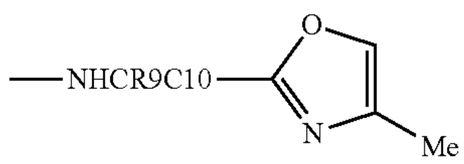
	NR1R2	CR9R10
MB		Rh
MC		Ri
MD		Rj
ME		Rk
MF		Rl

TABLE 6

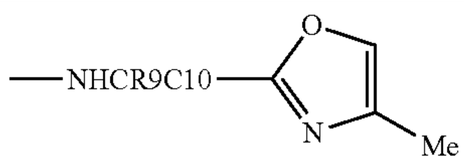
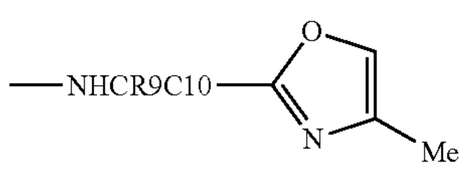
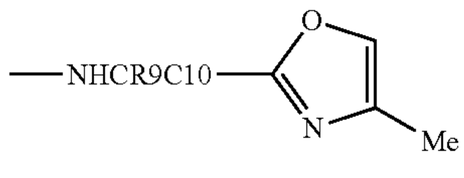
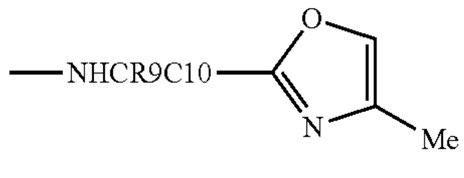
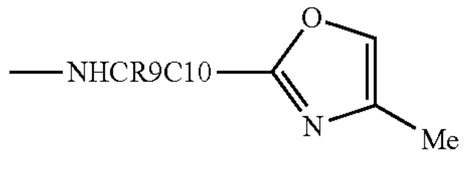
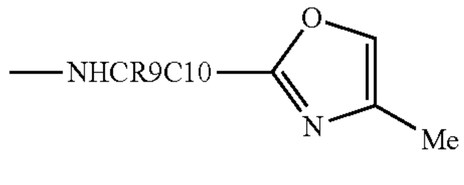
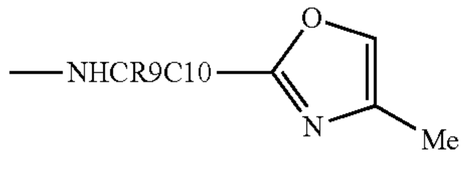
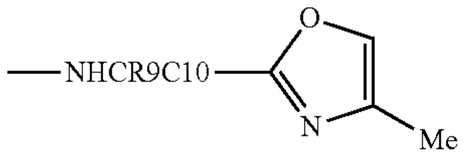
	NR1R2	CR9R10
MG		Rm
MH		Rn
MI		Ro
MJ		Rp
MK		Rq
ML		Rr
MM		Rs

TABLE 6-continued

	NR1R2	CR9R10
MN		Rt

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

TABLE 7

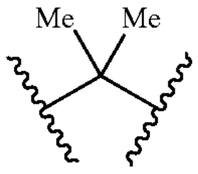
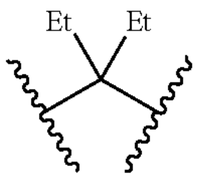
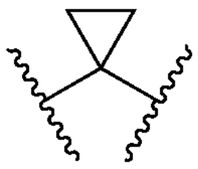
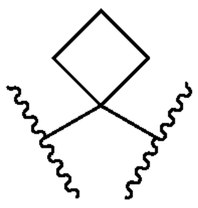
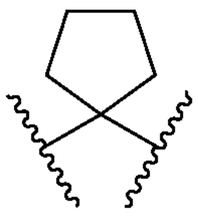
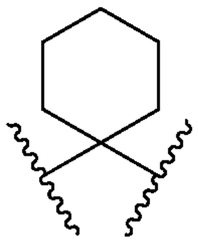
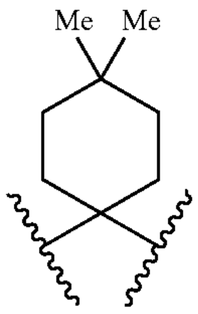
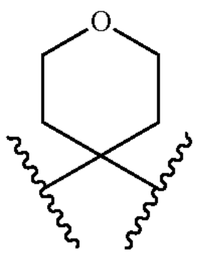
	CR9R10
Ra	
RB	
Rc	
Rd	
Re	
Rf	
Rg	
Rh	

TABLE 7-continued

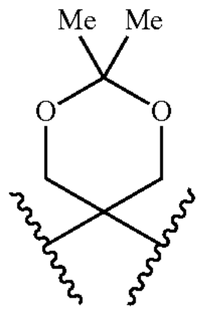
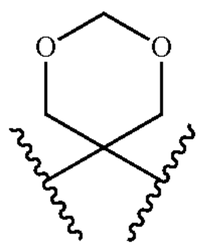
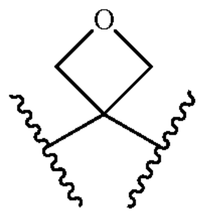
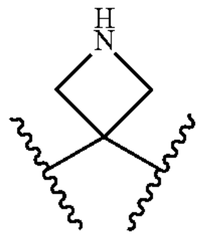
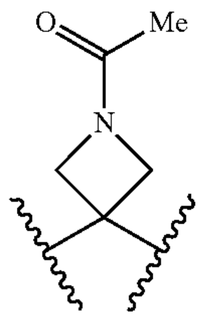
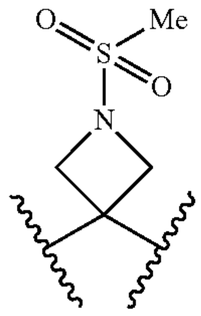
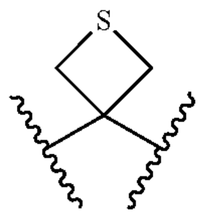
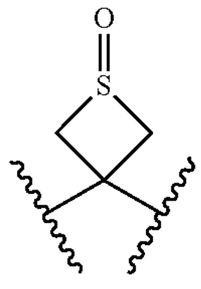
	CR9R10
Ri	
Rj	
Rk	
Rl	
Rm	
Rn	
Ro	
Rp	

TABLE 7-continued

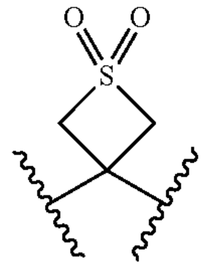
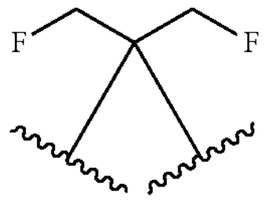
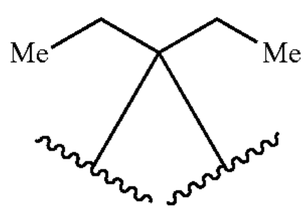
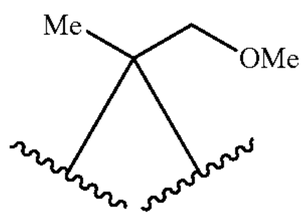
	CR9R10
Rq	
Rr	
Rs	
Rt	

TABLE 8

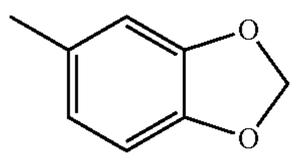
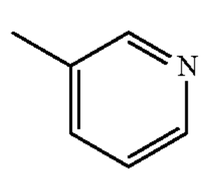
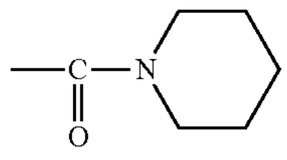
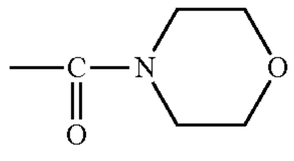
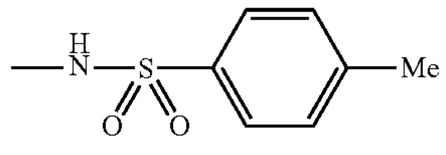
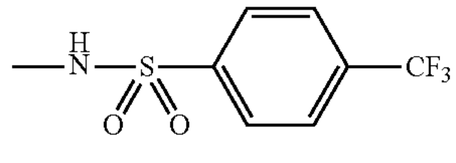
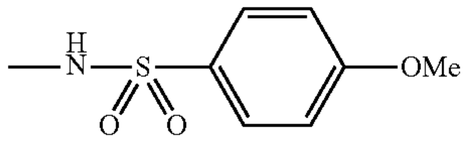
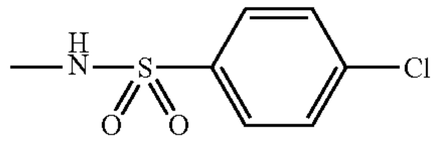
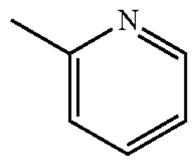
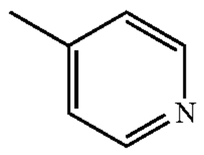
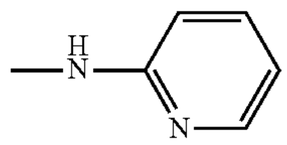
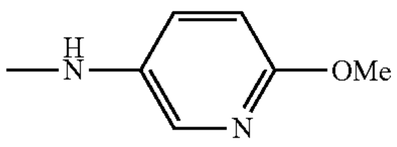
	R3
VA	H
VB	Me
VC	OH
VD	OMe
VE	CONH2
VF	CONHiPr
VG	NH2
VH	NHAc
VI	NHSO2Me
VJ	Ph
VK	
VL	
VM	
VN	
VO	
VP	

TABLE 8-continued

	R3
VQ	
VR	
VS	NHSO2Ph
VT	NHCOPh
VU	CONHMe
VV	CONMe2
VW	NHMe
VX	NHiPr
VY	NHPh
VZ	
WA	
WB	
WC	

(AA,VA), (AA,VB), (AA,VC), (AA,VD), (AA,VE), (AA, VF), (AA,VG), (AA,VH), (AA,VI), (AA,VJ), (AA,VK), (AA,VL), (AA,VM), (AA,VN), (AA,VO), (AA,VP), (AA, VQ), (AA,VR), (AA,VS), (AA,VT), (AA,VU), (AA,VV), (AA,VW), (AA,VX), (AA,VY), (AA,VZ), (AA,WA), (AA,WB), (AA,WC), (AB,VA), (AB,VB), (AB,VC), (AB, VD), (AB,VE), (AB,VF), (AB,VG), (AB, VH), (AB,VI), (AB,VJ), (AB,VK), (AB,VL), (AB,VM), (AB,VN), (AB, VO), (AB,VP), (AB,VQ), (AB,VR), (AB, VS), (AB,VT), (AB,VU), (AB,VV), (AB,VW), (AB,VX), (AB,VY), (AB, VZ), (AB,WA), (AB,WB), (AB,WC), (AC,VA), (AC,VB), (AC,VC), (AC,VD), (AC,VE), (AC, VF), (AC,VG), (AC, VH), (AC,VI), (AC,VJ), (AC,VK), (AC,VL), (AC,VM), (AC,VN), (AC,VO), (AC,VP), (AC, VQ), (AC,VR), (AC, VS), (AC,VT), (AC,VU), (AC,VV), (AC,VW), (AC,VX), (AC,VY), (AC,VZ), (AC,WA), (AC,WB), (AC,WC), (AD, VA), (AD,VB), (AD,VC), (AD,VD), (AD,VE), (AD,VF), (AD,VG), (AD,VH), (AD,VI), (AD,VJ), (AD,VK), (AD, VL), (AD,VM), (AD, VN), (AD,VO), (AD,VP), (AD,VQ), (AD,VR), (AD,VS), (AD,VT), (AD,VU), (AD,VW), (AD, VW), (AD,VX), (AD,VY), (AD,VZ), (AD,WA), (AD,WB), (AD,WC), (AE,VA), (AE,VB), (AE,VC), (AE, VD), (AE,VE), (AE, VF), (AE,VG), (AE,VH), (AE,VI), (AE,VJ), (AE,VK), (AE,VL), (AE,VM), (AE,VN), (AE, VO), (AE,VP), (AE, VQ), (AE,VR), (AE,VS), (AE,VT), (AE,VU), (AE,VV), (AE,VW), (AE,VX), (AE,VY), (AE, VZ), (AE,WA), (AE,WB), (AE,WC), (AF,VA), (AF,VB), (AF,VC), (AF, VD), (AF,VE), (AF,VF), (AF,VG), (AF,VH), (AF,VI), (AF,VJ), (AF,VK), (AF,VL), (AF,VM), (AF,VN), (AF,

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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.

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

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.

For each of emesis (rhythmic constriction 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 collected.

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

1) Preparation of Test Diet (Dye)

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

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

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

Morphine hydrochloride is dissolved in a physiological saline.

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

4) Method

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

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

Transport rate (%)=(dye movement distance (cm))/full length of small intestine (cm))×100

M.P.E. (%)={(small intestine transport rate (%) of each individual of test compound administration group−average small intestine transport rate (%) of solvent administration group)/(average small intestine transport rate (%) of control group−average small intestine transport rate (%) of solvent administration group)}×100

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%.

The present compound has the opioid receptor (particularly, opioid δ 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.

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 agonistic 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.

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.

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.).

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.

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.

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.

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.

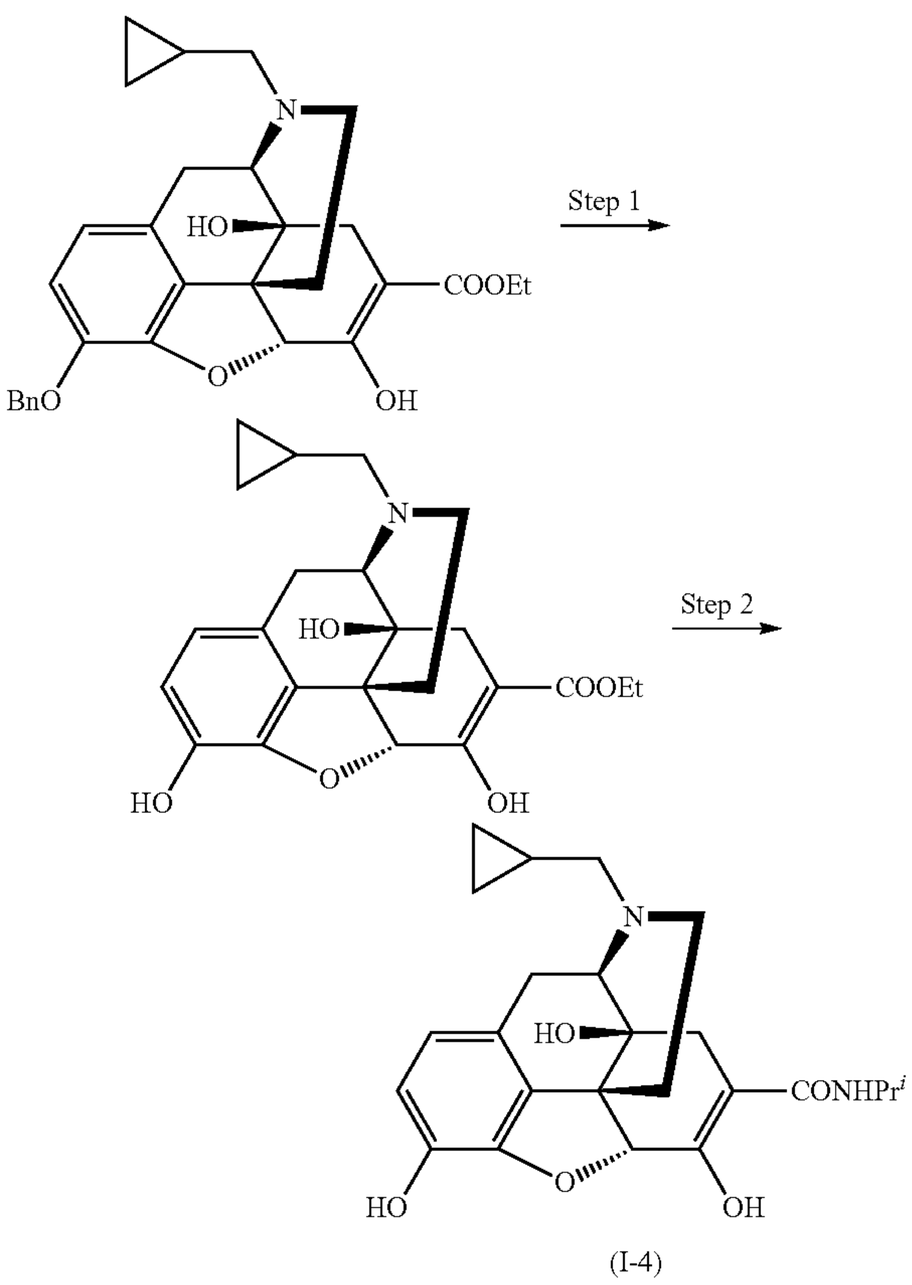
A dose is different depending on state of a disease, an administration route, and an age and a weight of a patient, and is usually 0.1 μg to 1 g/day, preferably 0.01 to 200 mg/day when orally administered to an adult, and is usually 0.1 μg to 10 g/day, preferably 0.1 to 2 g/day when parenterally administered.

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)

[Chemical formula 11]



(I-4)

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

(First Step) 7-ethoxycarbonylnaltrexone

To a suspension of 3-O-benzyl-7-ethoxycarbonylnaltrexone 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 (300 MHz, $CDCl_3$) 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=8.1 Hz), 12.12 (s, 1H).

Elemental analysis (C23H27NO6.0.2H2O) (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

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 5 mol/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%.

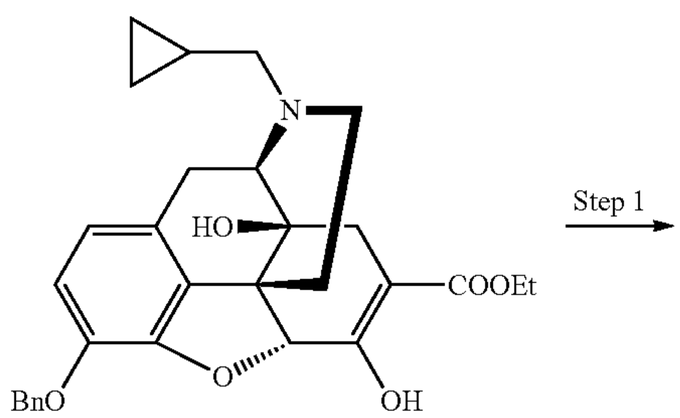
NMR (300 MHz, d6-DMSO) δ 0.12-0.15 (m, 2H), 0.44-0.53 (m, 2H), 0.83 (m, 1H), 1.02 (d, 3H, J=6.6 Hz), 1.08 (d, 3H, J=6.6 Hz), 1.41 (d, 1H, J=11.4 Hz), 1.85 (d, 1H, J=15.6 Hz), 2.04-2.62 (m, 8H), 3.04 (d, 1H, J=18.6 Hz), 3.24 (m, 1H), 3.96 (m, 1H), 4.71 (s, 1H), 4.74 (s, 1H), 6.51 (d, 1H, J=8.4 Hz), 6.56 (d, 1H, J=8.4 Hz), 7.40 (br d, 1H, J=7.2 Hz), 9.16 (s, 1H), 14.50 (s, 1H).

Elemental analysis (C24H30N2O5.0.2H2O) (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)

[Chemical formula 12]



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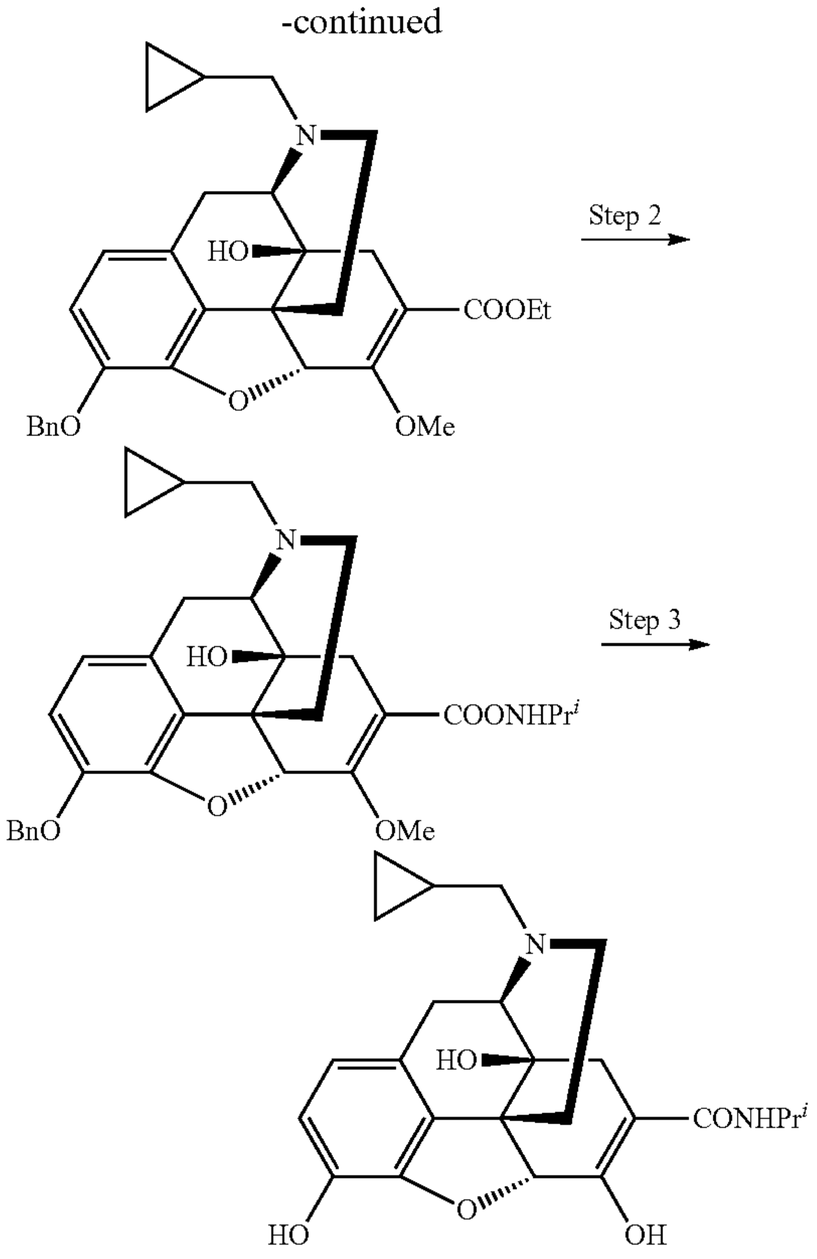


(I-44)

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

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

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-methylnaltrexone was used in the next reaction without purification. To a solution of the above residue in dimethylformamide (3 mL) were successively added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (40 mg, 0.2 mmol), 1-hydroxybenzotriazole (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), 0.50-0.65 (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)

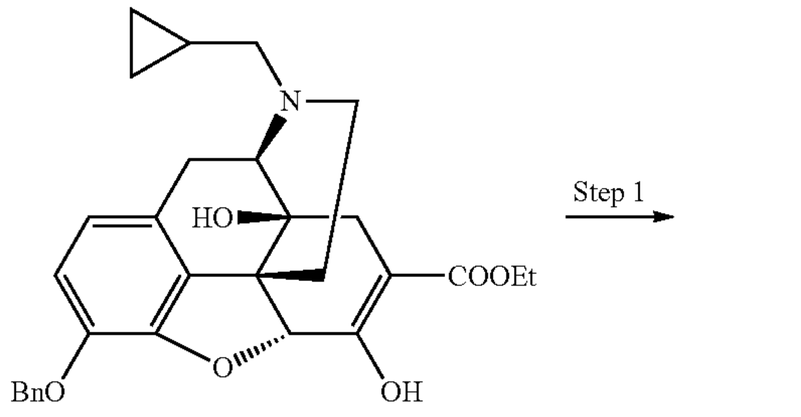
(Third Step) 7-isopropylaminocarbonyl-6-O-methylnaltrexone

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.

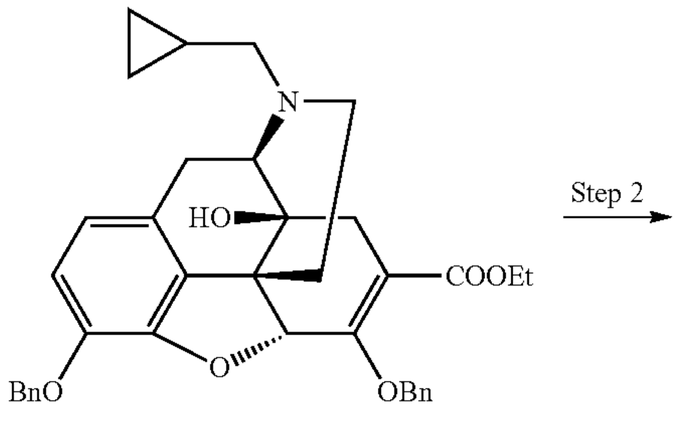
^{1}H NMR ($CDCl_3$, δ ppm): 0.10-0.15 (m, 2H), 0.50-0.70 (m, 2H), 0.85 (m, 1H), 1.12 (d, J=0.9 Hz, 3H), 1.14 (d, J=0.9 Hz, 3H), 1.66 (d, J=11.4 Hz, 1H), 2.06-2.80 (m, 8H), 3.00-3.30 (m, 2H), 3.92 (s, 3H), 4.05 (m, 1H), 4.80 (br s, 1H), 5.26 (br s, 1H), 6.56 (d, J=8.1 Hz, 1H), 6.69 (d, J=8.1 Hz, 1H), 7.36 (d, J=7.8 Hz, 1H)

EXAMPLE 3

[Chemical formula 13]



1



2

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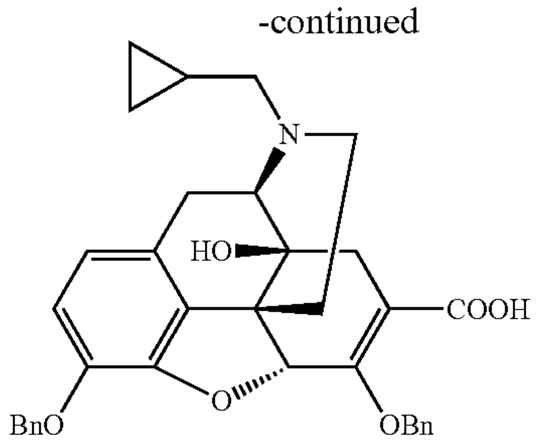
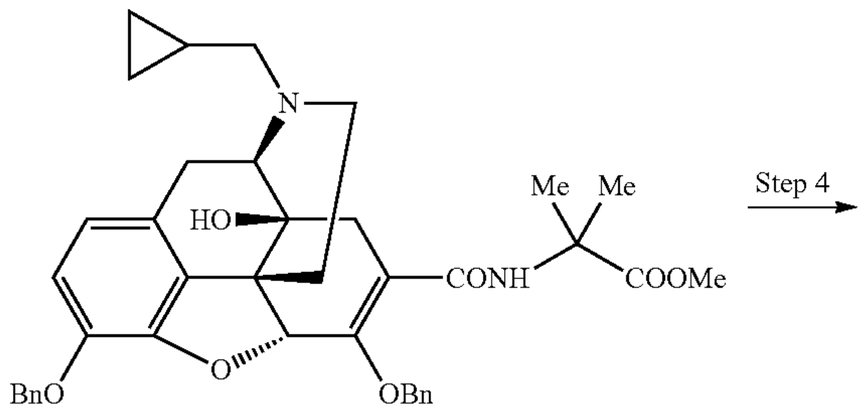
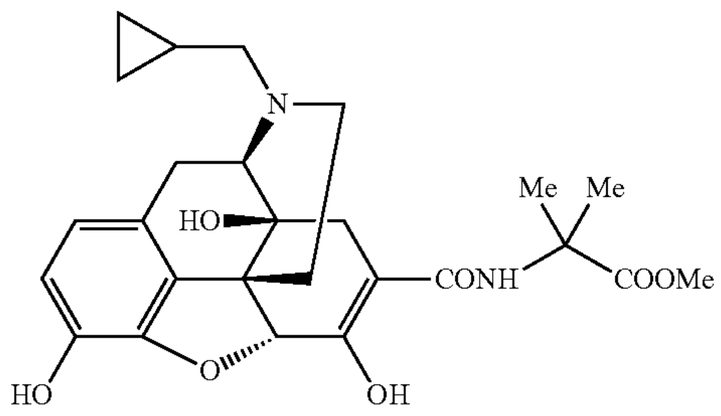


3



4



(I-49)

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

(First Step)

A solution of compound (1) (28.7 g, 57.0 mmol) in tetrahydrofuran (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)

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)

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-methyl-morpholine (82 μL, 0.743 mmol), and the mixture was stirred at room temperature overnight. The reaction solution was poured into ice-water and 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)

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, δ 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)

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

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

In addition, in Tables,

[Chemical formula 14]

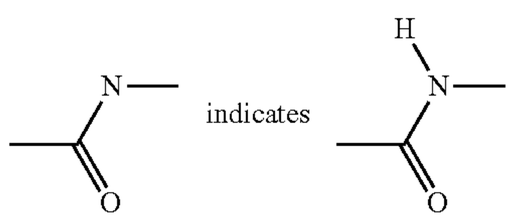


TABLE 9

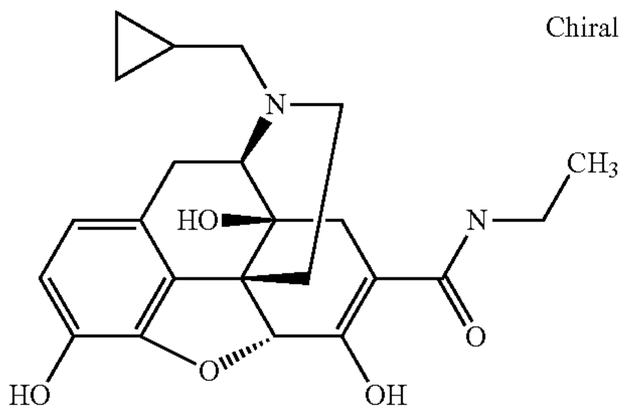
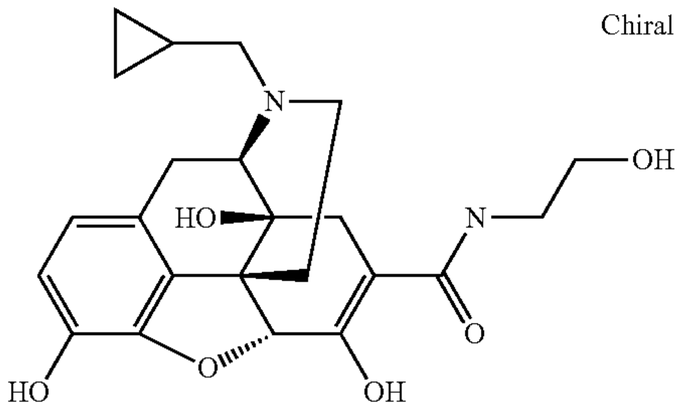
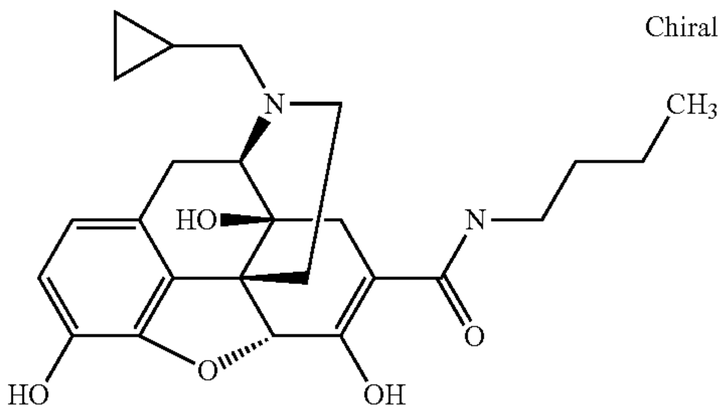
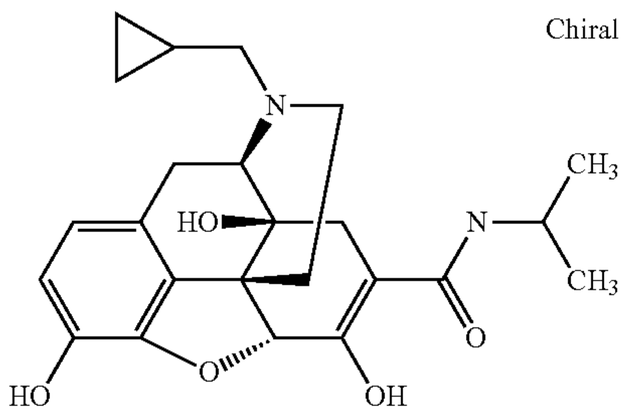
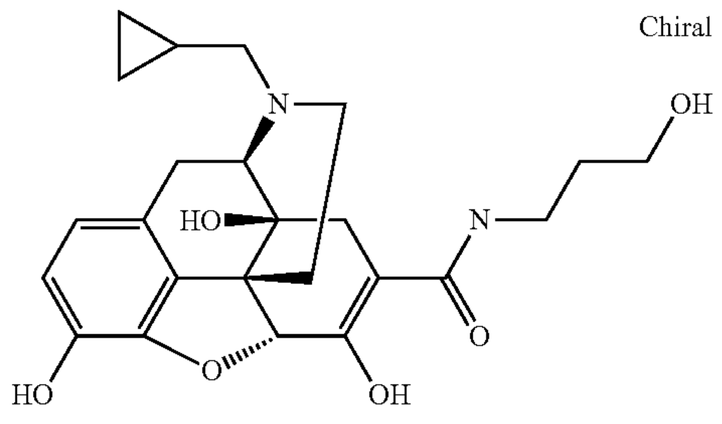
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-1		Chiral	0.10-0.25 (m, 2H), 0.50-0.60 (m, 2H), 1.87 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H), 1.68 (d, J = 11.4 Hz, 1H), 2.20-2.80 (m, 7H), 3.00-3.35 (m, 5H), 4.94 (s, 1H), 5.40 (m, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 14.20 8br s, 1H)
I-2		Chiral	0.10-0.20 (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), 6.55 (d, J = 8.1 Hz, 1H), 7.77 (br s, 1H)
I-3		Chiral	(CDCl3) 0.10-0.25 (m, 2H), 0.50-0.62 (m, 2H), 0.81-0.98 (m, 4H), 1.24-1.74 (m, 6H), 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 = 8.7 Hz, 1H), 14.21 (s, 1H).
I-4		Chiral	0.12-0.15 (m, 2H), 0.44-0.53 (m, 2H), 0.83 (m, 1H), 1.02 (d, 3H, J = 6.6 Hz), 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 = 8.4 Hz), 7.40 (br d, 1H, J = 7.2 Hz), 9.16 (s, 1H), 14.50 (s, 1H)
I-5		Chiral	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 = 8.7 Hz, 1H), 7.70 (s, 1H). 9.15 (br s, 1H), 14.42 (s, 1H).

TABLE 9-continued

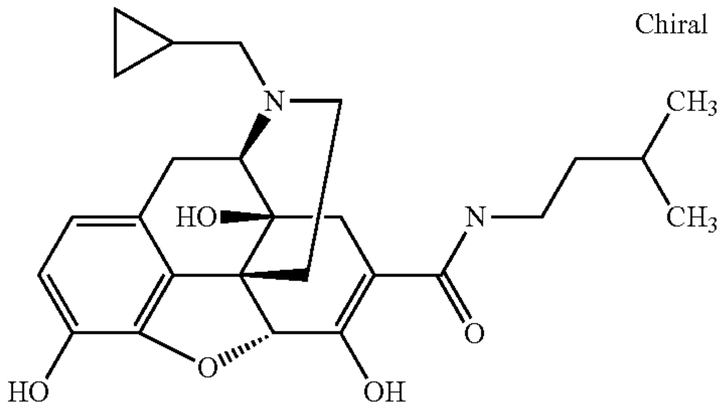
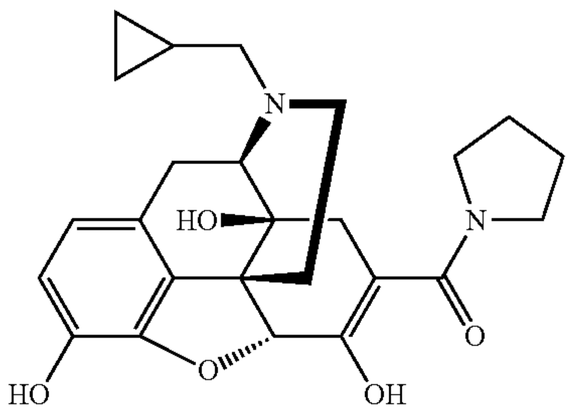
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-6	 Chiral	0.10-0.25 (m, 2H), 0.50-0.62 (m, 2H), 0.85 (m, 1H), 1.42 (d, J = 11.7 Hz, 1H), 1.83-2.64 (m, 10H), 2.10 (s, 6H), 3.00-3.18 (m, 3H), 4.72 (s, 1H), 4.74 (s, 1H), 6.51 (d, J = 8.7 Hz), 6.56 (d, J = 8.7 Hz, 1H), 7.65 (s, 1H), 9.10 (br s, 1H).
I-7		0.10-0.25 (m, 2H), 0.50-0.60 (m, 2H), 1.90 (m, 1H), 1.57 (dd, J = 2.4, 12.6 Hz, 2H), 1.85-2.80 (m, 10H), 3.00-3.25 (m, 3H), 3.35-3.60 (m, 3H), 4.20 (m, 1H), 4.76 (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

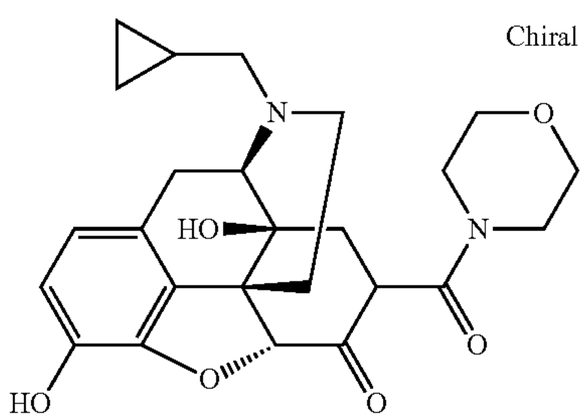
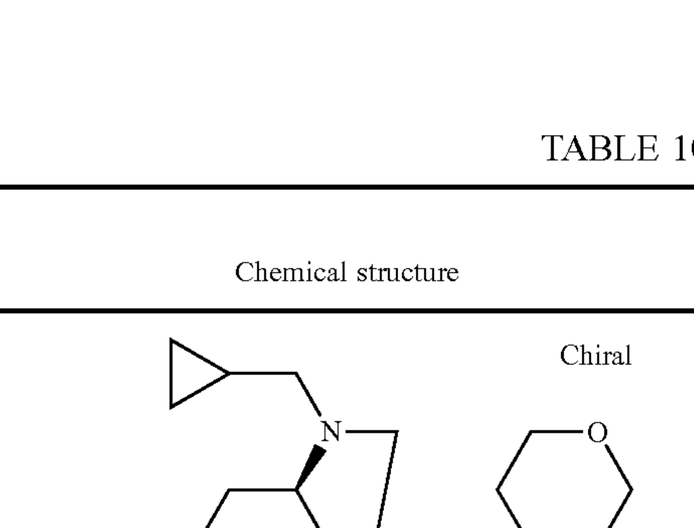
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-8	 Chiral	0.10-0.20 (m, 2H), 0.45-0.68 (m, 2H), 1.88 (m, 1H), 1.35 (d, J = 11.4 Hz, 1H), 1.65-2.20 (m, 4H), 2.30-3.60 (m, 13H), 4.29 (dd, J = 4.8, 12.6 Hz, 1H), 5.08 (s, 1H), 5.23 (br s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 9.25 (br s, 1H)
I-9	Chiral	(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 = 18.6 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), 6.55 (d, J = 8.7 Hz), 6.72 (d, J = 8.7 Hz, 1H), 7.22-7.39 (m,5H), 14.15 (s, 1H).
I-10	 Chiral	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, 1H), 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)

TABLE 10-continued

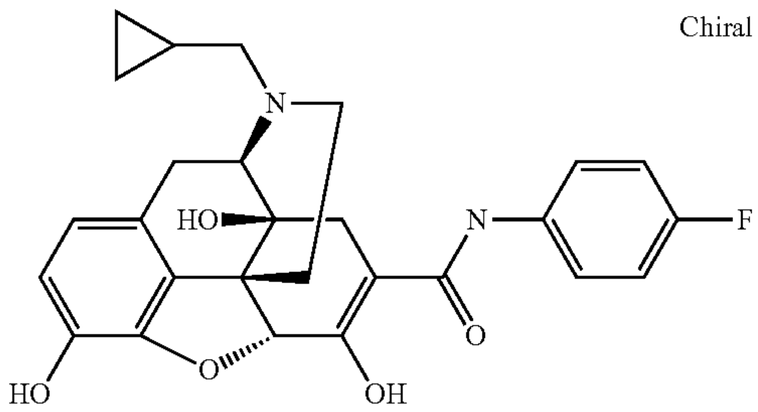
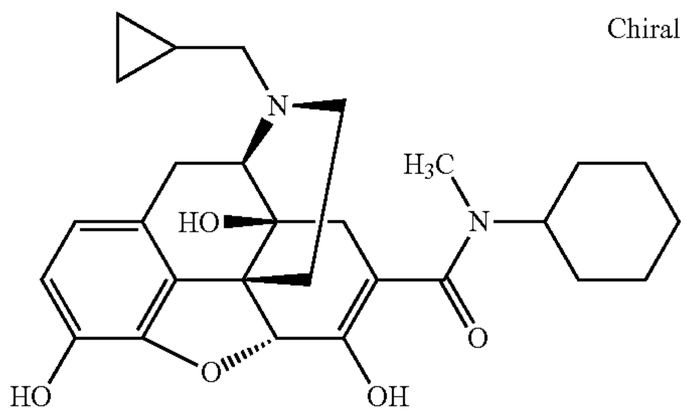
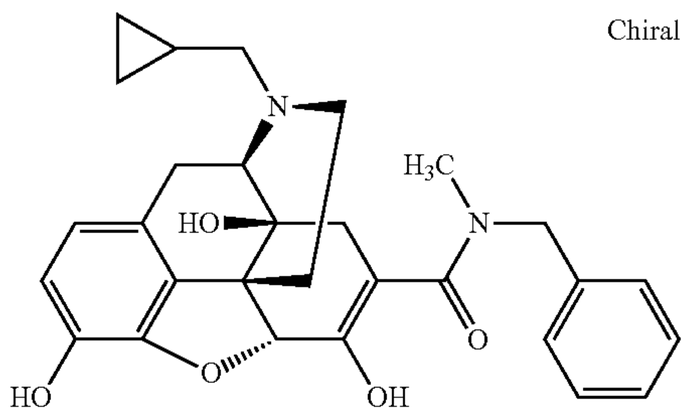
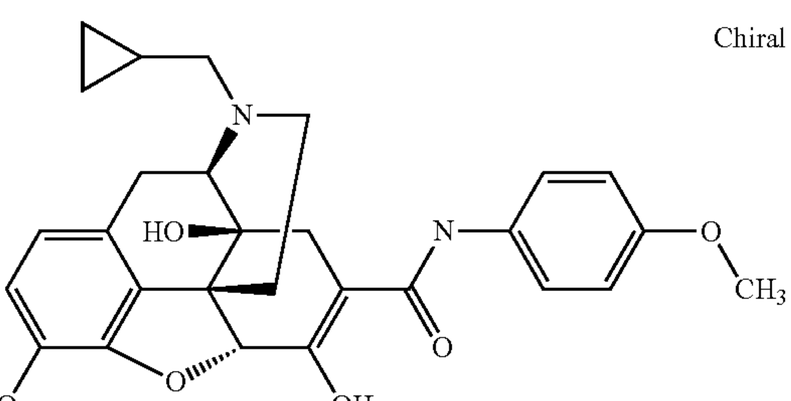
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-11		Chiral	0.10-0.22 (m, 2H), 0.44-0.58 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.75-3.40 (m, 10H), 4.78 (s, 1H), 4.83 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.13 (t, J = 8.7 Hz, 2H), 7.48-7.56 (m, 2H), 9.17 (s, 1H), 9.27 (br s, 1H), 13.90 (br s, 1H)
I-12		Chiral	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		Chiral	0.10-0.25 (m, 2H), 0.50-0.60 (m, 2H), 0.87 (m, 1H), 1.58 (d, J = 111.7 Hz, 1H), 2.05-2.50 (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 Hz, 1H), 7.20-7.40 (m,5H)
I-14		Chiral	0.10-0.22 (m, 2H), 0.45-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 2.10-3.40 (m, 10H), 3.78 (s, 3H), 4.96 (s, 1H), 6.36 (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

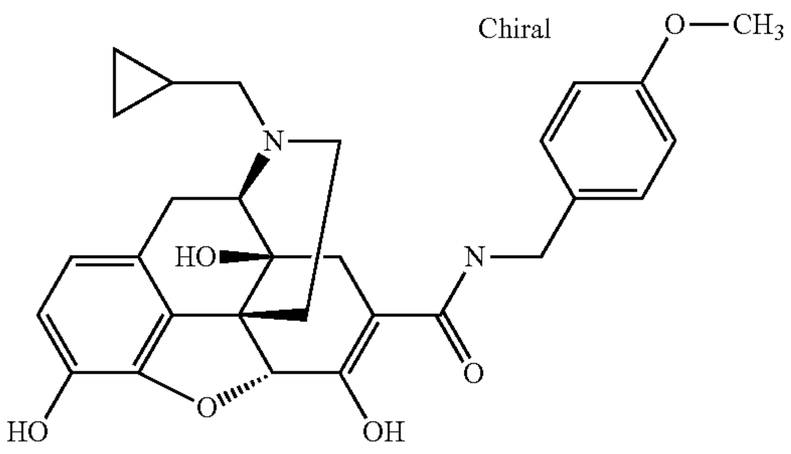
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-15		Chiral	0.05-0.20 (m, 2H), 0.45-0.60 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 2.00-3.35 (m, 10H), 3.78 (s, 3H), 4.34 (d, J = 5.1 Hz, 2H), 4.91 (s, 1H), 5.61 (br s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 14.13 (br s, 1H)

TABLE 11-continued

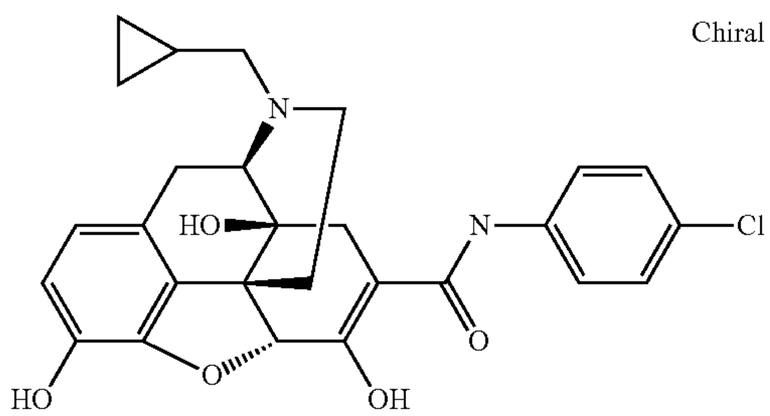
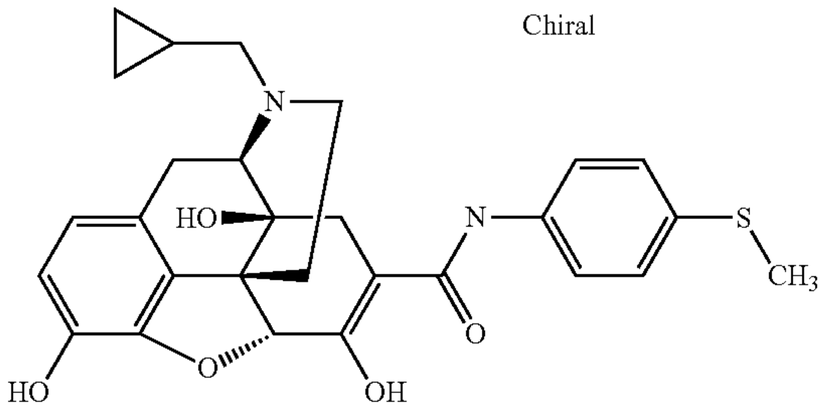
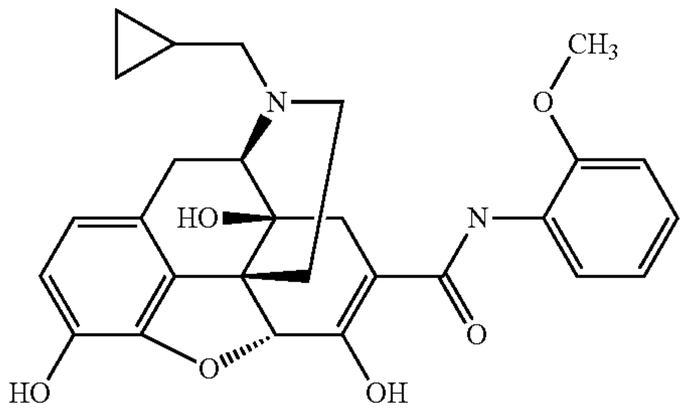
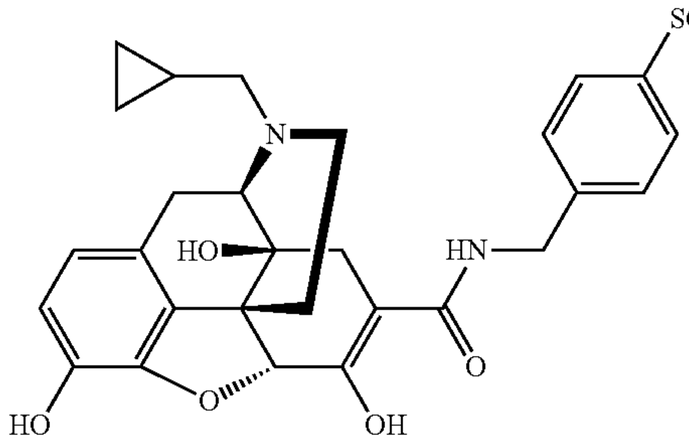
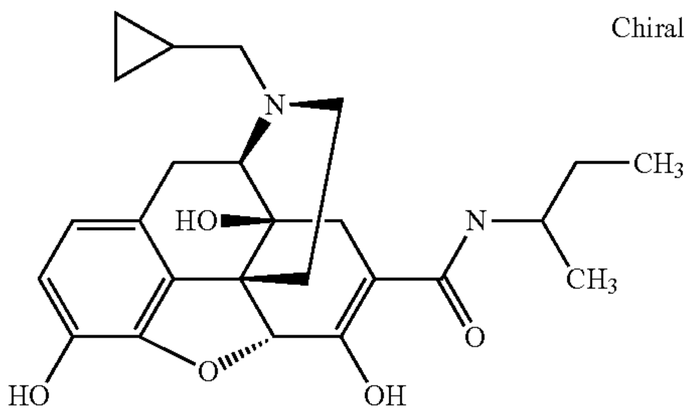
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-16		Chiral	0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.77 (s, 1H), 4.84 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.30-7.38 (m, 2H), 7.53-7.60 (m, 2H), 9.17 (s, 1H), 9.28 (br s, 1H), 13.80 (br s, 1H)
I-17		Chiral	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), 4.77 (s, 1H), 4.82 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 9.17 (s, 1H), 9.27 (br s, 13.90 (br s, 1H)
I-18		Chiral	0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.65-3.40 (m, 10H), 3.80 (s, 3H), 4.81 (br s, 2H), 6.52 (d, J = 8.1 Hz, 1H), 6.58 (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			
I-20		Chiral	0.12-0.14 (d, J = 4.5 Hz, 2H), 0.46-0.52 (t, 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), 6.50-6.57 (dd, J = 8.1, 14.4 Hz, 2H), 7.31-7.38 (m, 1H), 9.15 (br s, 1H), 14.52 (br s, 1H)

TABLE 11-continued

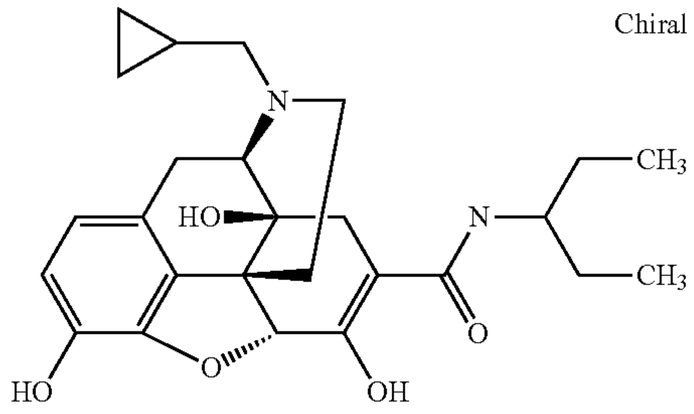
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-21	 Chiral	0.12-0.14 (d, J = 4.2 Hz, 2H), 0.49 (t, J = 8.1 Hz, 2H), 0.69-0.86 (m, 6H), 1.32-1.47 (m, 5H), 1.88 (d, J = 15.3 Hz, 1H), 2.06-2.30 (m, 4H), 2.45-2.61 (m), 3.04 (d, J = 18.0 Hz, 1H), 3.19-3.24 (m, 1H), 4.71-4.75 (m, 2H), 6.05-6.58 (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

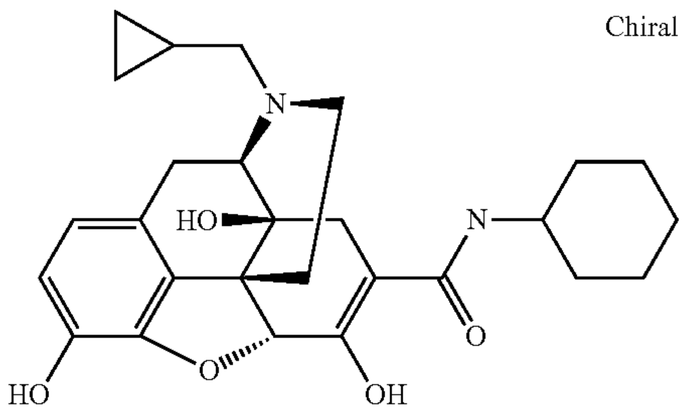
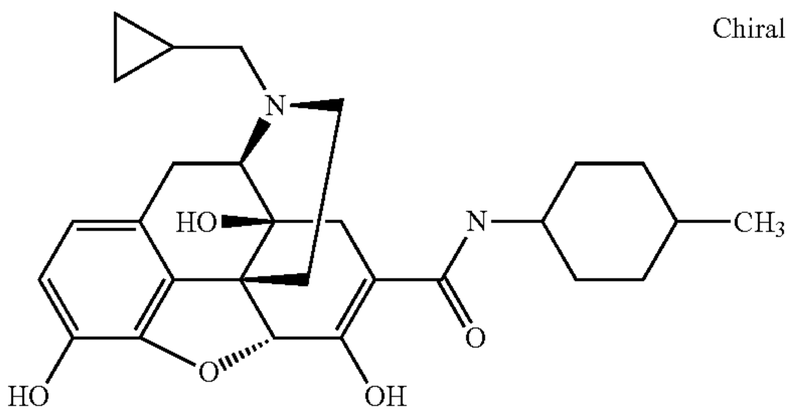
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-22	 Chiral	0.12-0.14 (d, J = 4.5 Hz, 2H), 0.49 (t, J = 8.1 Hz, 2H), 0.85 (m, 1H), 1.06 (m, 1H), 1.16-1.28 (m, 4H), 1.39-1.43 (d, J = 11.4 Hz, 1H), 1.54-1.70 (m, 6H), 1.84-1.89 (d, J = 15.6 Hz, 1H), 2.08-2.60 (m, 6H), 3.00-3.07 (d, J = 18.6 Hz, 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	 Chiral	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	Chiral	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 = 8.1 Hz, 1H), 9.13 (br s, 1H), 14.46 (br s, 1H)
I-25	Chiral	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), 6.50-6.57 (dd; J = 8.1, 18.9 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 9.12 (br s, 1H), 14.41 (br s, 1H)

TABLE 12-continued

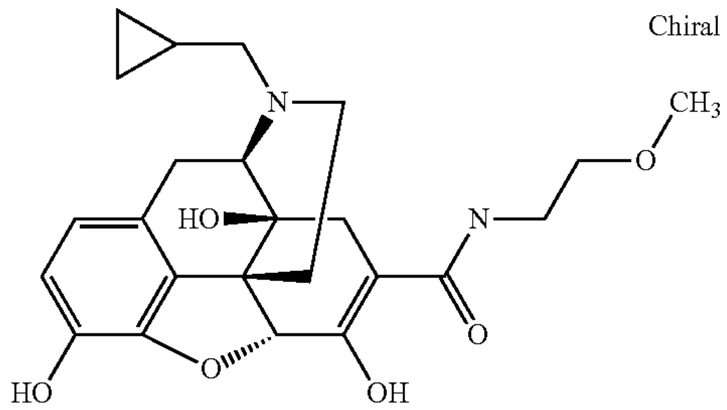
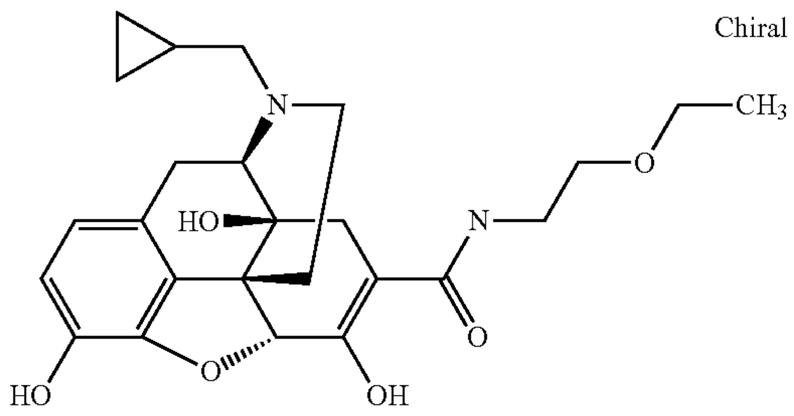
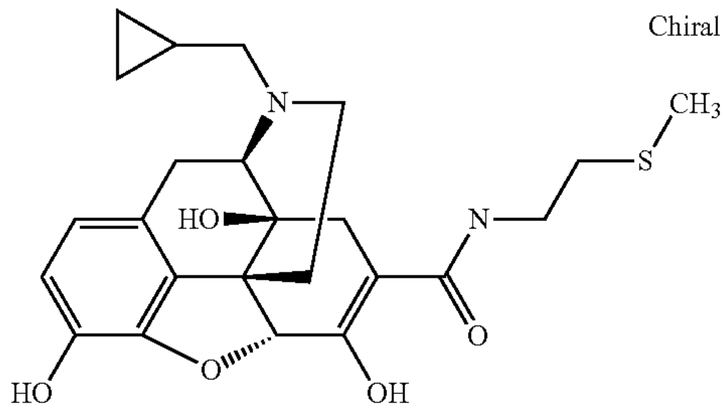
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-26		Chiral	0.16-0.19 (m, 2H), 0.48-0.57 (m, 2H), 0.88 (m, 1H), 1.46 (d, J = 11.2 Hz, 1H), 1.92 (d, J = 15.6 Hz, 1H), 2.04-2.66 (m, 6H), 3.08 (d, J = 18.8 Hz, 1H), 3.17-3.40 (m, 6H), 3.24 (s, 3H), 4.77 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 7.76 (br t, 1H), 9.15 (s, 1H), 14.33 (s, 1H).
I-27		Chiral	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), 6.55 (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		Chiral	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

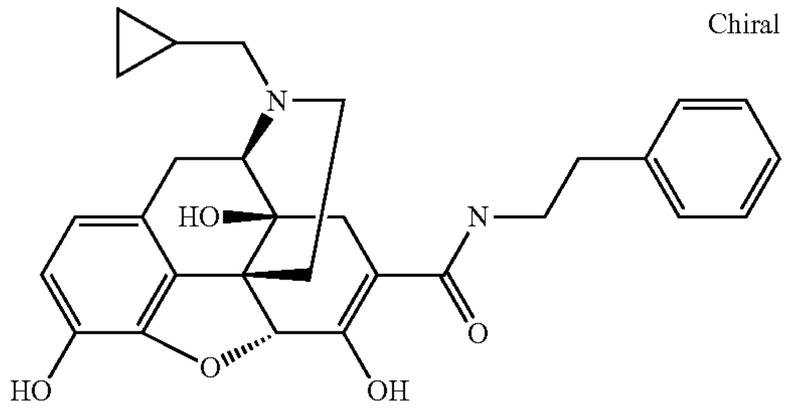
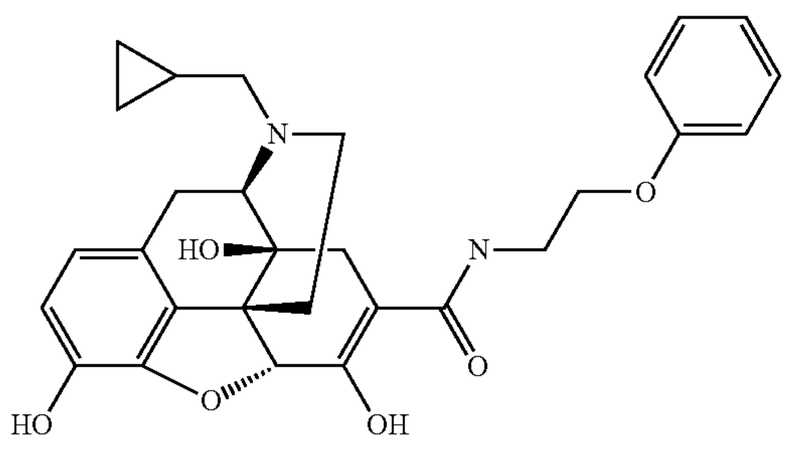
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-29		Chiral	0.17-0.18 (m, 2H), 0.51-0.57 (m, 2H), 0.90 (m, 1H), 1.46 (d, J = 11.6 Hz, 1H), 1.93 (d, J = 16.0 Hz. 1H), 2.11-2.78 (m, 6H), 3.08 (d, J = 18.4 Hz, 1H), 3.21 (d, J = 6.0 Hz, 1H), 3.27-3.32 (m, 5H), 4.77 (s, 1H), 6.56 (d, J = 8.0 Hz, 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		Chiral	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), 6.63 (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).

TABLE 13-continued

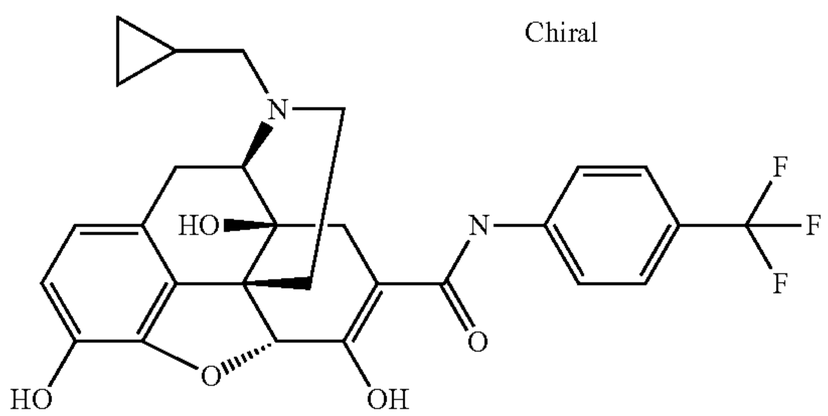
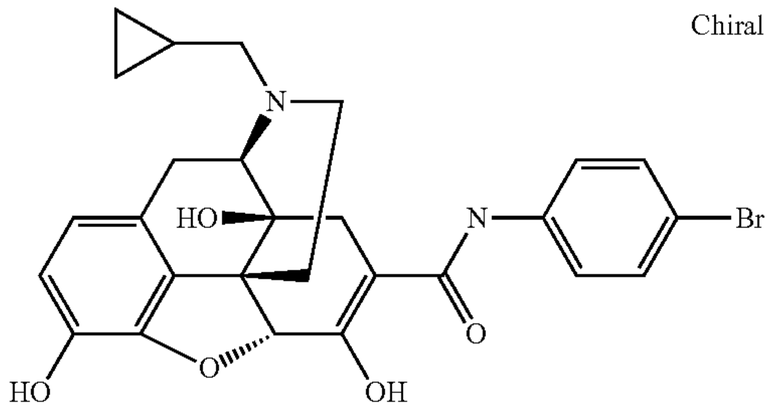
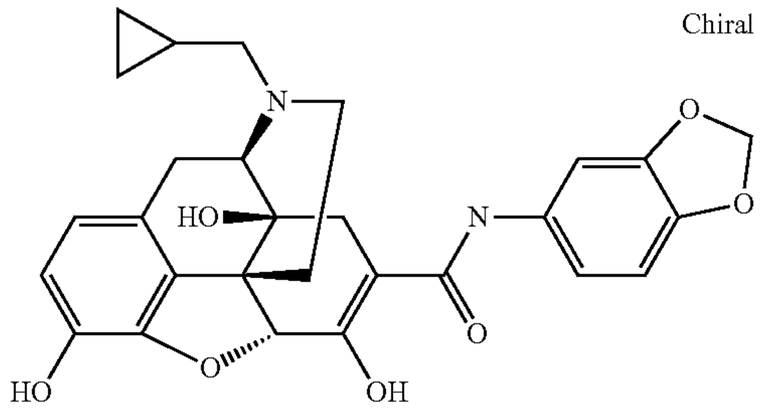
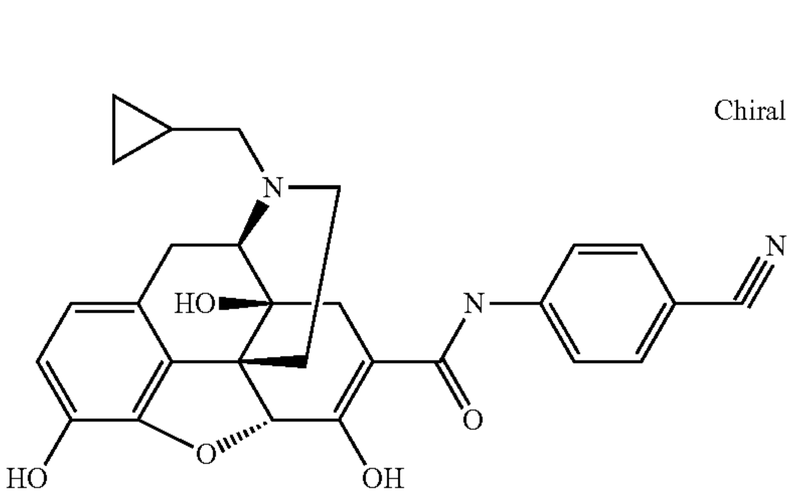
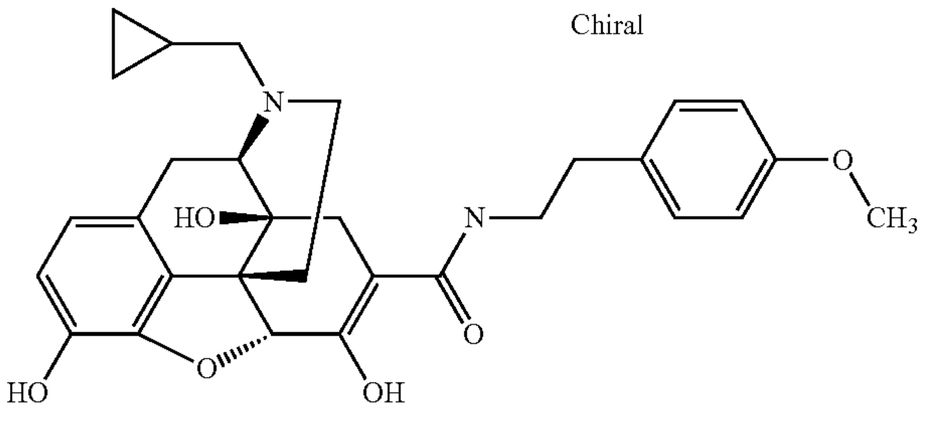
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-31	 Chiral	0.10-0.28 (m, 2H), 0.44-0.65 (m, 2H), 0.94 (m, 1H), 1.50 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.72 (br s, 1H), 4.86 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.54-7.80 (m, 4H), 9.16 (s, 1H), 9.32 (s, 1H), 13.90 (br s, 1H)
I-32	 Chiral	0.10-0.25 (m, 2H), 0.42-0.62 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 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	 Chiral	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), 6.58 (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	 Chiral	0.20-0.40 (m, 2H), 0.45-0.65 (m, 2H), 0.96 (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	 Chiral	0.10-0.20 (m, 2H), 0.50-0.62 (m, 2H), 0.88 (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 = 8.4 Hz, 2H), 14.17 (br s, 1H)

TABLE 14

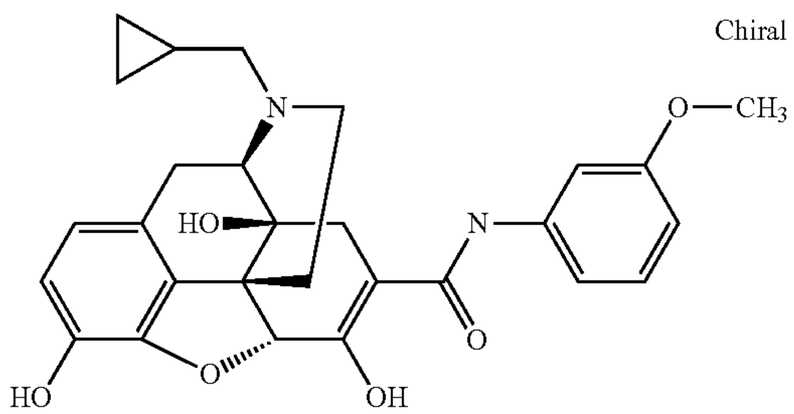
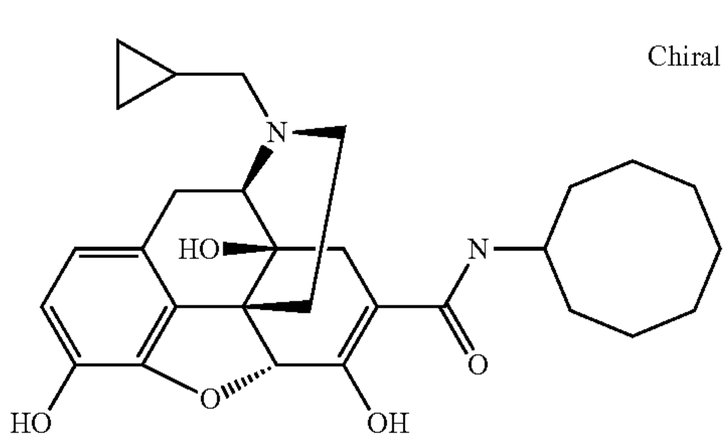
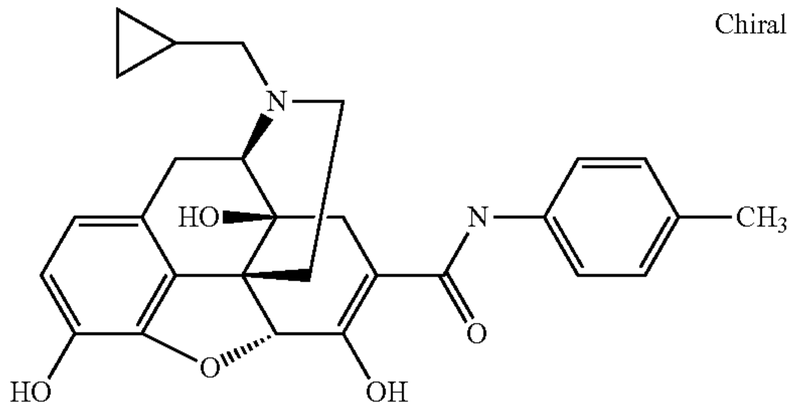
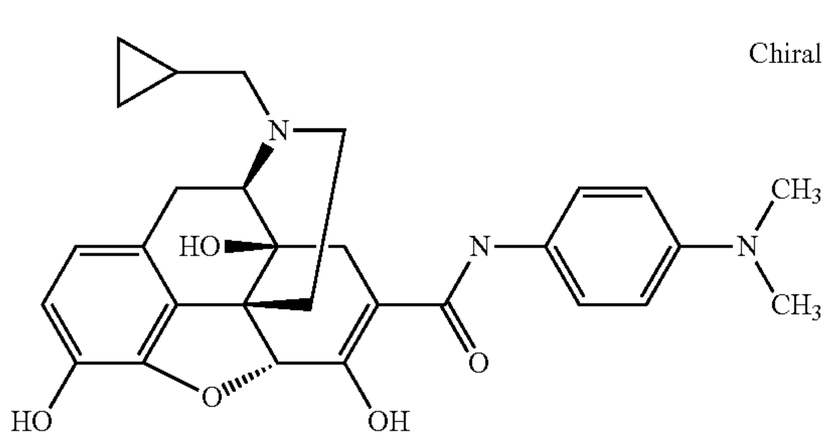
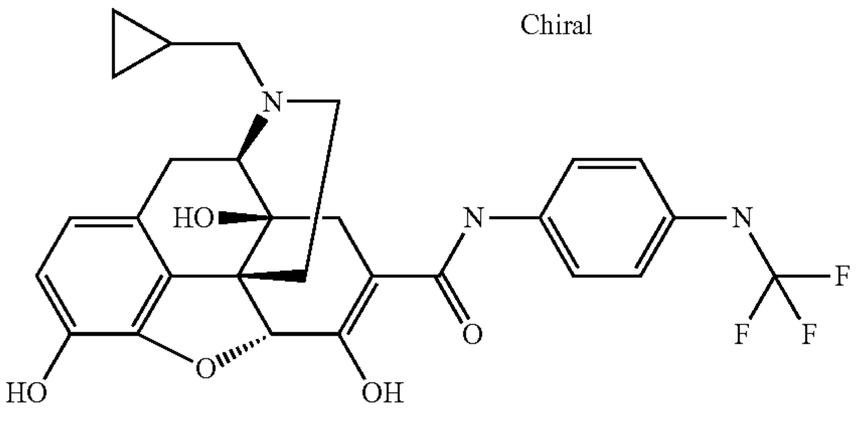
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-36	 Chiral	0.10-0.25 (m, 2H), 0.43-0.63 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 3.71 (s, 3H), 4.77 (s, 1H), 4.82 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.64 (m, 1H), 7.00-7.25 (m, 3H), 9.17 (s, 1H), 9.27 (s, 1H), 13.90 (br s, 1H)
I-37	 Chiral	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), 3.18-3.20 (d, J = 6 Hz, 1H), 3.87 (br s, 1H), 4.71-4.76 (m, 2H), 6.49-6.57 (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	 Chiral	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), 6.58 (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	 Chiral	0.10-0.20 (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	 Chiral	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

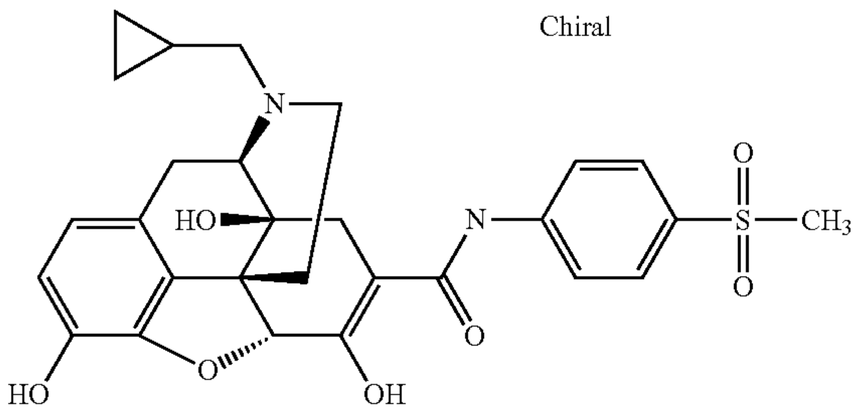
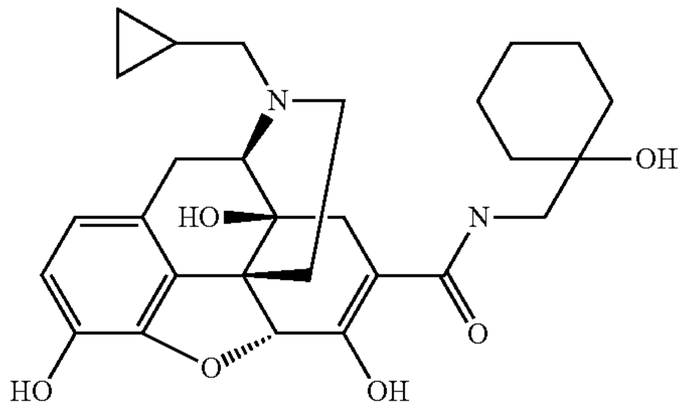
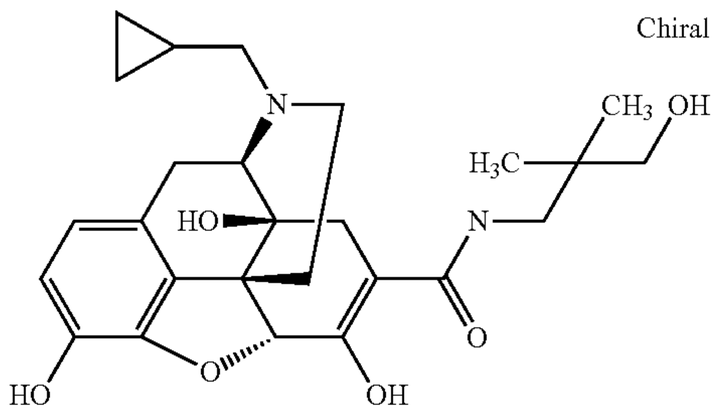
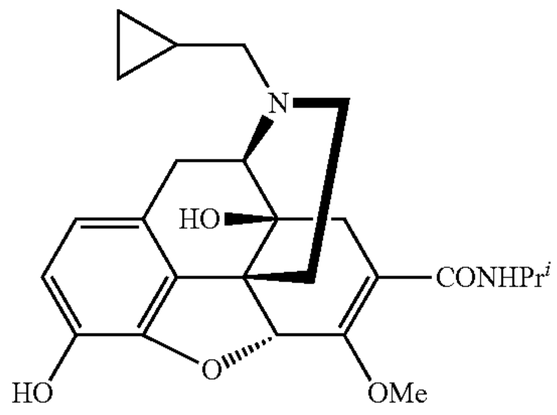
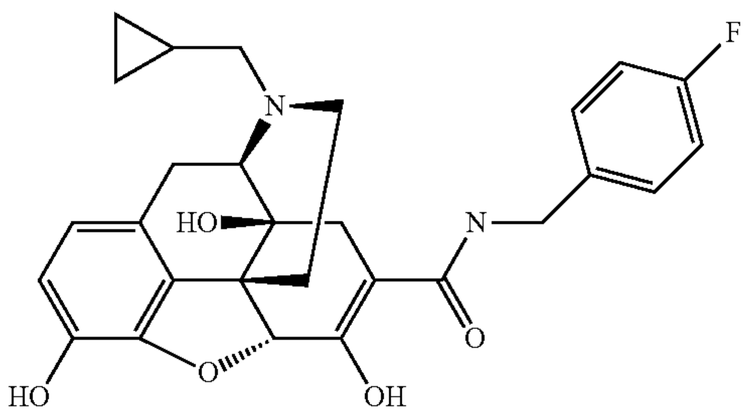
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-41	 Chiral	0.20-0.40 (m, 2H), 0.45-0.70 (m, 2H), 0.96 (m, 1H), 1.50 (m, 1H), 1.70-3.40 (m, 13H), 4.67 (br s, 1H), 4.88 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.76 (s, 4H), 9.18 (s, 1H), 9.31 (s, 1H), 14.00 (br s, 1H)
I-42	 Chiral	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	 Chiral	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), 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)
I-45	 Chiral	

TABLE 16

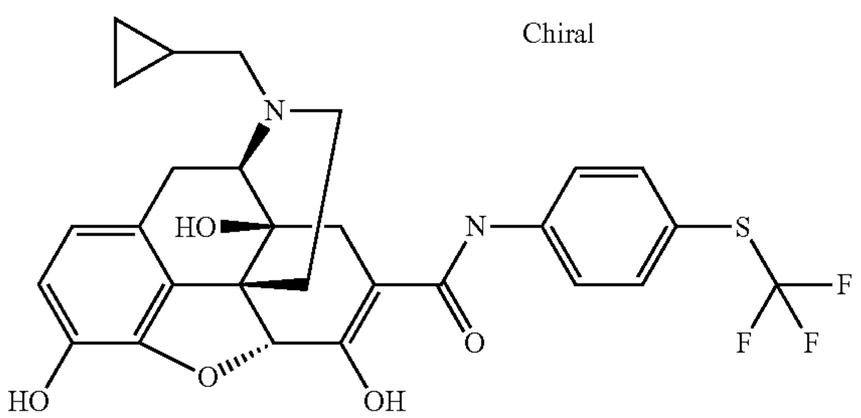
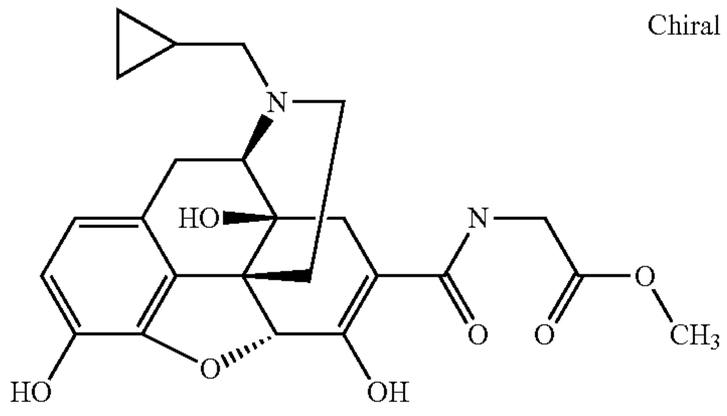
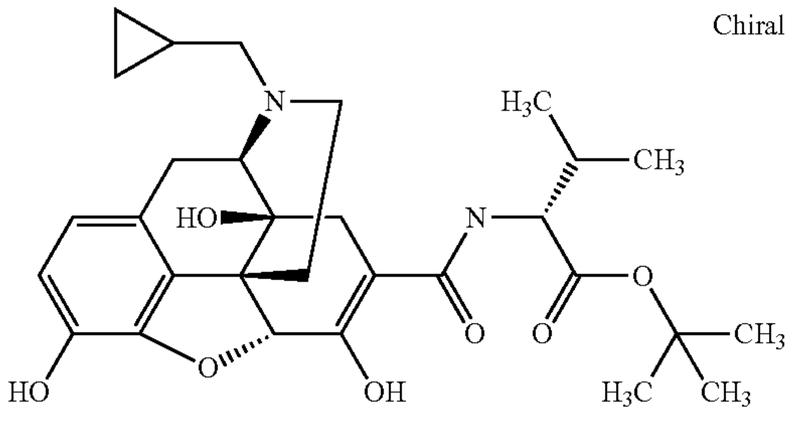
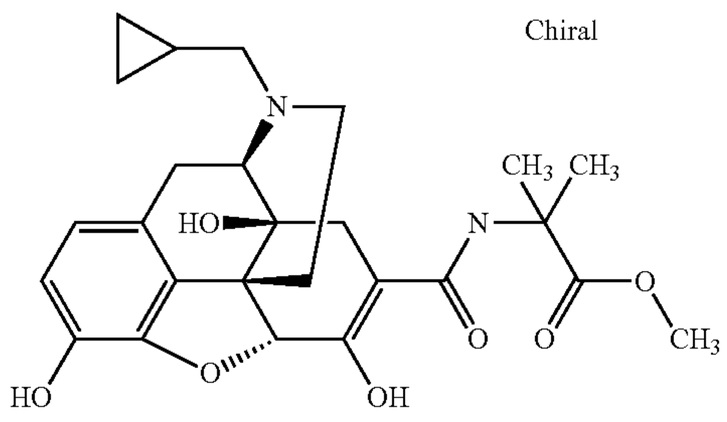
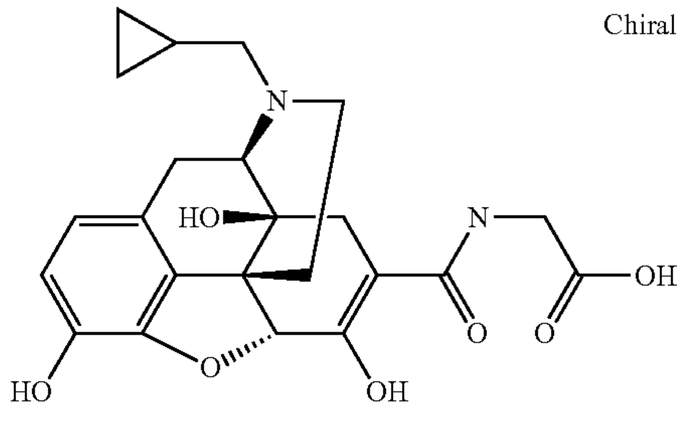
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-46	 Chiral	0.15-0.35 (m, 2H), 0.45-0.70 (m, 2H), 0.92 (m, 1H), 1.50 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.72 (br s, 1H), 4.86 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.54-7.74 (m, 4H), 9.16 (s, 1H), 9.27 (s, 1H), 14.00 (br s, 1H)
I-47	 Chiral	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, 1H), 6.58 (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	 Chiral	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	 Chiral	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	 Chiral	0.10-0.20 (m, 2H), 0.40-0.60 (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 = 4.5 hz, 1H), 9.18 (br s, 1H), 14.00 (br s, 1H)

TABLE 17

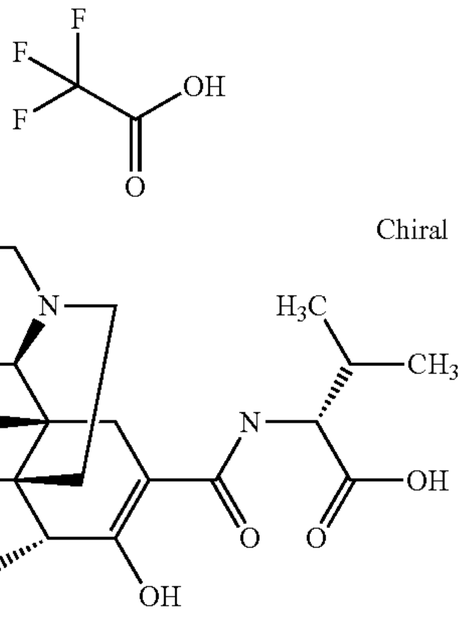
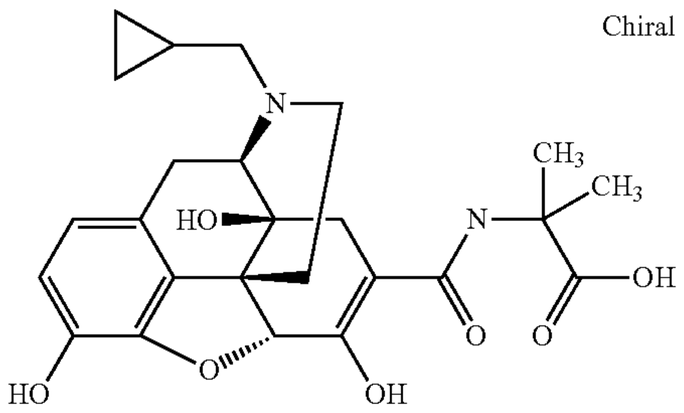
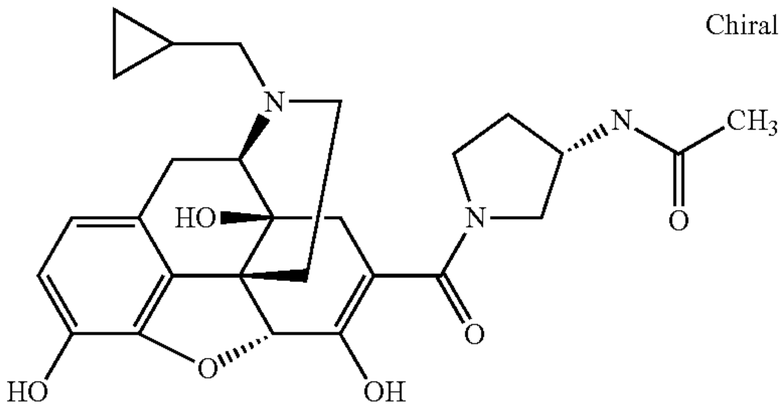
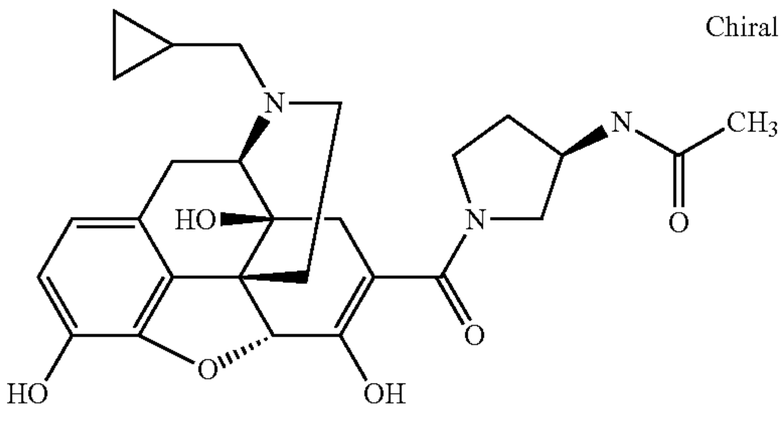
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-51	 Chiral	0.30-0.50 (m, 2H), 0.55-0.75 (m, 2H), 0.89 (d, J = 3.3 Hz, 3H), 0.91 (d, J = 3.3 Hz, 3H), 1.04 (m, 1H), 1.65 (d, J = 13.5 Hz, 1H), 2.00-3.92 (m, 11H), 4.10 (t, J = 6.6 Hz, 1H), 4.95 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 9.43 (s, 1H), 13.66 (br s, 1H)
I-52	 Chiral	0.10-0.25 (m, 2H), 0.45-0.60 (m, 2H), 0.89 (m, 1H), 1.34 (s, 3H), 1.36 (s, 3H), 1.46 (d, J = 9.6 Hz, 1H), 1.90-3.40 (m, 10H), 4.75 (s, 1H), 6.54 (d, J = 8.1 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	 Chiral	0.13-0.14 (m, 2H), 0.47-0.49 (m, 2H), 0.88 (m, 1H), 1.30 (m, 1H), 1.63-2.10 (m, 6H), 2.30-2.70 (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	 Chiral	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), 5.06 (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 = 6.4 Hz, 1H), 8.32 (s, 1H), 9.23 (br, 1H), 10.97 (s, 1H).

TABLE 18

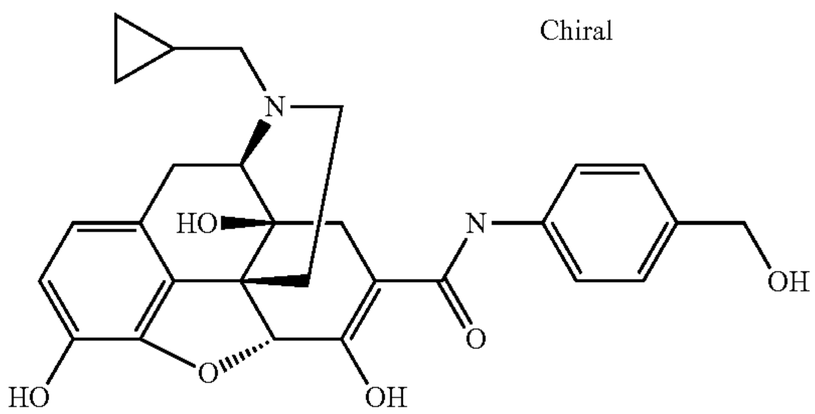
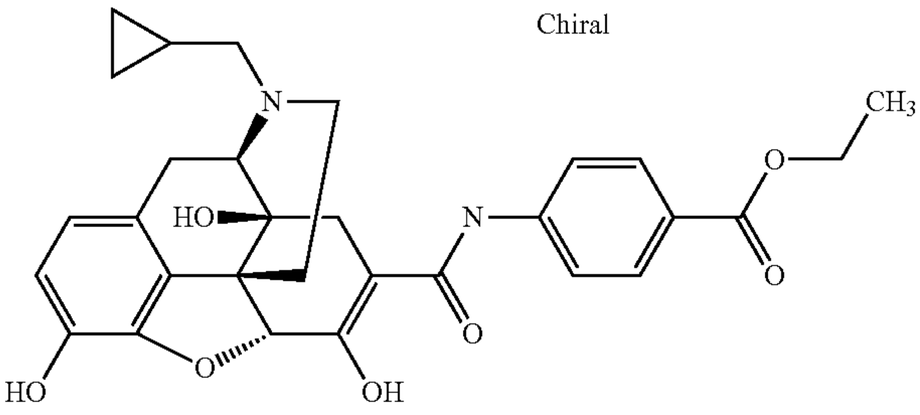
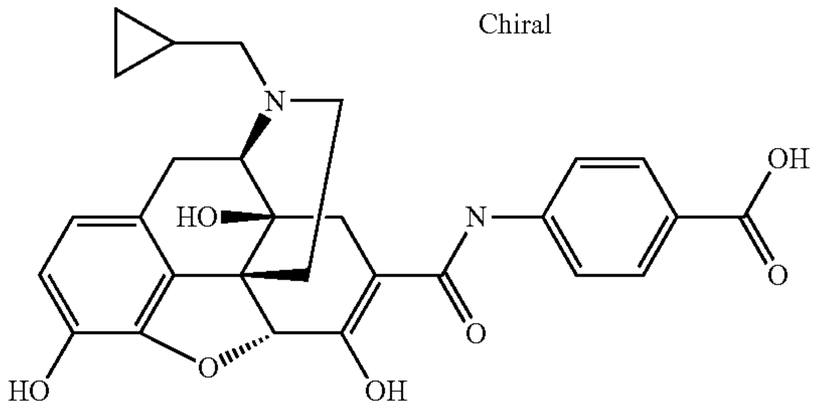
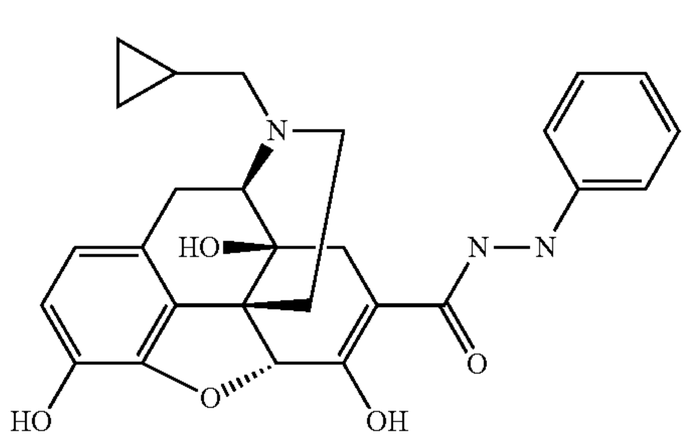
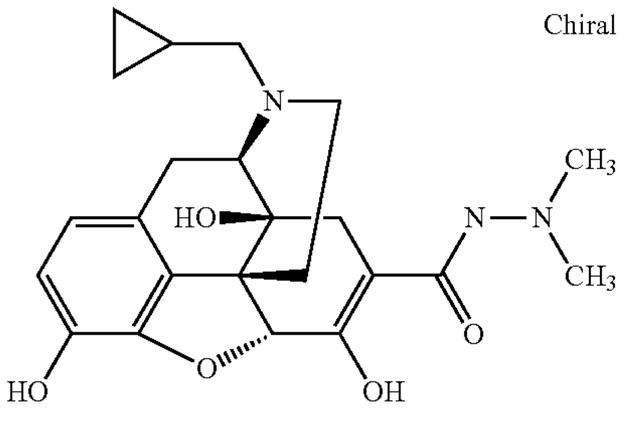
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-55	 Chiral	0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.42 (s, 2H), 4.77 (s, 1H), 5.12 (s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 9.20 (s, 1H), 9.28 (s, 1H), 14.00 (br s, 1H)
I-56	 Chiral	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	 Chiral	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	 Chiral	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	 Chiral	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

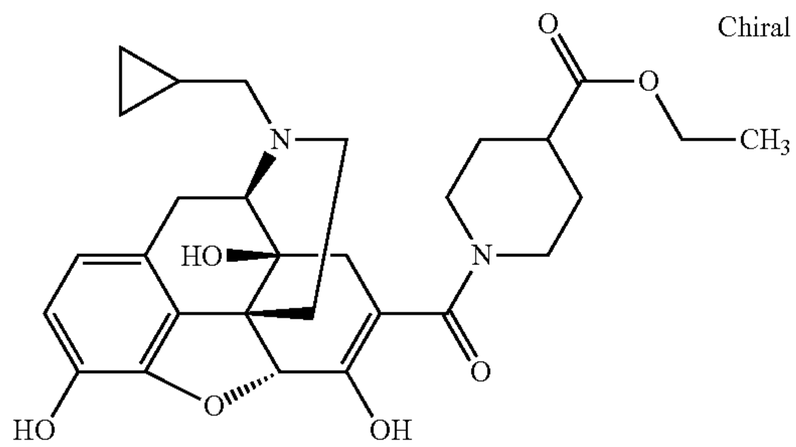
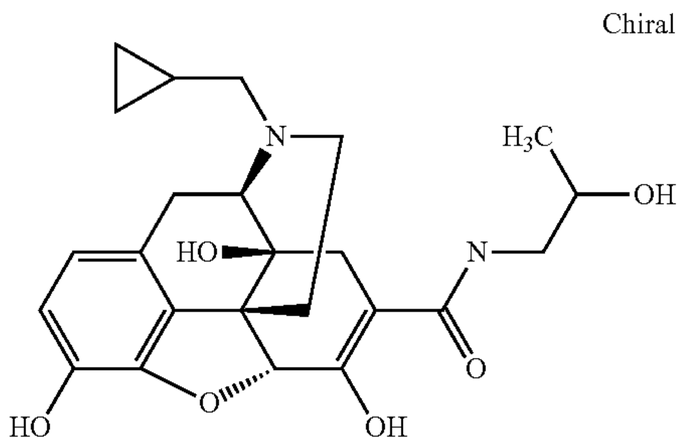
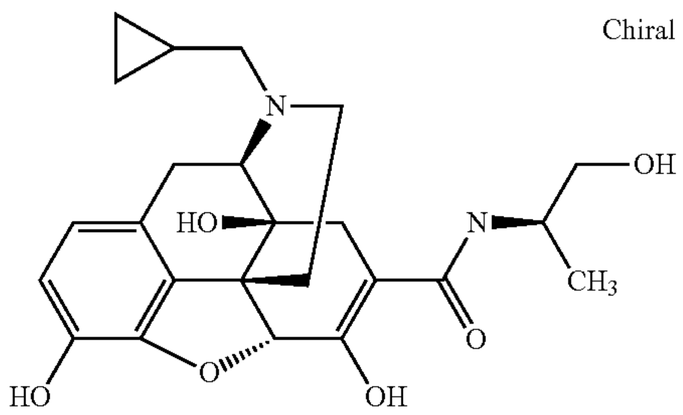
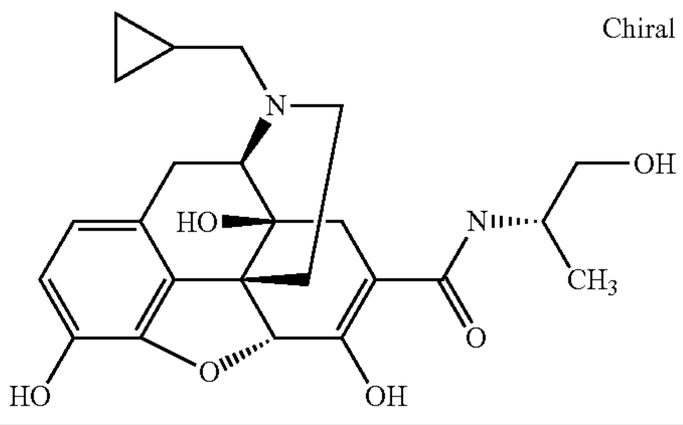
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-60	 Chiral	0.10-0.20 (m, 2H), 0.45-0.55 (m, 2H), 0.88 (m, 1H), 1.81 (t, J = 7.2 Hz, 3H), 1.20-3.75 (m, 20H), 4.07 (q, J = 7.2 Hz, 2H), 5.13 (s, 1H), 5.21 (br s, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 9.21b (br s, 1H)
I-61	 Chiral	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	 Chiral	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), 1.88 (d, J = 15.6 Hz, 1H), 2.04-2.31 (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	 Chiral	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), 2.04-2.32 (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), 6.50-6.58 (m, 2H), 7.24 (m, 1H), 9.14 (s, 1H), 14.41 (br, s, 1H)

TABLE 20

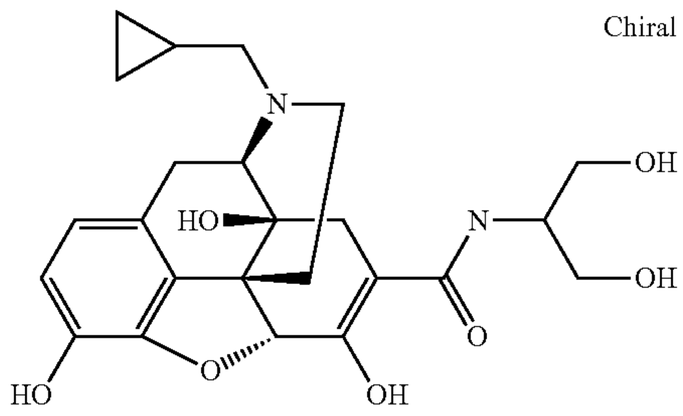
Compound No.	Chemical structure	NMR 1H-NMR (d6-DMSO) δ)
I-64	 Chiral	0.13 (d, J = 4.8 Hz, 2H), 0.43-0.55 (m, 2H), 0.85 (m, 1H), 1.41 (d, J = 12.3 Hz, 1H), 1.92 (d, J = 16.2 Hz, 1H), 2.06-2.32 (m, 4H), 2.43-2.61 (m, 3H), 3.04 (d, J = 18.3 Hz, 1H), 3.20 (d, J = 6.6 Hz, 1H), 3.33-3.44 (m, 4H), 3.82 (m, 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)

TABLE 20-continued

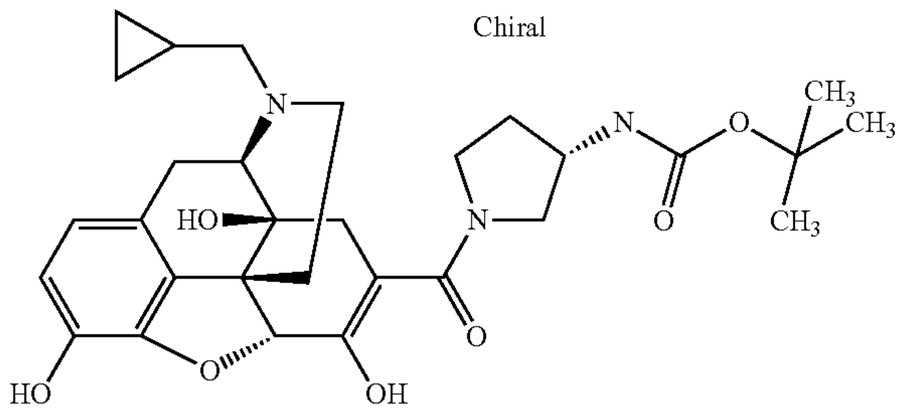
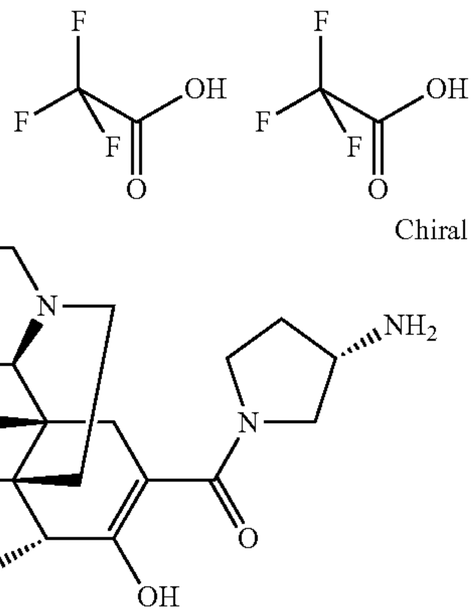
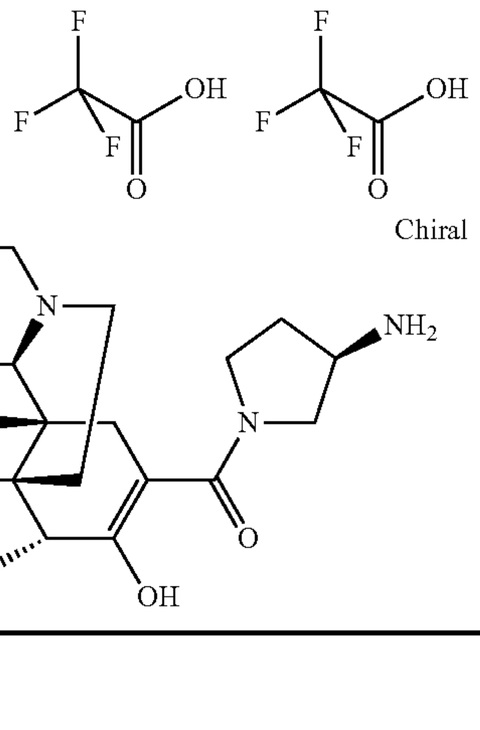
Compound No.	Chemical structure	NMR 1H-NMR (d6-DMSO) δ)
I-65	 Chiral	0.17-0.18 (m, 2H), 0.51-0.53 (m, 2H), 0.92 (m, 1H), 1.34 (m, 1H), 1.35 (br s, 9H), 1.71-3.49 (m, 14H), 3.95-4.20 (m, 3H), 5.10 (br, 1H), 5.26 (br, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 7.10 (br, 1H), 8.35 (s, 1H), 9.24 (s, 1H).
I-66	 Chiral	0.41 (m, 1H), 0.50 (m, 1H), 0.60 (m, 1H), 0.69 (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	 Chiral	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 = 8.4 Hz, 1H), 8.21 (br, 1H), 8.26 (br, 1H), 8.99 (br, 1H).

TABLE 21

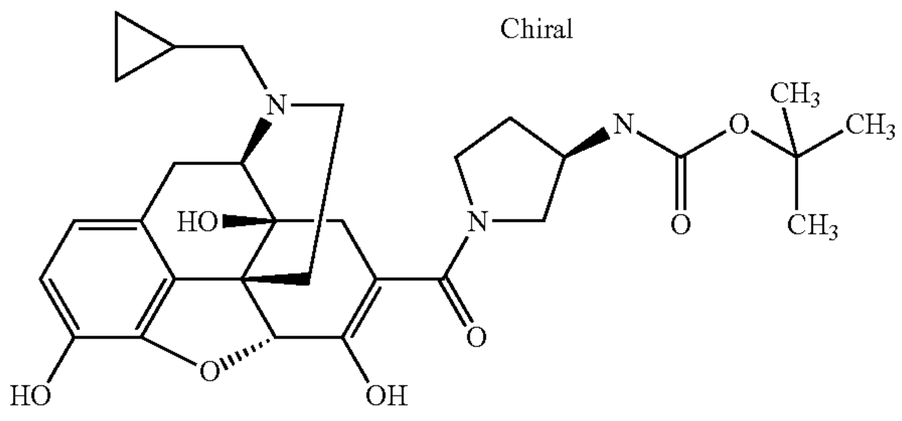
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-68	 Chiral	0.17-0.18 (m, 2H), 0.51-0.53 (m, 2H), 0.92 (m, 1H), 1.34 (m, 1H), 1.43 (br s, 9H), 1.71-2.03 (m, 5H), 2.18-2.74 (m, 4H), 2.92-3.69 (m, 5H), 3.95-4.20 (m, 2H), 5.07 (s, 1H), 5.26 (br, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 7.20 (br, 1H), 9.25 (s, 1H).

TABLE 21-continued

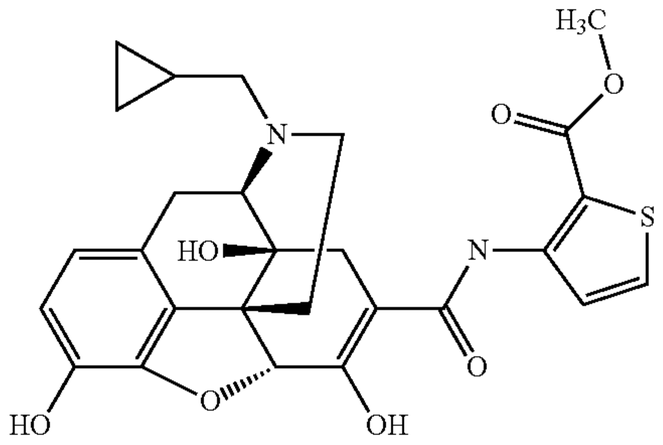
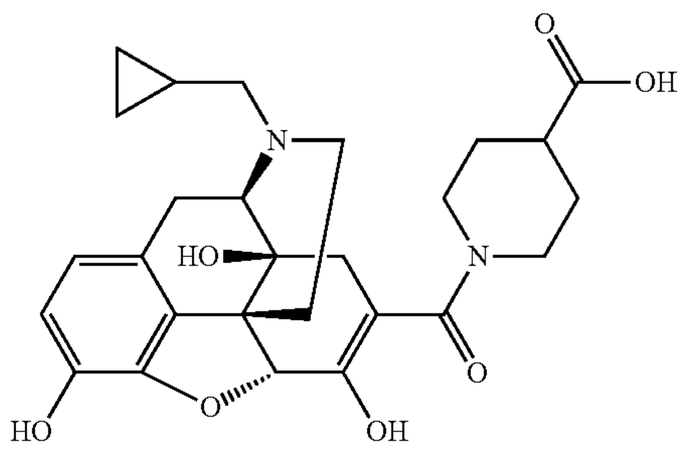
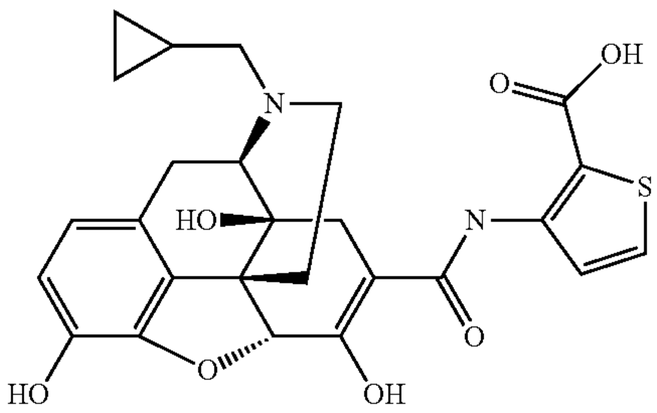
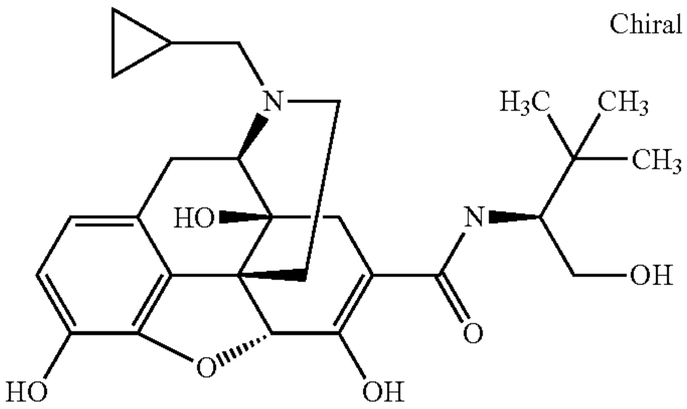
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-69	 Chiral	0.10-0.26 (m, 2H), 0.42-0.60 (m, 2H), 0.90 (m, 1H), 1.47 (d, J = 10.5 Hz, 1H), 1.90-3.40 (m, 10H), 3.84 (s, 3H), 4.81 (br s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.80 (br s, 1H), 8.08 (br s, 1H), 9.18 (br s, 1H), 11.60 (br s, 1H)
I-70	 Chiral	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	 Chiral	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 (br s, 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	 Chiral	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, 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

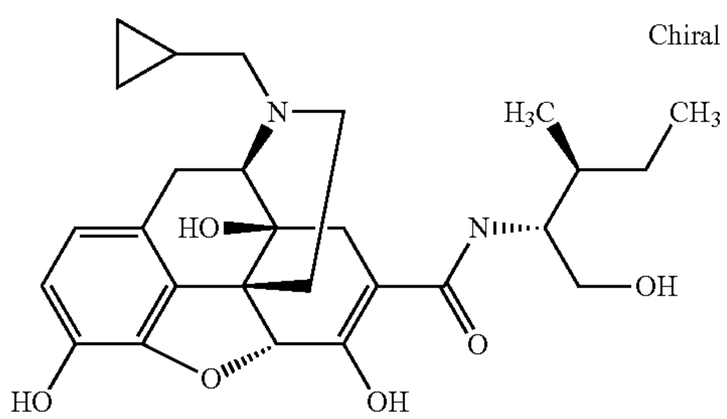
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-73	 Chiral	0.14 (d, J = 4.5 Hz, 2H), 0.40-0.58 (m, 3H), 0.74-1.01 (m, 10H), 1.25-1.61 (m, 4H), 1.88 (m, 1H), 2.06-2.62 (m, 8H), 3.03 (m, 1H), 3.21 (d, J = 6.0 Hz, 1H), 3.45 (t, J = 5.4 Hz, 2H) 3.68 (m, 1H), 4.57 (m, 1H), 4.72 (s, 1H), 4.76 (br, s, 1H), 6.51-6.58 (m, 2H), 7.14-7.27 (m, 2H), 9.15 (s, 1H), 14.44 (s, 1H)

TABLE 22-continued

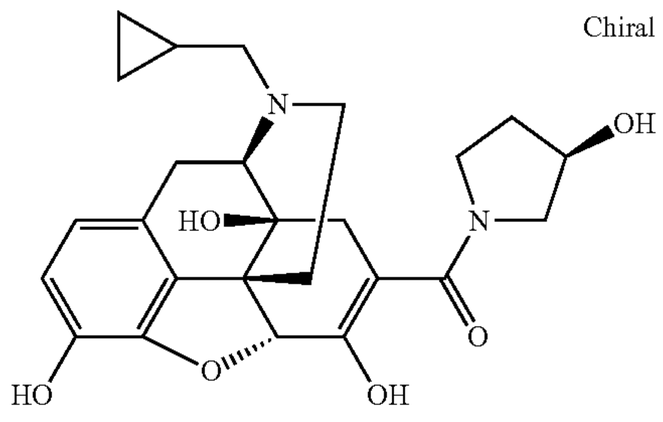
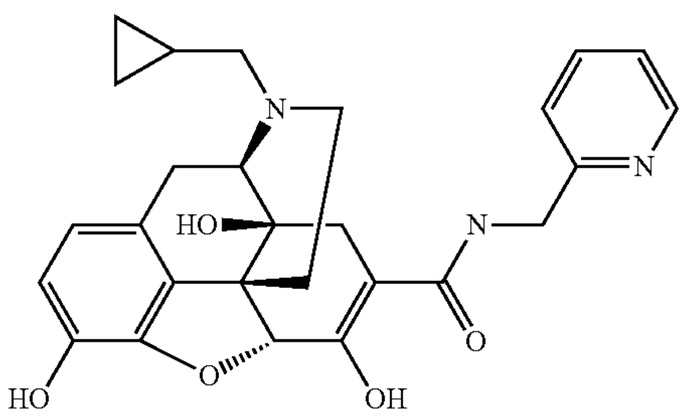
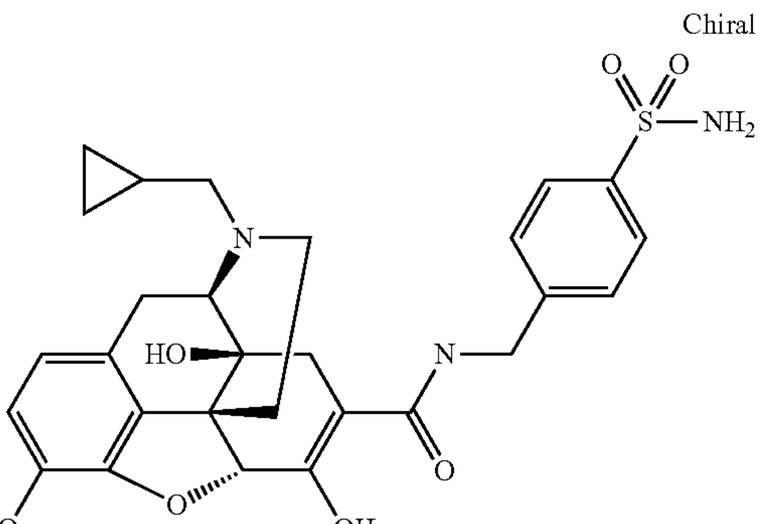
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-74	 Chiral	0.16-0.18 (m, 2H), 0.52 (br d, J = 7.6 Hz, 2H), 0.92(m, 1H), 1.35 (d, J = 11.2 Hz, 1H), 1.72-3.48 (m, 16H), 4.11-4.29 (m, 3H), 4.73-5.25 (m, 2H), 6.57 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 9.23 (s, 1H), 11.16 (s, 1H).
I-75	 Chiral	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	 Chiral	0.16-0.71 (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), 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

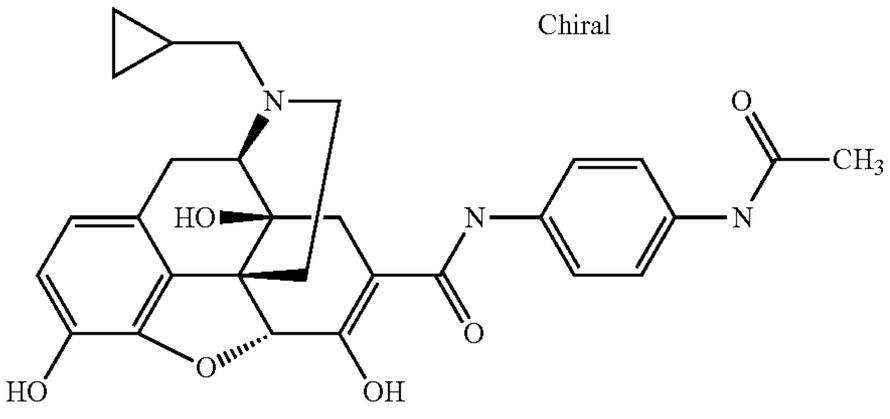
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-77	 Chiral	0.10-0.25 (m, 2H), 0.44-0.60 (m, 2H), 0.88 (m, 1H), 1.45 (d, 2 = 11.1 Hz, 1H), 1.70-3.40 (m, 13H), 4.78 (s, 1H), 4.81 (s, 1H), 6.53 (d, 2 = 8.1 Hz, 1H), 6.58 (d, 2 = 8.1 Hz, 1H), 7.46 (d, 2 = 9.0 Hz, 2H), 7.48 (d, 2 = 9.0 Hz, 2H), 9.15 (s, 1H), 9.25 (s, 1H), 9.88 (s, 1H), 14.00 (br s, 1H)

TABLE 23-continued

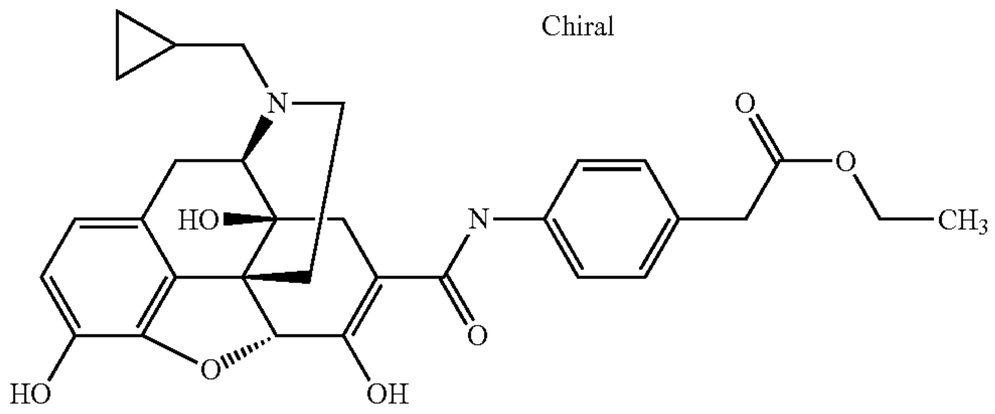
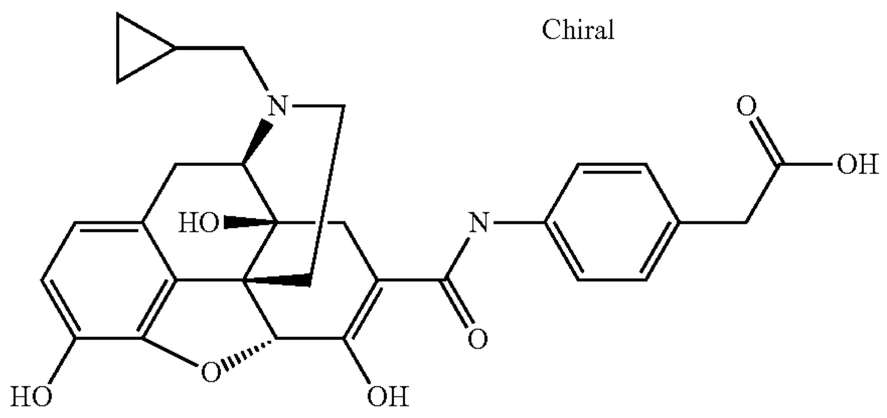
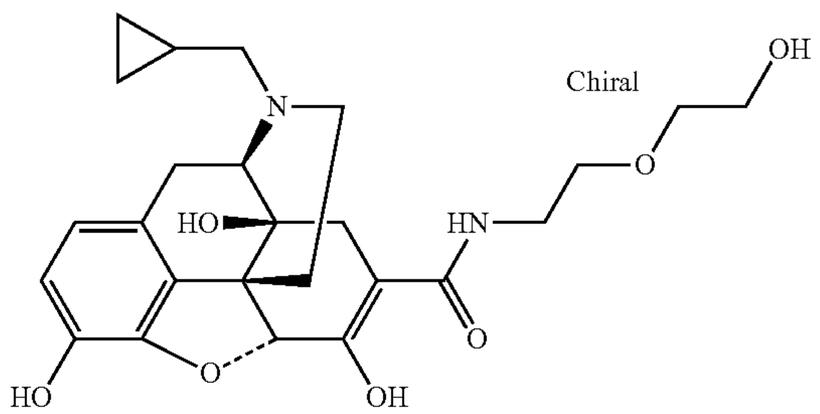
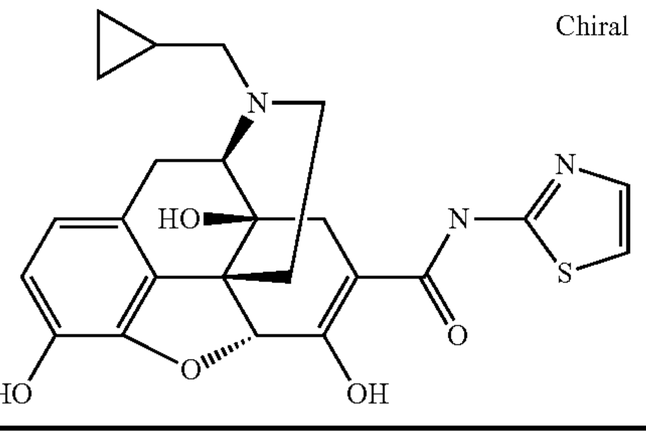
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-78	 Chiral	0.10-0.25 (m, 2H), 0.44-0.60 (m, 2H), 0.89 (m, 1H), 1.17 (t, 2 = 7.2 Hz, 3H), 1.45 (d, 2 = 11.4 Hz, 1H), 1.70-3.40 (m, 10H), 3.60 (s, 2H), 4.06 (q, 2 = 7.2 Hz, 2H), 4.78 (s, 1H), 4.83 (s, 1H), 6.58 (d, 2 = 8.1 Hz, 1H), 7.17 (d, 2 = 8.7 Hz, 2H), 7.45 (d, 2 = 8.7 Hz, 2H), 9.16 (s, 1H), 9.26 (s, 1H), 13.95 (br s, 1H)
I-79	 Chiral	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)
I-80	 Chiral	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	 Chiral	0.30-0.50 (m, 2H), 0.50-0.70 (m, 2H) 1.05 (m, 1H), 1.50-3.40 (m, 11H), 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), 9.15 (m, 1H)

TABLE 24

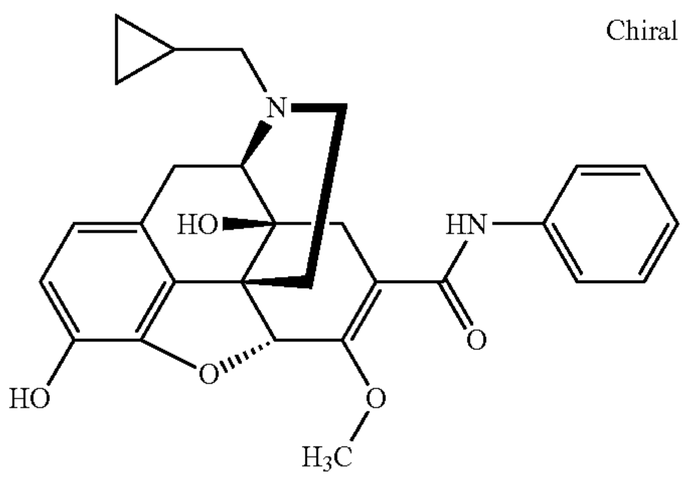
Compound No.	Chemical structure	NMR (1H-NMR (d6-DMSO) δ)
I-82	 Chiral	1H-NMR (CDCl3 + CD3OD) d: 0.17 (brs, 2H), 0.59 (brs, 2H), 0.89 (brs, 1H), 1.71 (d, J = 10.8 Hz, 1H), 2.17 (d.d, J = 17.1 & 1.8 Hz, 1H), 2.22-2.57 (m, 4H), 2.60-2.84 (m, 3H), 3.06 (d, J = 15.6 Hz, 1H), 3.24 (brs, 1H), 4.07 (s, 3H), 5.31 (s, 1H), 6.56 (d, J = 8.4 Hz, 1 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).

TABLE 24-continued

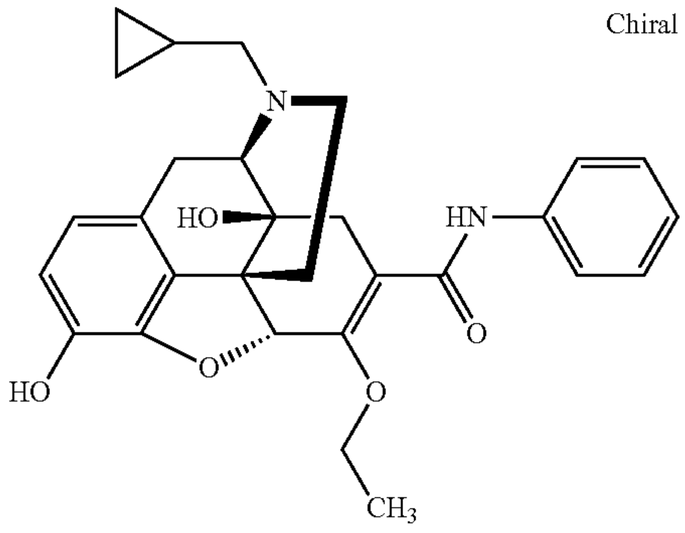
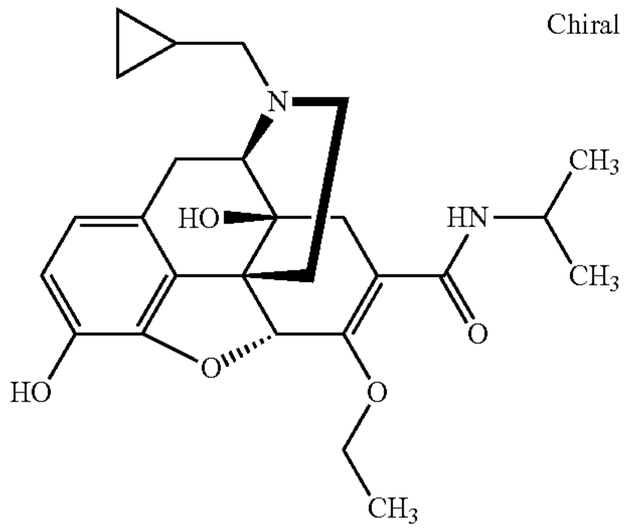
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-83		Chiral	1H-NMR (CDCl3 + CD3OD) d: 0.15 (brs, 2H), 0.58 (brs, 2H), 0.88 (brs, 1H), 1.49 (t, J = 6.9 Hz, 3H), 1.68 (d, J = 9.9 Hz, 1H). 2.15 (d.d, J = 17.1 & 1.5 Hz, 1H), 2.28 (brs, 2H), 2.39 (brs, 2H). 2.60-2.80 (m, 3H), 3.06 (d, J = 18.3 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).
I-84		Chiral	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

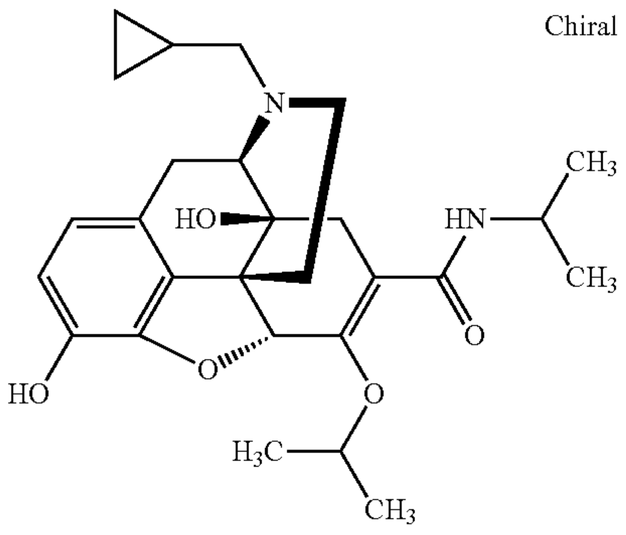
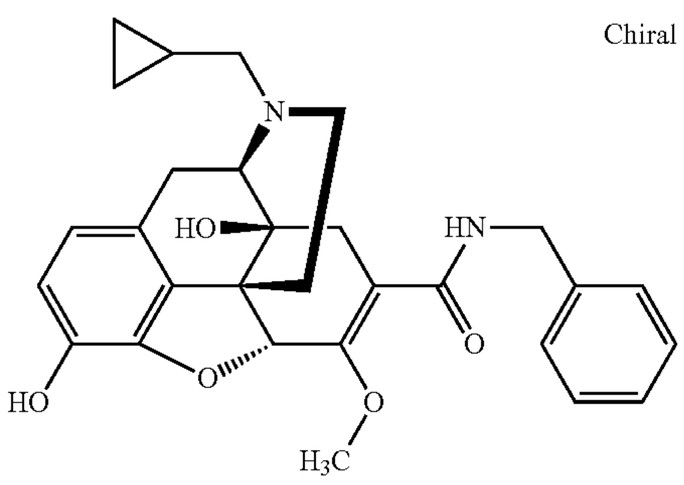
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-85		Chiral	1H-NMR (CDCl3 + CD3OD) d: 0.14 (brs, 2 H), 0.56 (brs, 2 H), 0.86 (brs, 1 H), 1.14 (d, J = 6.6 Hz, 3 H), 1.15 (d, J = 6.6 Hz, 3 H), 1.32 (d, J = 4.8 Hz, 1 H), 1.34 (d, J = 4.8 Hz, 3 H), 1.64 (d, J = 9.9 Hz, 1 H), 2.10 (d.d, J = 17.1 & 1.5 Hz, 1 H), 2.27 (brs, 2 H), 2.39 (brs, 2 H), 2.55-2.77 (m, 3 H), 3.04 (d, J = 18.3 Hz, 1 H), 3.22 (brs, 1 H), 4.03 (quint, J = 6.6 Hz, 1 H), 4.81 (quint., J = 6.0 Hz, 1 H), 5.10 (s, 1 H), 6.54 (d, J = 8.4 Hz, 1 H), 6.67 (d, J = 8.4 Hz, H), 7.76 (d, J = 6.9 Hz, 1 H).
I-86		Chiral	1H-NMR CDCl3 + CD3OD) d: 0.16 (brs, 2 H), 0.568 (brs, 2 H), 0.87 (brs, 1 H), 1.67 (d, J = 9.9 Hz, 1 H), 2.14 (d.d, J = 18.3 & 1.2 Hz, 1 H), 2.27 (brs, 2 H), 2.41 (brs, 2 H), 3.05 (d, J = 18.6 Hz, 1 H), 3.25 (brd, J = 4.5 Hz, 1 H), 3.92 (s, 1 H), 4.46 (d, J = 5.7 Hz, 2 H), 5.23 (s, 1 H), 6.54 (d, J = 8.1 Hz, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 7.20-7.36 (m, 5 H), 8.03 (bit, J = 5.7 Hz, 1 H).

TABLE 25-continued

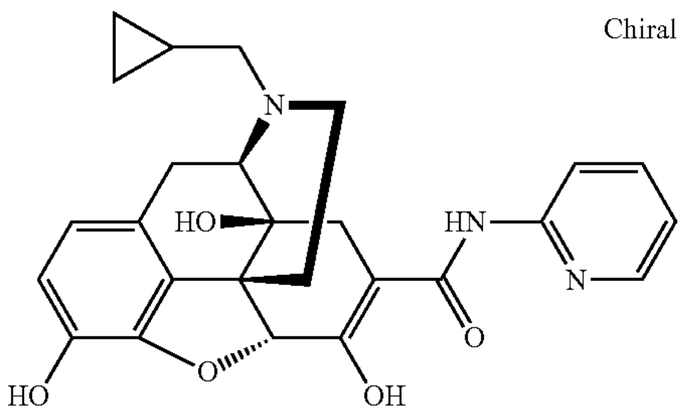
Compound No.	Chemical structure		NMR (1H-NMR (d6-DMSO) δ)
I-87		Chiral	1H-NMR (CDCl3 + CD3OD) d: 0.26 (brs, 2 H), 0.63 (brs, 2 H), 0.94 brs, 1 H), 1.72 (brd, J = 9.0 Hz, 1 H), 2.09-2.93 (m, 8 H), 3.15 (d, J = 18.9 Hz, 1 H), 4.97 (s, 1 H), 6.61 (d, J = 8.1 Hz, 1 H), 6.70 (d, J = 8.1 Hz, 1H), 7.04-7.08 (m, 1 H), 7.69-7.75 (m, 1 H), 8.13 (d, J = 14.0 Hz, 2 H), 8.23 (d, J = 3.9 Hz, 1 H).

TABLE 26

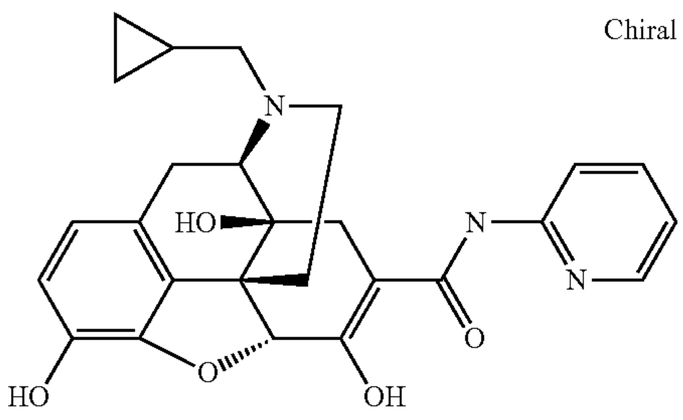
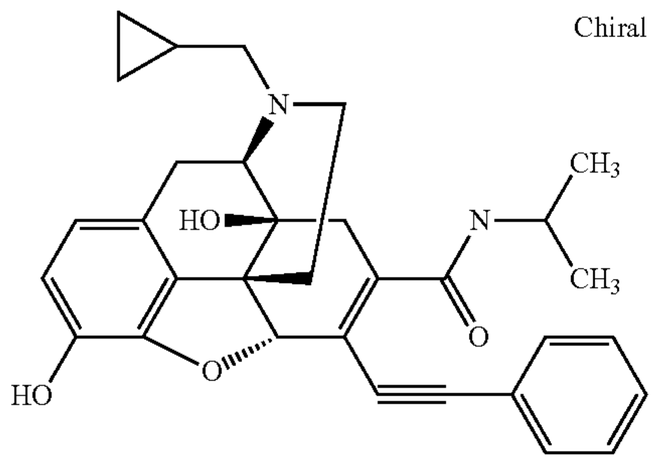
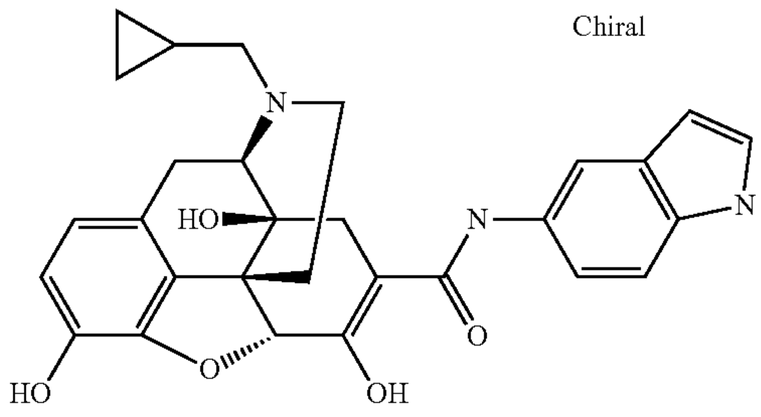
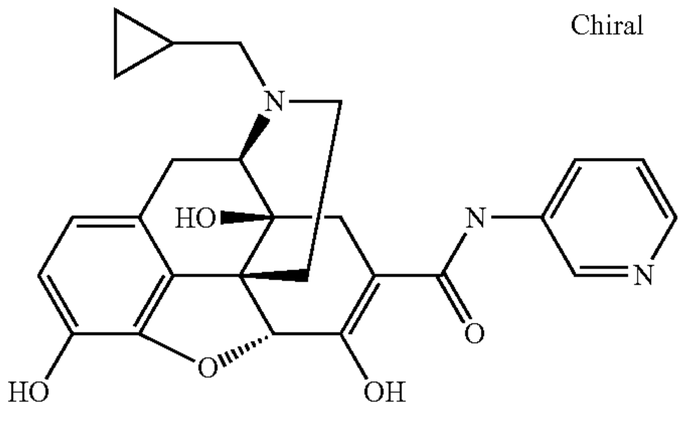
Compound No.	Chemical structure		LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-89		Chiral	m/z 462 $[M + H]^+$ 0.94 min	
I-90		Chiral	m/z 511 $[M + H]^+$ 0.63 min	
I-91		Chiral	m/z 500 $[M + H]^+$ 0.44 min	
I-92		Chiral	m/z 462 $[M + H]^+$ 0.44 min	

TABLE 26-continued

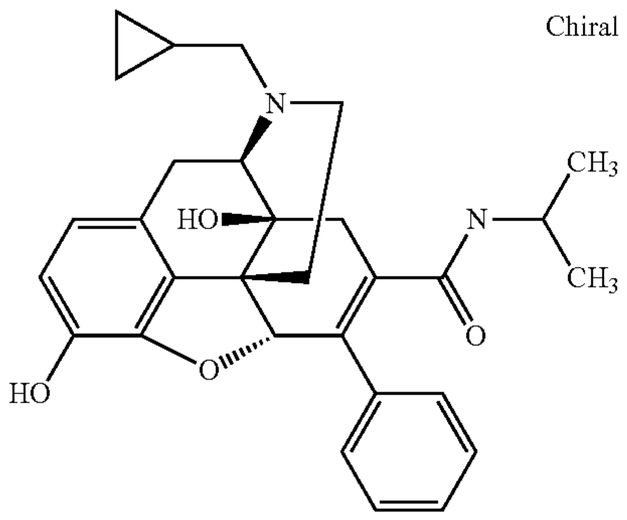
Compound No.	Chemical structure		LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-93		Chiral	m/z 487 $[M + H]^+$ 0.50 min	

TABLE 27

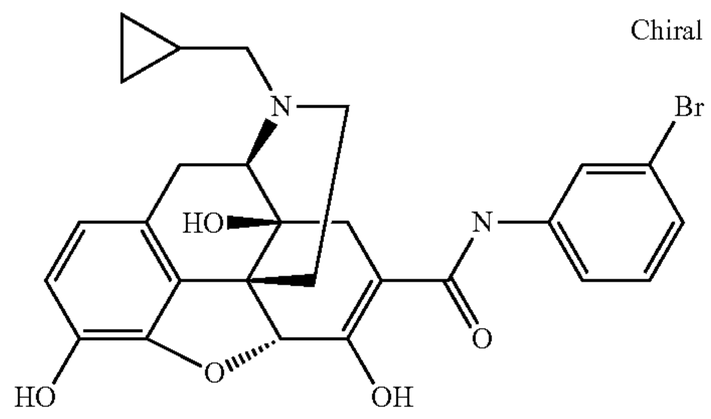
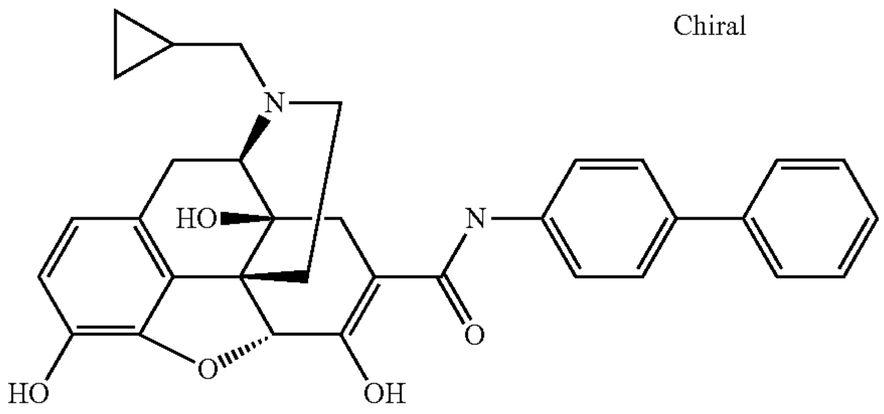
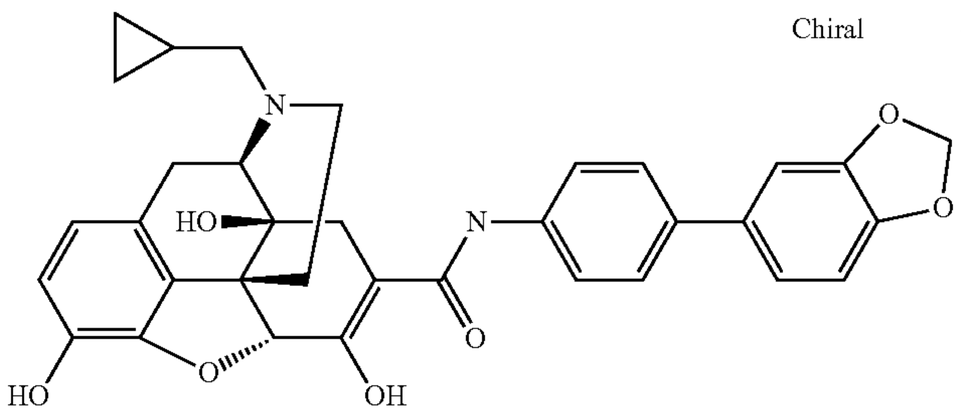
Compound No.	Chemical structure		LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-94		Chiral	m/z 540 $[M + H]^+$ 1.07 min	
I-95		Chiral	m/z 537 $[M + H]^+$ 1.12 min	
I-96		Chiral	m/z 581 $[M + H]^+$ 1.15 min	

TABLE 27-continued

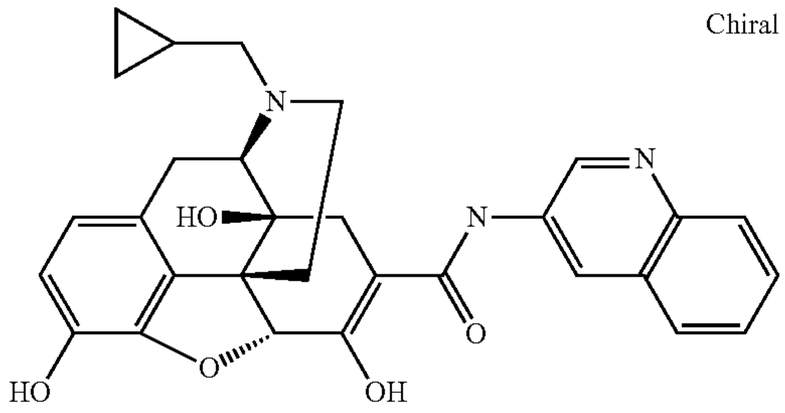
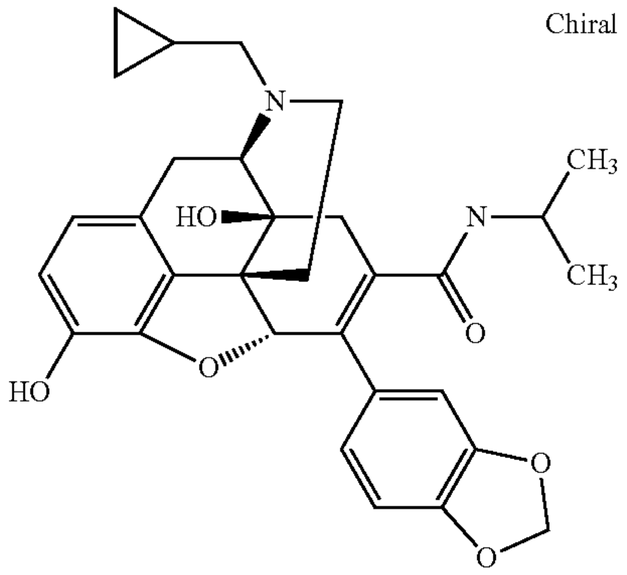
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-97		Chiral m/z 512 $[M + H]^+$ 0.50 min	
I-98		Chiral m/z 531 $[M + H]^+$ 0.50 min	

TABLE 28

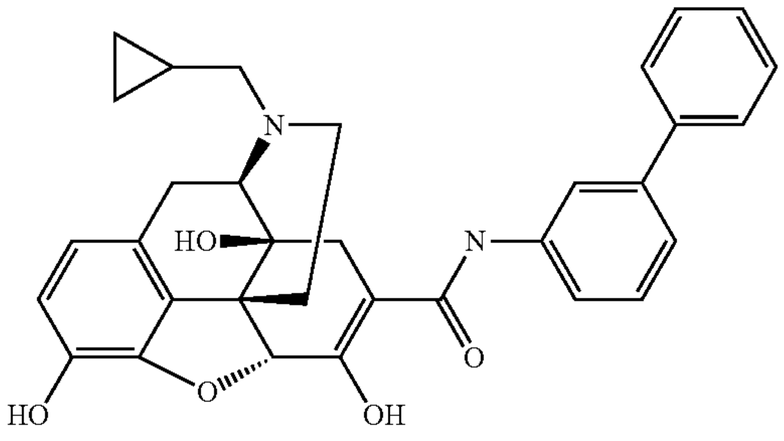
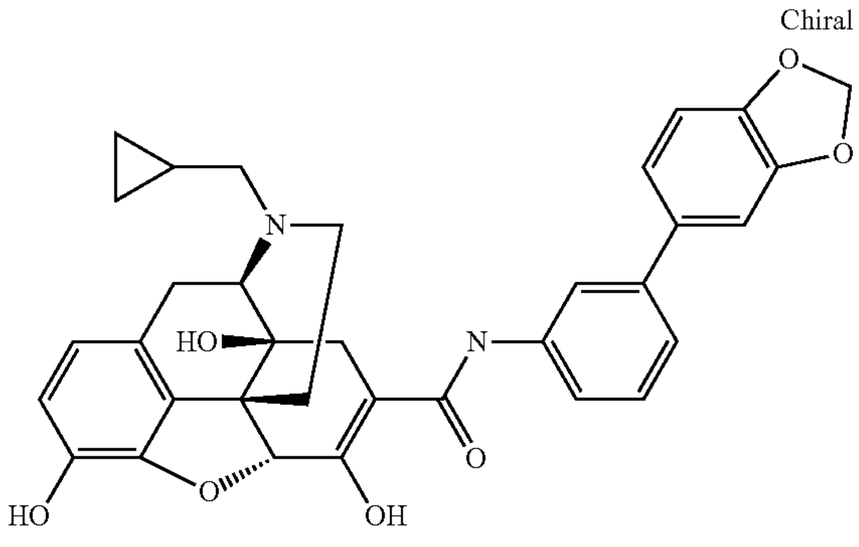
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-99		Chiral m/z 537 $[M + H]^+$ 1.17 min	
I-100		Chiral m/z 581 $[M + H]^+$ 1.15 min	

TABLE 28-continued

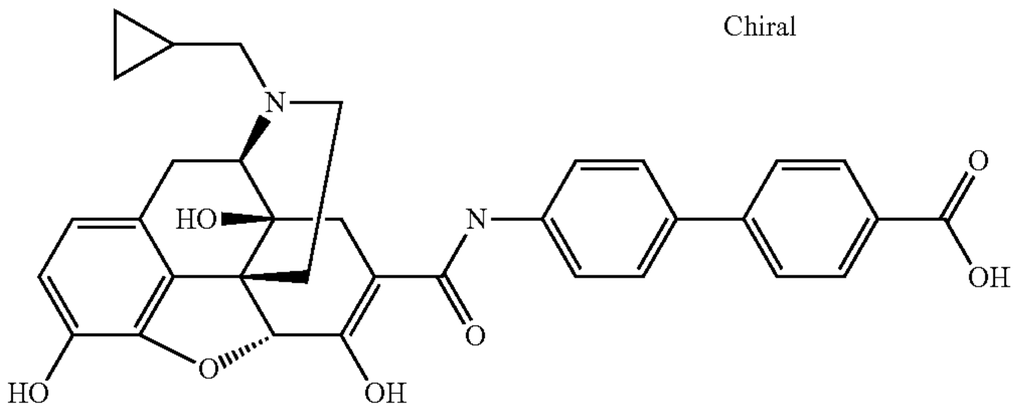
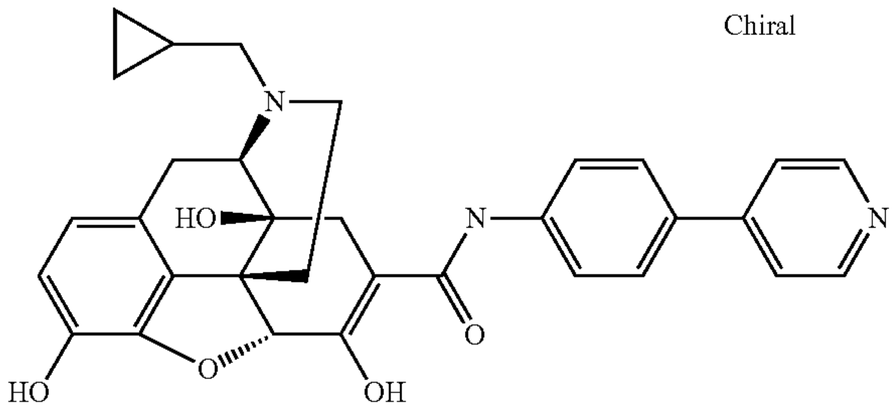
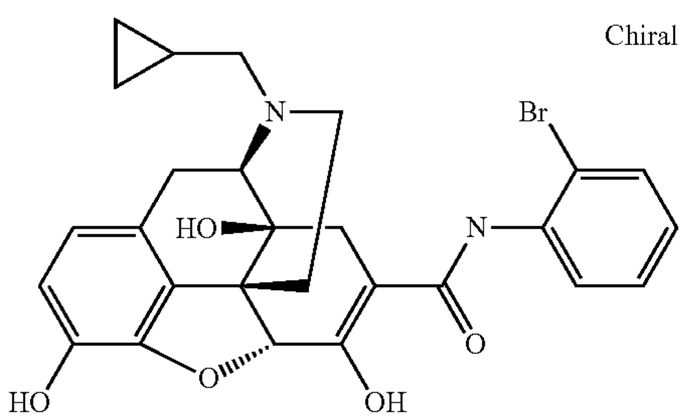
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-101	 Chiral	m/z 581 $[M + H]^+$ 1.03 min	
I-102	 Chiral	m/z 538 $[M + H]^+$ 0.85 min	
I-103	 Chiral	m/z 540 $[M + H]^+$ 1.05 min	

TABLE 29

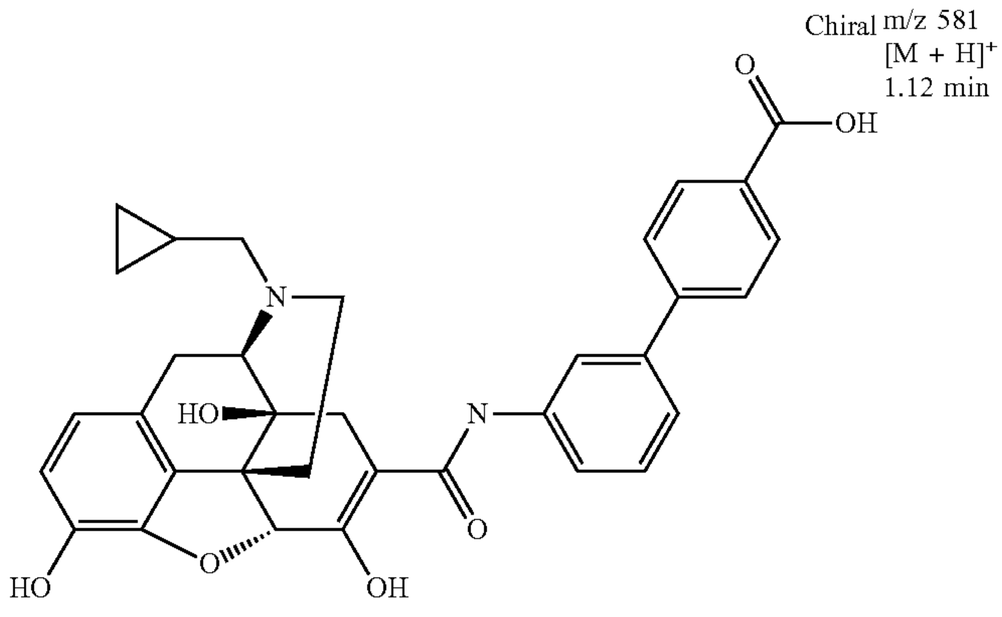
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-104	 Chiral	m/z 581 $[M + H]^+$ 1.12 min	

TABLE 29-continued

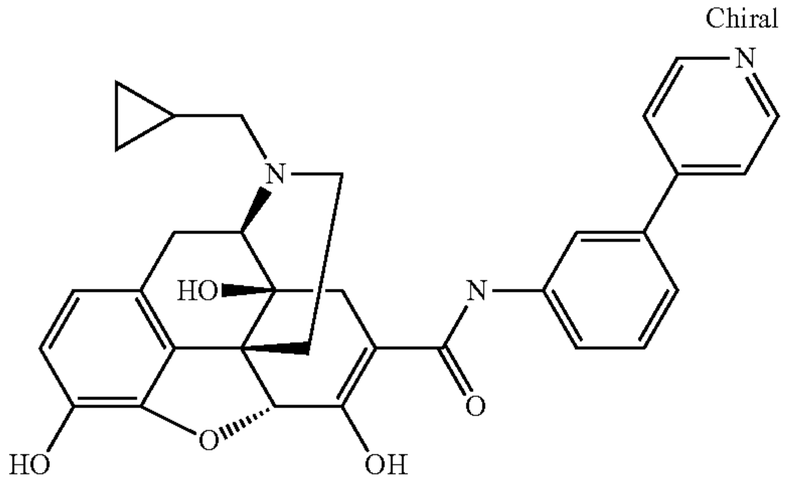
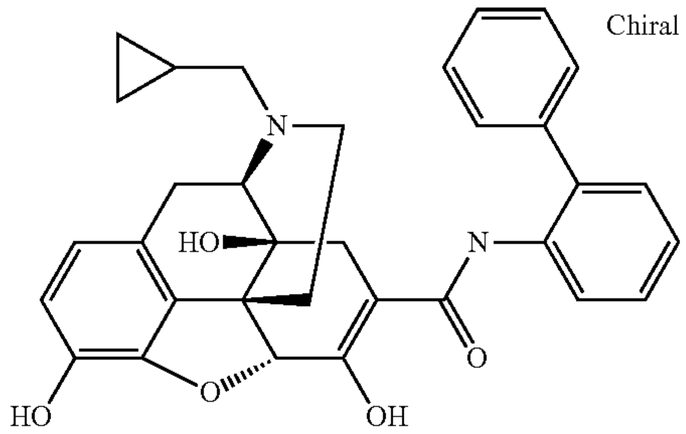
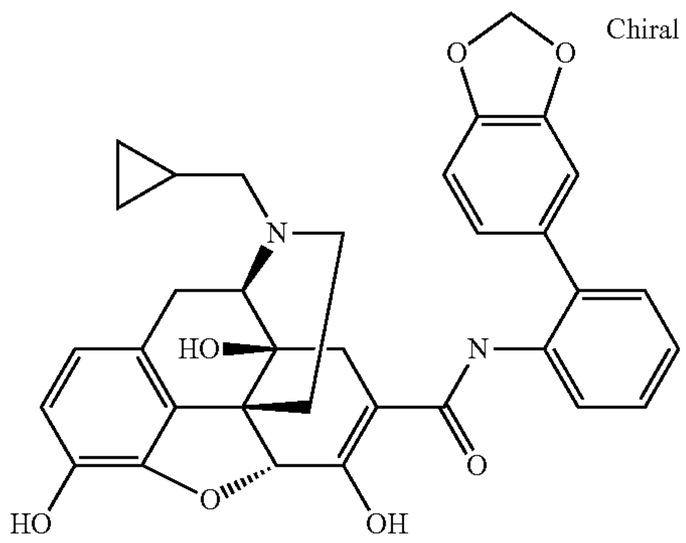
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-105	 Chiral	m/z 538 $[M + H]^+$ 0.90 min	
I-106	 Chiral	m/z 537 $[M + H]^+$ 1.05 min	
I-107	 Chiral	m/z 581 $[M + H]^+$ 1.09 min	

TABLE 30

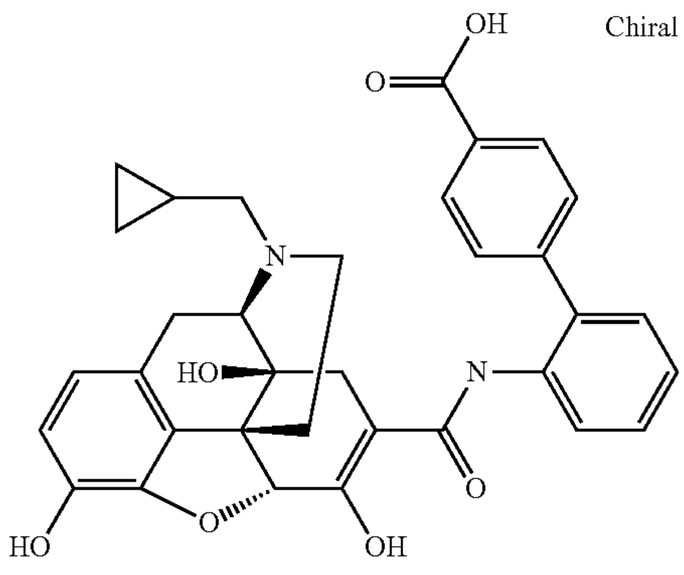
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-108	 Chiral	m/z 581 $[M + H]^+$ 1.03 min	

TABLE 30-continued

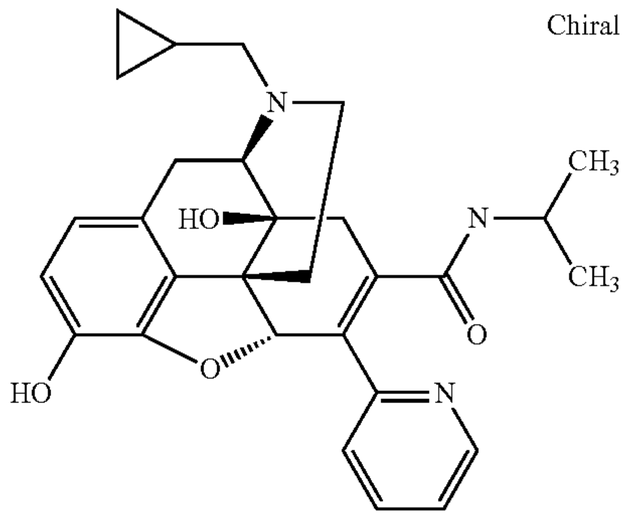
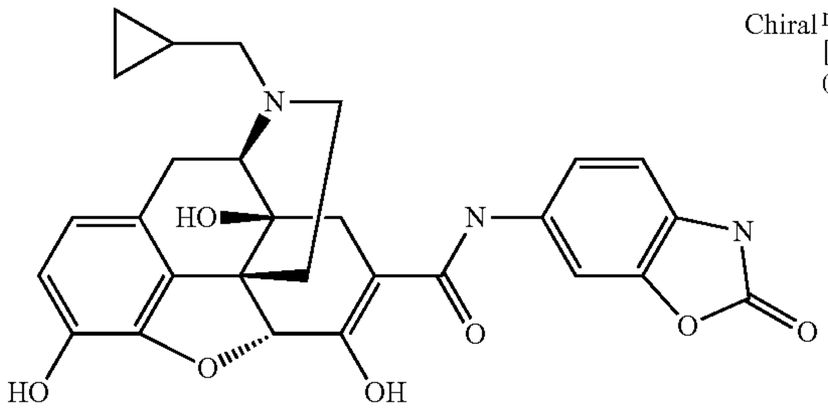
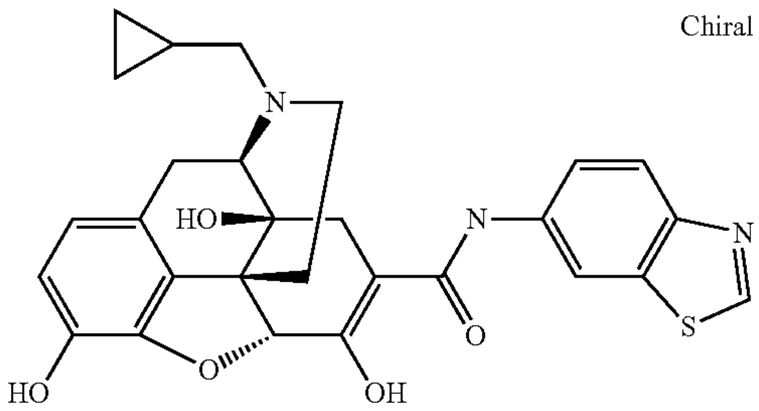
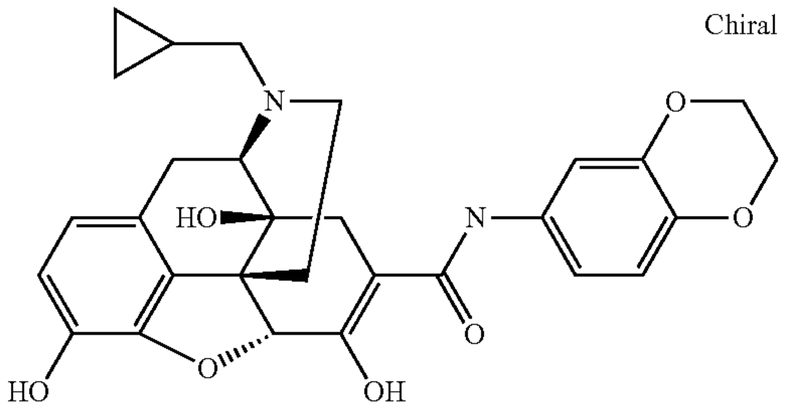
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-109	 Chiral	m/z 488 $[M + H]^+$ 0.50 min	
I-110	 Chiral	m/z 518 $[M + H]^+$ 0.50 min	
I-111	 Chiral	m/z 518 $[M + H]^+$ 0.56 min	
I-112	 Chiral	m/z 519 $[M + H]^+$ 0.50 min	

TABLE 31

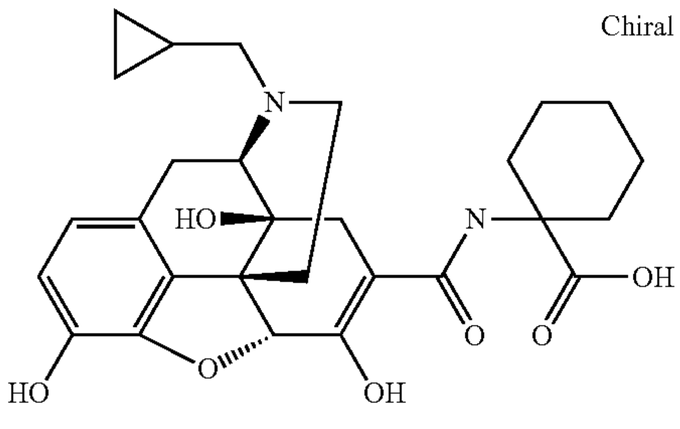
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-113	 Chiral	m/z 511 $[M + H]^+$ 0.50 min	

TABLE 31-continued

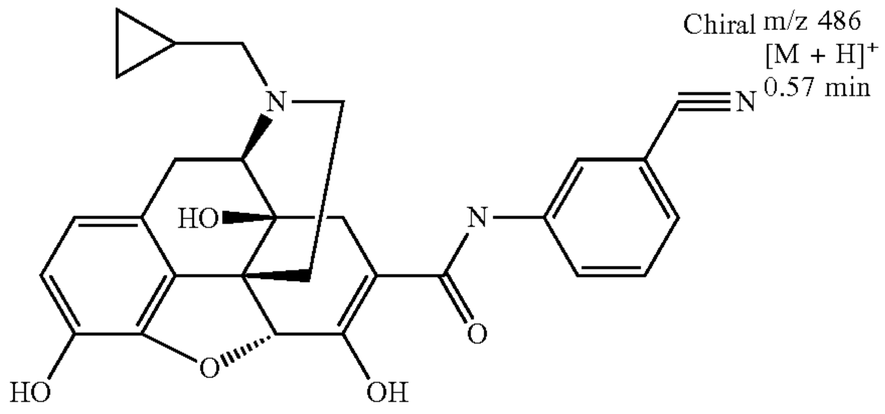
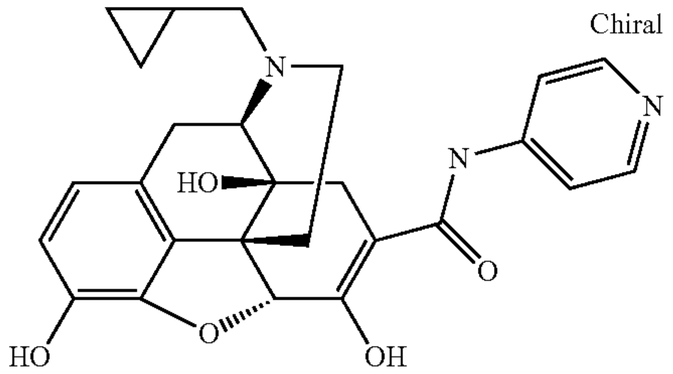
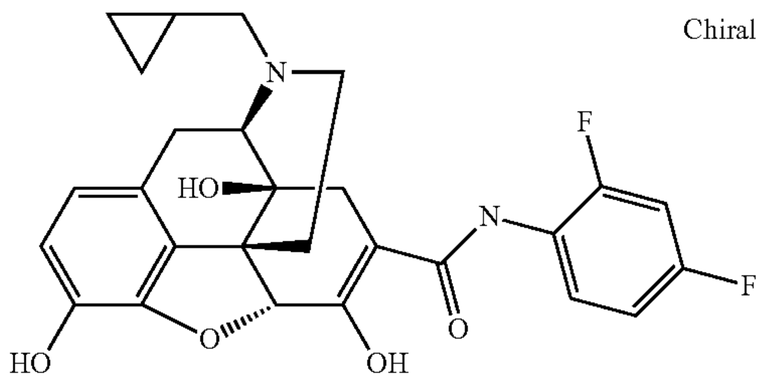
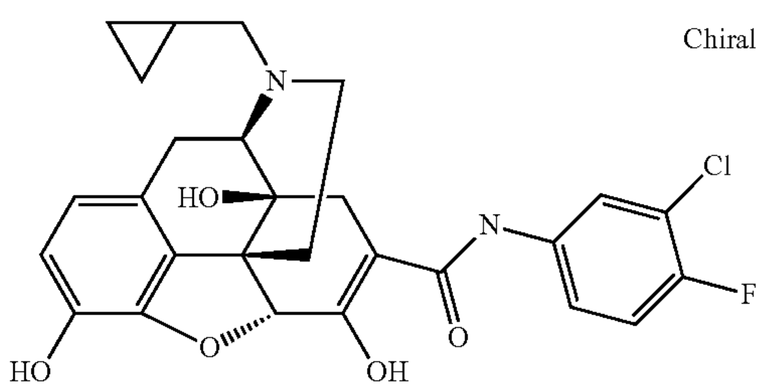
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-114		Chiral m/z 486 $[M + H]^+$ 0.57 min	
I-115		Chiral m/z 462 $[M + H]^+$ 0.44 min	
I-116		Chiral m/z 497 $[M + H]^+$ 0.63 min	
I-117		Chiral m/z 513 $[M + H]^+$ 0.69 min	

TABLE 32

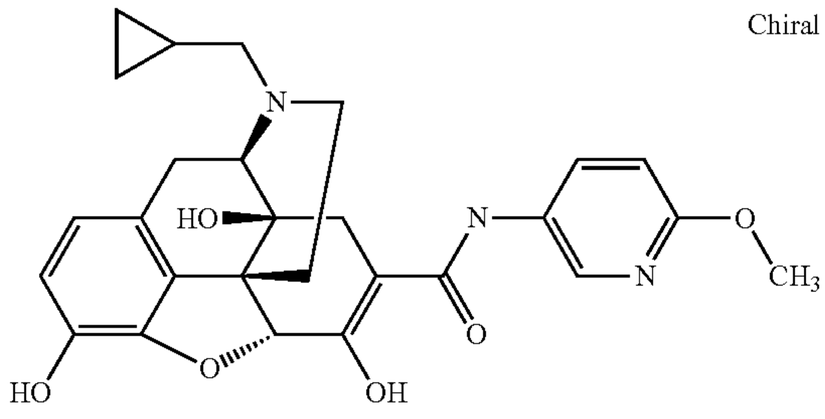
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-118		Chiral m/z 493 $[M + H]^+$ 1.06 min	

TABLE 32-continued

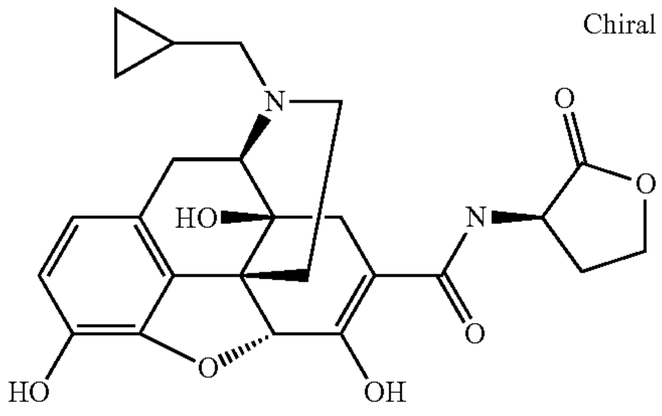
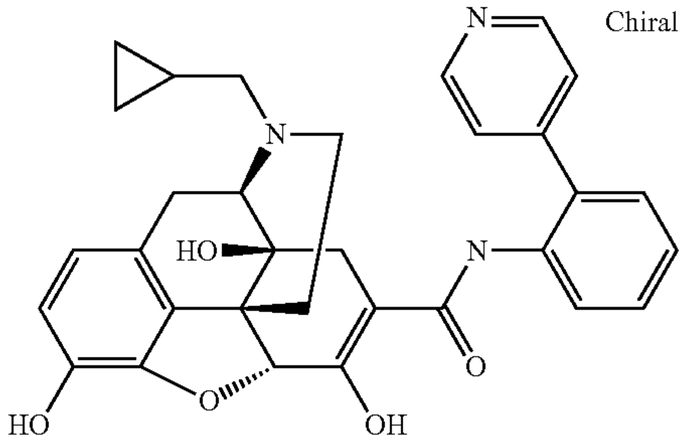
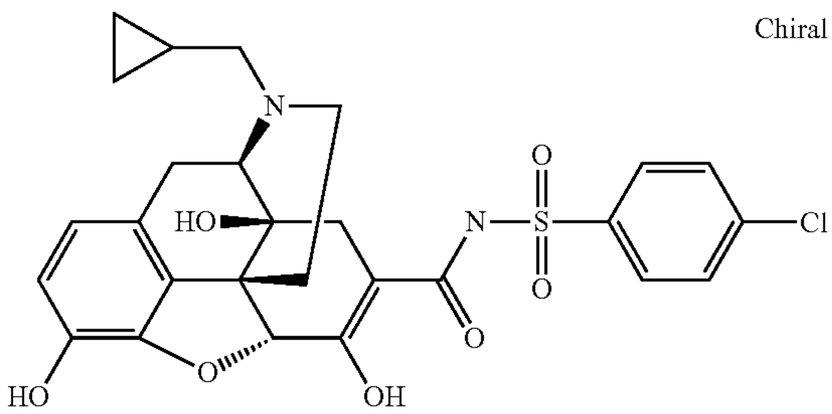
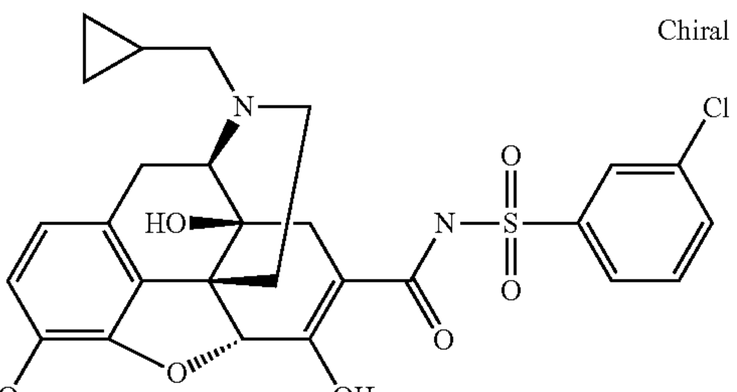
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-119	 Chiral	m/z 469 $[M + H]^+$ 0.44 min	
I-120	 Chiral	m/z 538 $[M + H]^+$ 0.94 min	
I-121	 Chiral	m/z 559 $[M + H]^+$ 0.69 min	
I-122	 Chiral	m/z 559 $[M + H]^+$ 0.69 min	

TABLE 33

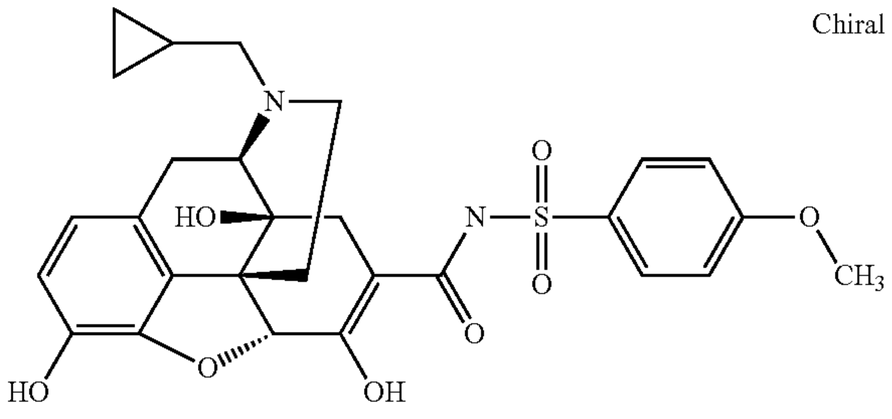
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-123	 Chiral	m/z 555 $[M + H]^+$ 0.56 min	

TABLE 33-continued

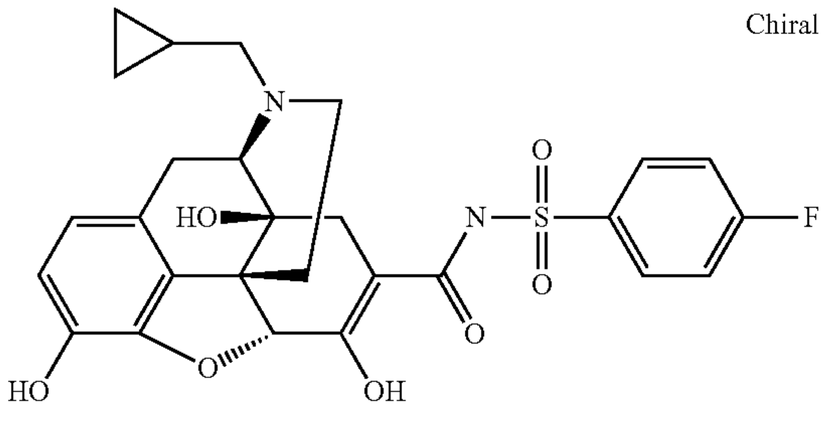
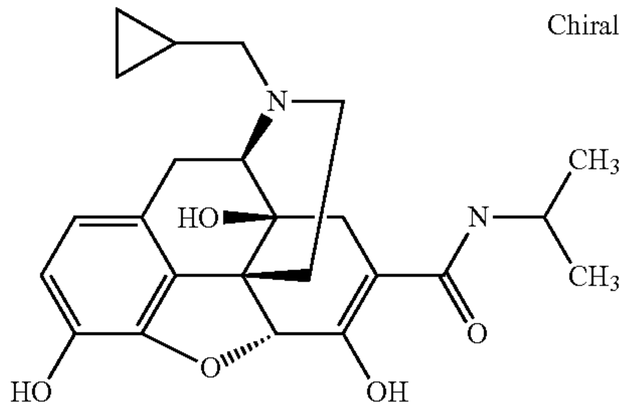
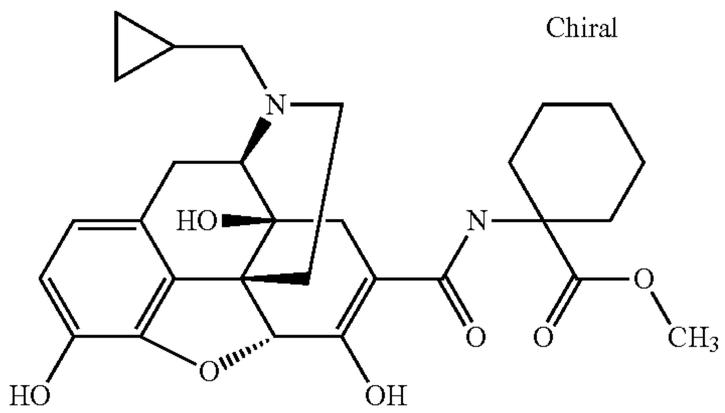
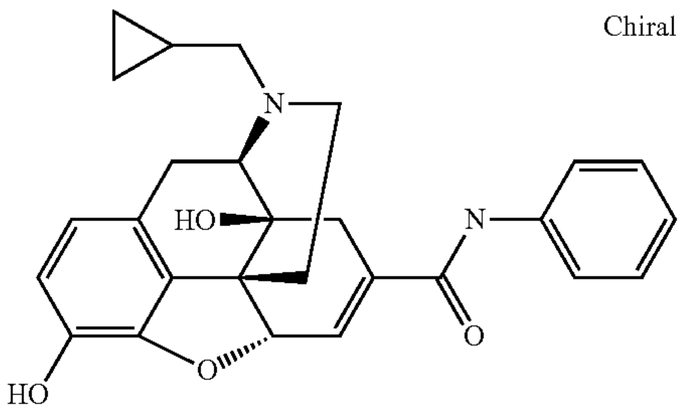
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-124		Chiral	m/z 543 $[M + H]^+$ 0.63 min
I-125		Chiral	m/z 425 $[M + H]^+$ 0.50 min
I-126		Chiral	m/z 525 $[M + H]^+$ 0.56 min
I-127		Chiral	(CDCl3 + CD3OD) d: 0.10-0.21 (m, 2 H), 0.48-0.63 (m, 2 H), 0.78-0.94 (m, 1 H), 1.67 (d, J = 9.6 Hz, 1 H), 2.10-2.50 (m, 6 H), 2.57-2.80 (m, 2 H), 3.06 (d, J = 18.6 Hz, 1 H), 3.27 (brs, 1 H), 5.10 (d, J = 1.7 Hz, 1 H), 6.31-6.40 (m, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.65 (d, J = 8.1 Hz, 1 H), 7.02-7.12 (m, 1 H), 7.22-7.34 (m, 2 H), 7.44-7.56 (m, 2 H).

TABLE 34

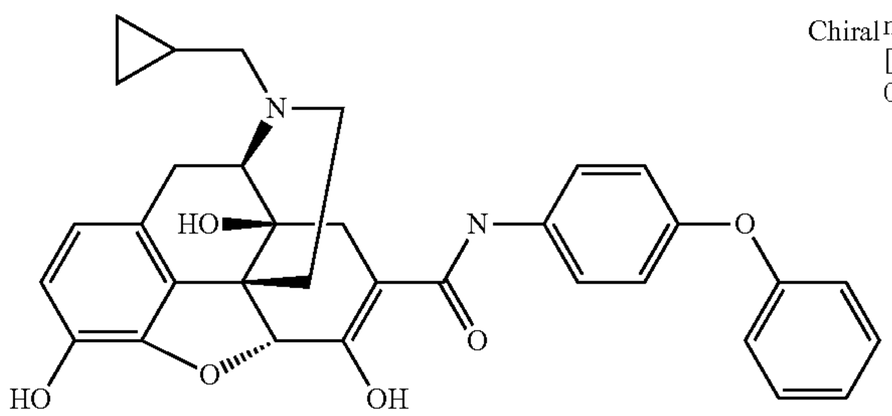
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-128		Chiral	m/z 553 $[M + H]^+$ 0.94 min

TABLE 34-continued

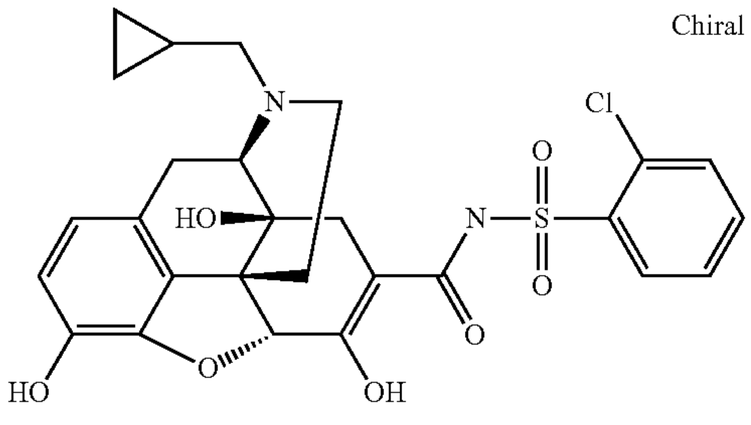
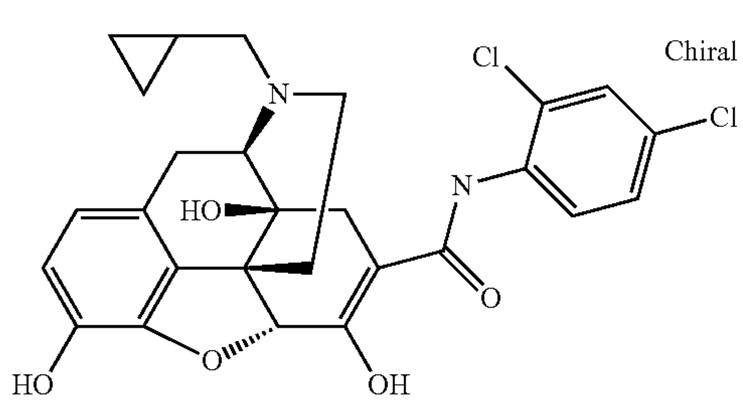
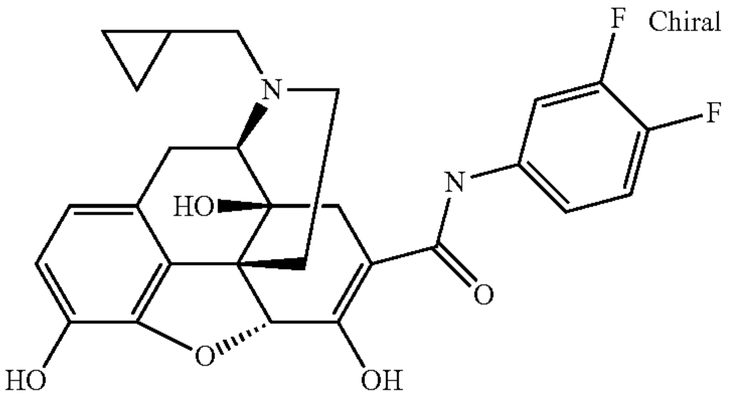
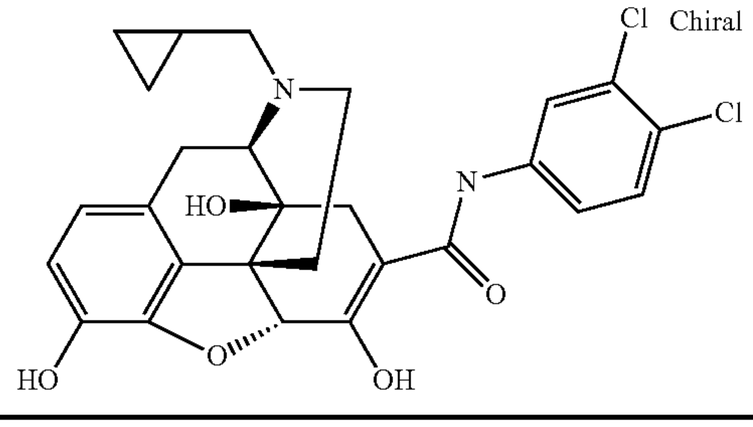
Compound No.	Chemical structure		LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-129		Chiral	m/z 559 $[M + H]^+$ 0.63 min	
I-130		Chiral	m/z 529 $[M + H]^+$ 0.75 min	
I-131		Chiral	m/z 497 $[M + H]^+$ 0.63 min	
I-132		Chiral	m/z 529 $[M + H]^+$ 0.88 min	

TABLE 35

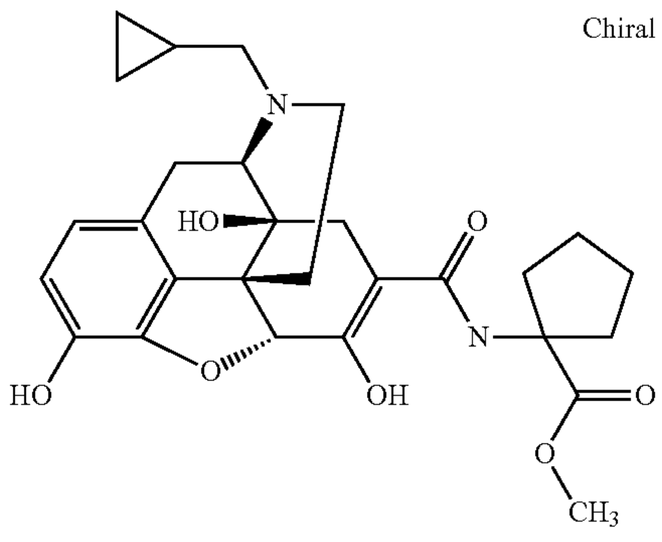
Compound No.	Chemical structure		LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-133		Chiral	m/z 511 $[M + H]^+$ 0.97 min	0.12-0.16 (m, 2 H), 0.46-0.52 (m, 2 H), 0.86 (m, 1 H), 1.42 (d, J = 10.5 Hz, 1 H), 1.86 (d, J = 15.6 Hz, 1 H), 2.06-2.65 (m, 15 H), 3.05 (d, J = 18.3 Hz, 1 H), 3.26 (d, J = 5.9 Hz, 1 H), 3.55 (s, 3 H), 4.73 (s 1 H), 6.52 (d, J = 8.1 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 7.76 (brs, 1 H), 9.31 (brs, 1 H), 13.8 (brs, 1 H)

TABLE 35-continued

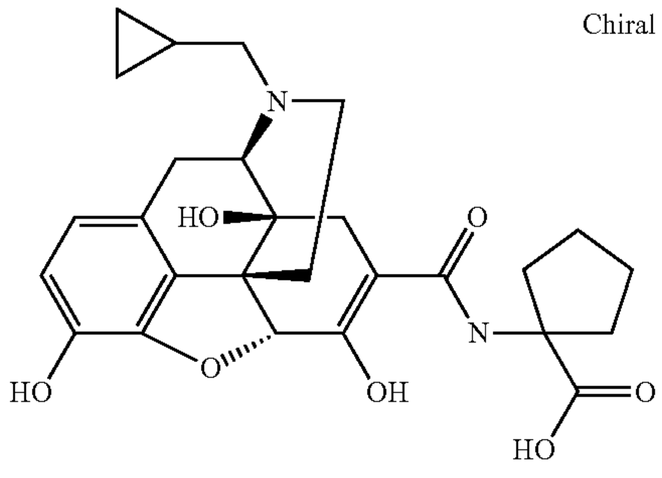
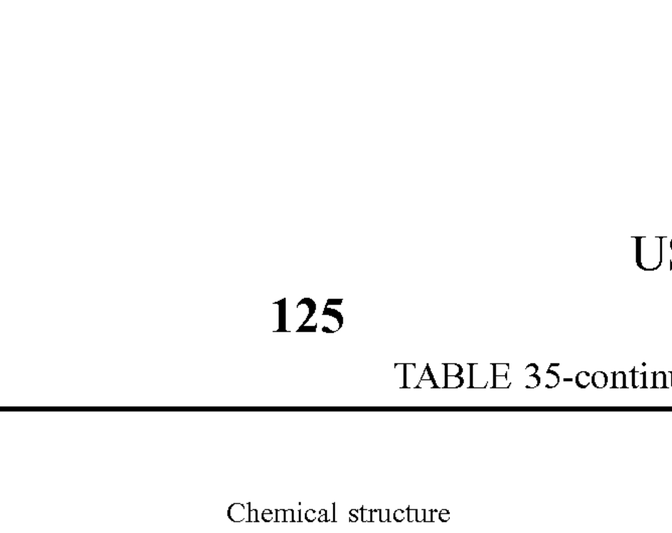
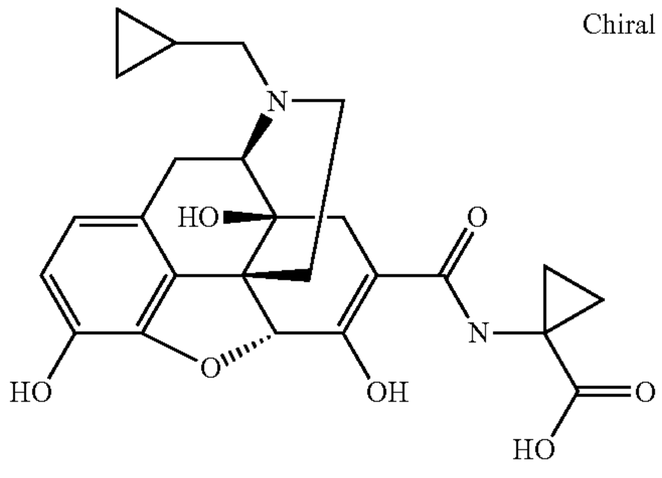
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-134		Chiral m/z 498 $[M + H]^+$ 0.96 min	0.13-0.16 (m, 2 H), 0.48-0.54 (m, 2 H), 0.87 (m, 1 H), 1.43 (d, J = 10.5 Hz, 1 H), 1.86 (d, J = 15.6 Hz, 1 H), 2.06-2.67 (m, 15 H), 3.06 (d, J = 18.6 Hz, 1 H), 3.27 (d, J = 6.0 Hz, 1 H), 4.73 (s 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 7.72 (brs, 1 H), 9.20 (brs, 1 H), 14.1 (brs, 1 H)
I-135		Chiral m/z 483 $[M + H]^+$ 0.87 min	0.12-0.14 (m, 2 H), 0.46-0.51 (m, 2 H), 0.85 (m, 1 H), 1.06-1.09 (m, 2 H), 1.35-1.36 (m, 2 H), 1.41 (d, J = 11.7 Hz, 1 H), 1.86 (d, J = 15.6 Hz, 1 H), 2.17-2.61 (m, 7 H), 3.03 (d, J = 18.3 Hz, 1 H), 3.17 (d, J = 6.0 Hz, 1 H), 3.56 (s, 3 H), 4.74 (s, 1 H), 4.77 (brs, 1 H), 6.51 (d, J = 8.1 Hz, 1 H), 6.56 (d, J = 8.1 Hz, 1 H), 9.17 (brs, 1 H), 14.1 (brs, 1 H)
I-136		Chiral m/z 469 $[M + H]^+$ 0.89 min	0.12-0.16 (m, 2 H), 0.43-0.51 (m, 2 H), 0.85 (m, 1 H), 1.06-1.12 (m, 2 H), 1.35-1.36 (m, 2 H), 1.42 (d, J = 11.7 Hz, 1 H), 1.86 (d, J = 15.6 Hz, 1 H), 2.06-2.63 (m, 7 H), 3.02 (d, J = 18.3 Hz, 1 H), 3.13 (d, J = 5.4 Hz, 1 H), 4.76 (s 1 H), 4.77 (brs, 1 H), 6.52 (d, J = 8.1 Hz, 1 H), 6.56 (d, J = 8.1 Hz, 1 H), 9.18 (brs, 1 H), 14.1 (brs, 1 H)

TABLE 36

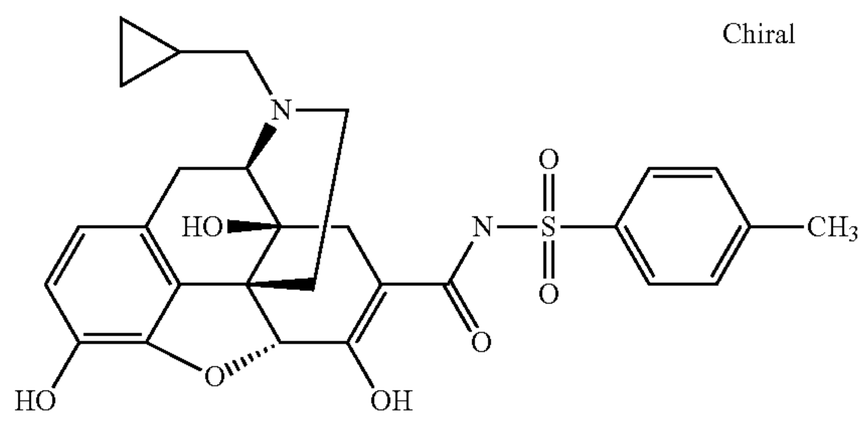
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-137		Chiral m/z 539 $[M + H]^+$ 0.50 min	

TABLE 36-continued

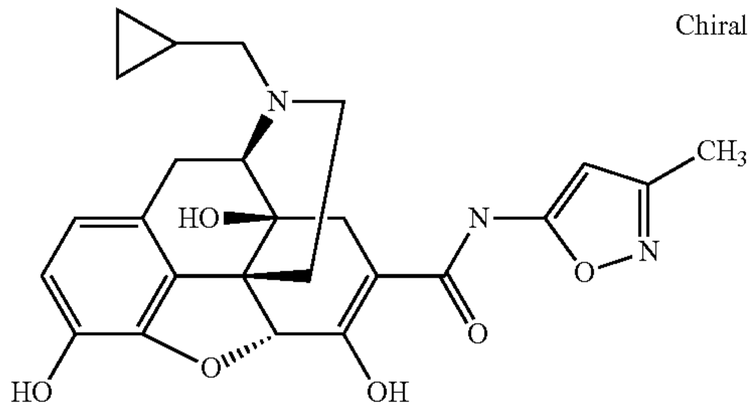
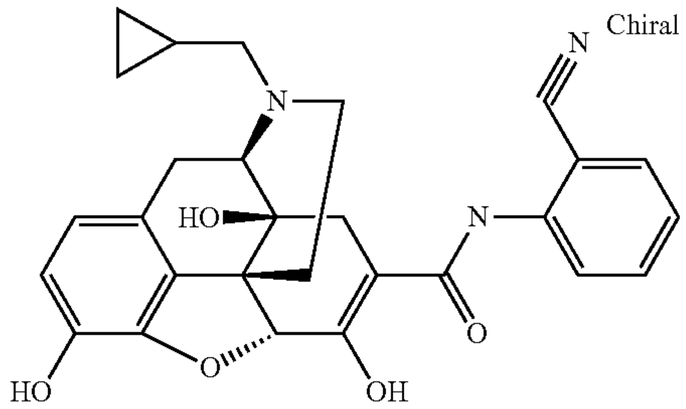
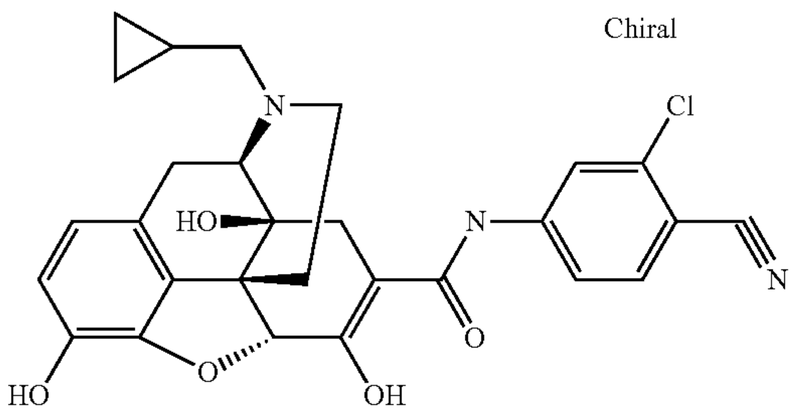
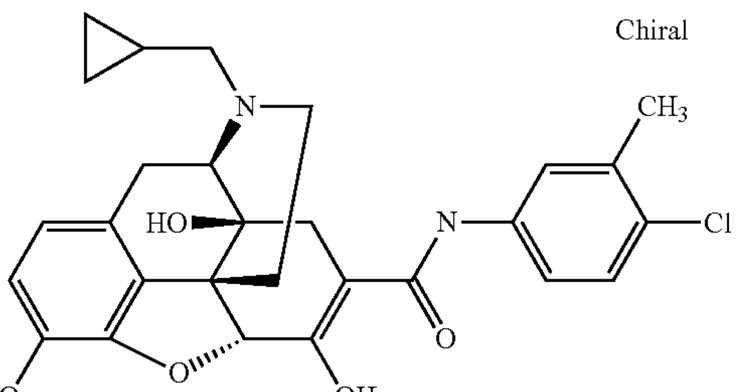
Compound No.	Chemical structure		LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-138		Chiral	m/z 466 $[M + H]^+$ 0.57 min	
I-139		Chiral	m/z 486 $[M + H]^+$ 0.44 min	
I-140		Chiral	m/z 520 $[M + H]^+$ 0.56 min	
I-141		Chiral	m/z 510 $[M + H]^+$ 0.75 min	

TABLE 37

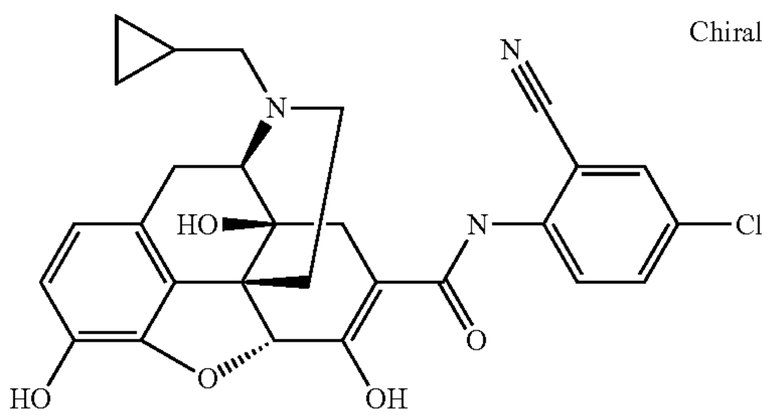
Compound No.	Chemical structure		LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-142		Chiral	m/z 521 $[M + H]^+$ 0.50 min	

TABLE 37-continued

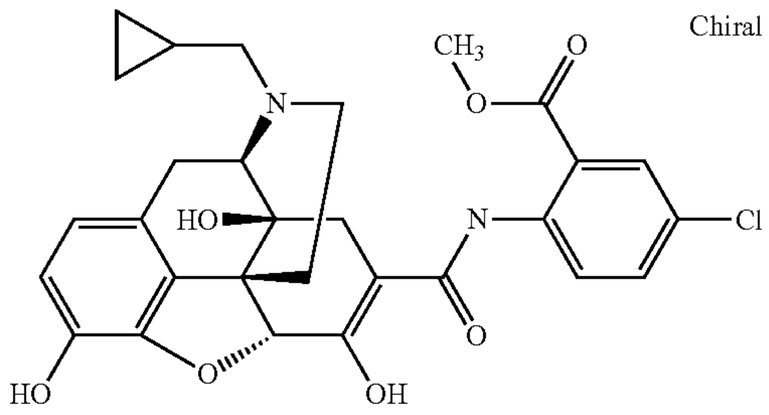
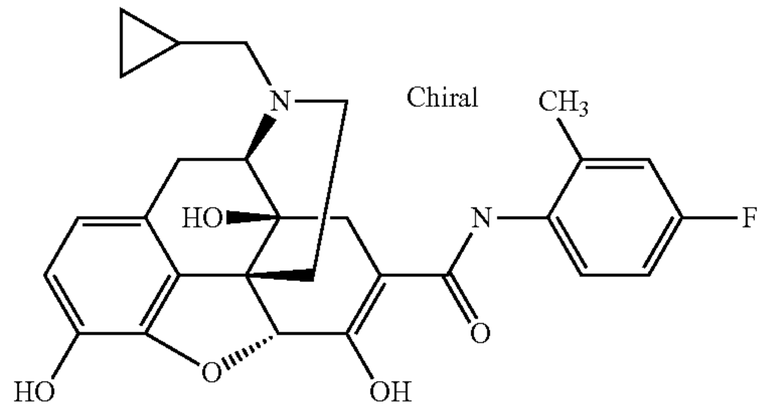
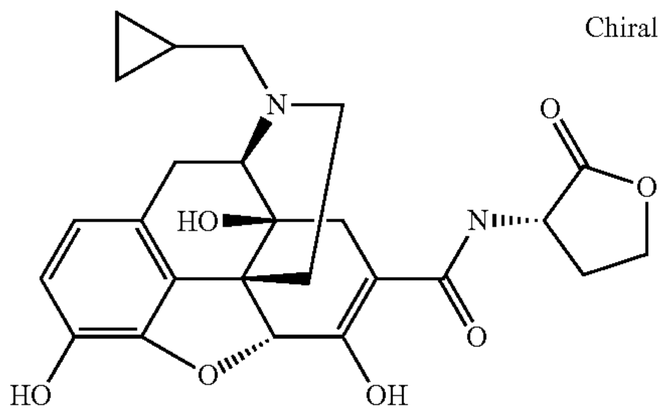
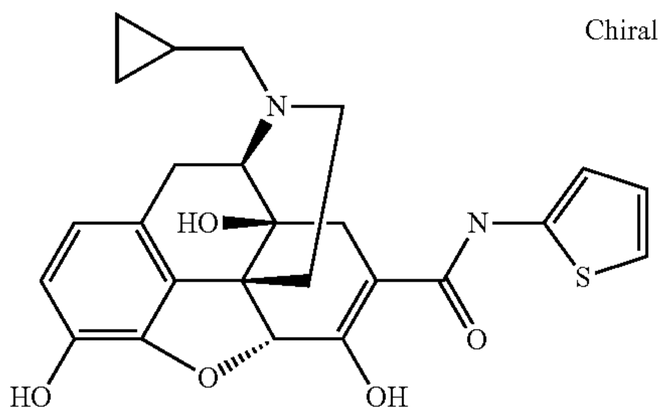
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-143		Chiral m/z 553 $[M + H]^+$ 0.88 min	
I-144		Chiral m/z 494 $[M + H]^+$ 0.57 min	
I-145		Chiral m/z 469 $[M + H]^+$ 0.83 min	
I-146		Chiral m/z 467 $[M + H]^+$ 1.01 min	

TABLE 38

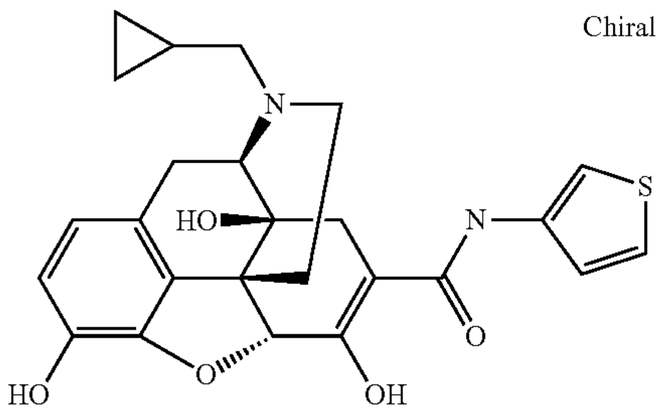
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-147		Chiral m/z 467 $[M + H]^+$ 1.00 min	

TABLE 38-continued

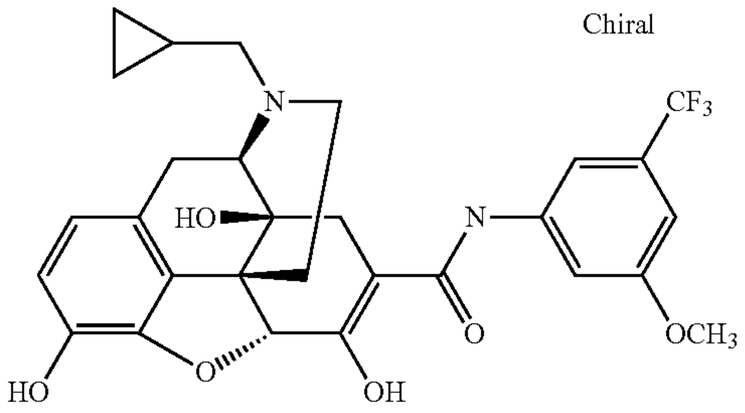
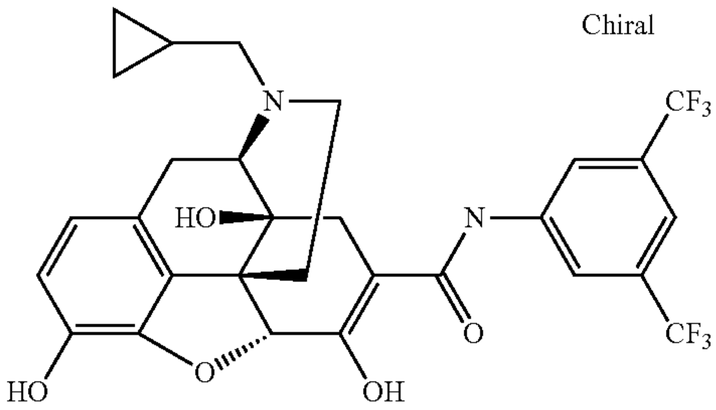
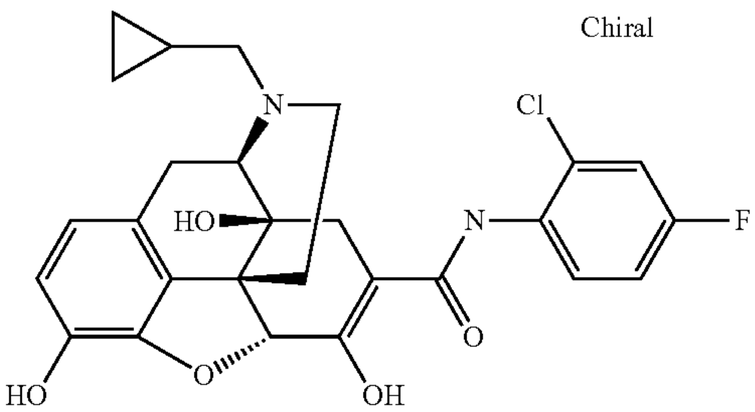
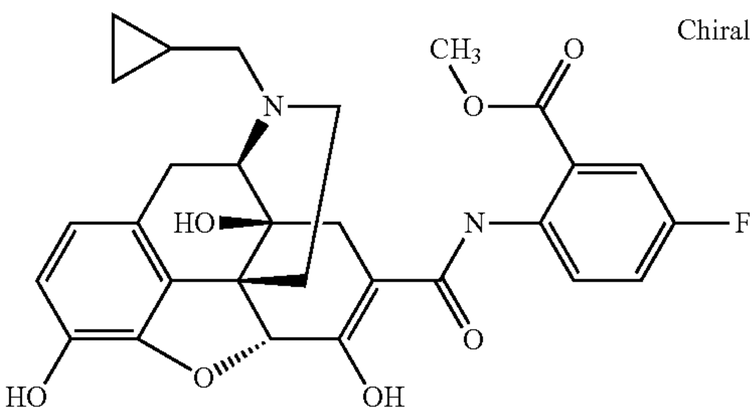
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-148	 Chiral	m/z 559 $[M + H]^+$ 1.16 min**	
I-149	 Chiral	m/z 598 $[M + H]^+$ 1.34 min**	
I-150	 Chiral	m/z 514 $[M + H]^+$ 0.50 min	
I-151	 Chiral	m/z 538 $[M + H]^+$ 0.63 min	

TABLE 39

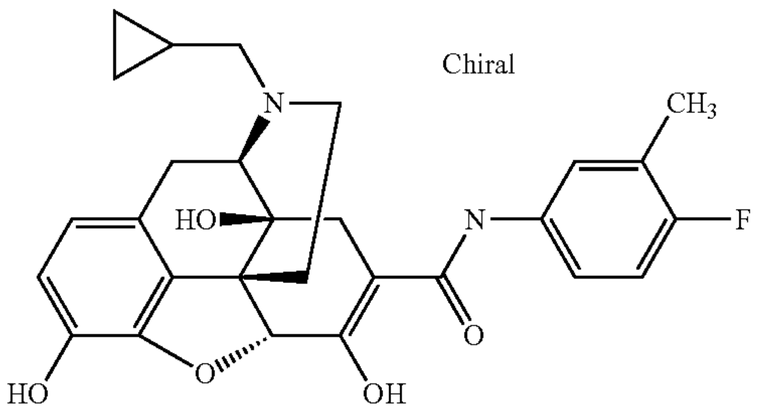
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-152	 Chiral	m/z 494 $[M + H]^+$ 0.56 min	

TABLE 39-continued

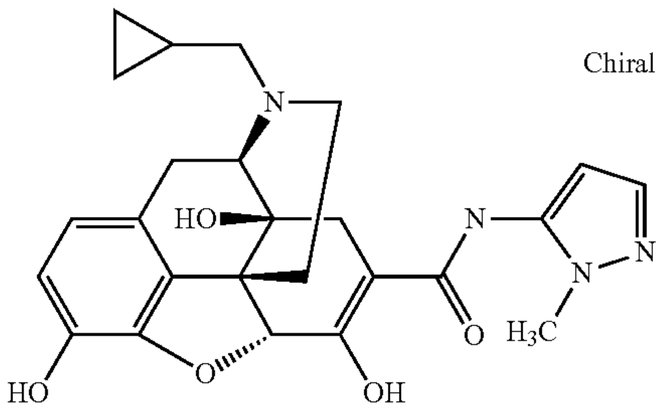
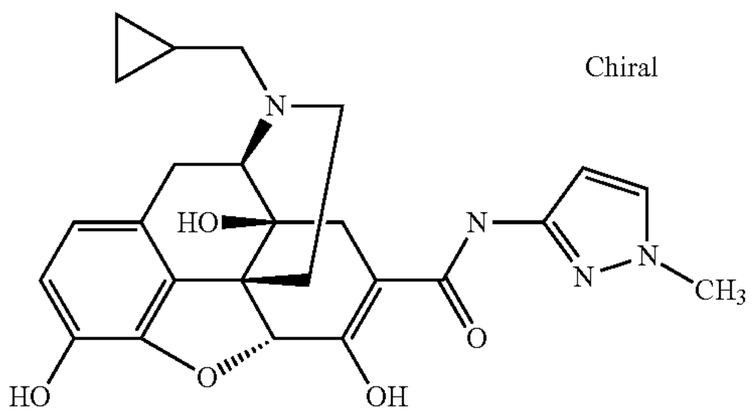
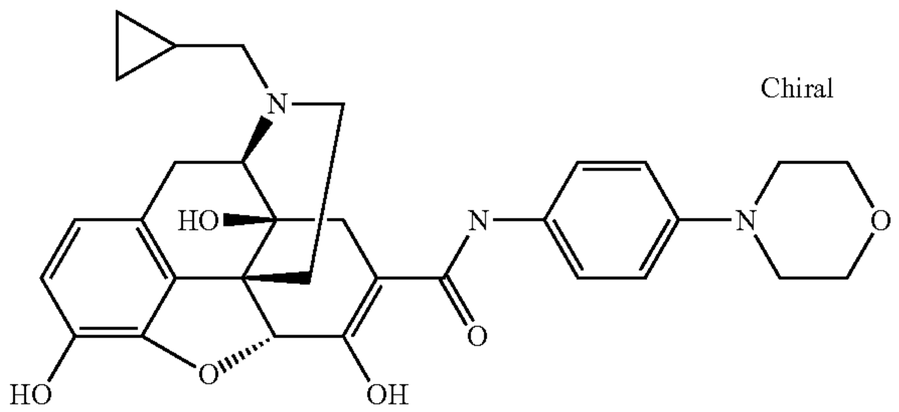
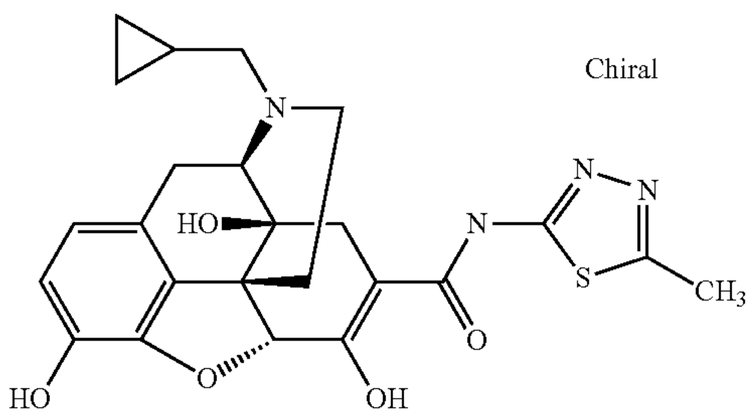
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-153	 Chiral	m/z 465 $[M + H]^+$ 0.90 min	
I-154	 Chiral	m/z 465 $[M + H]^+$ 0.96 min	
I-155	 Chiral	m/z 544 $[M + H]^+$ 1.00 min	
I-156	 Chiral	m/z 483 $[M + H]^+$ 0.35 min	

TABLE 40

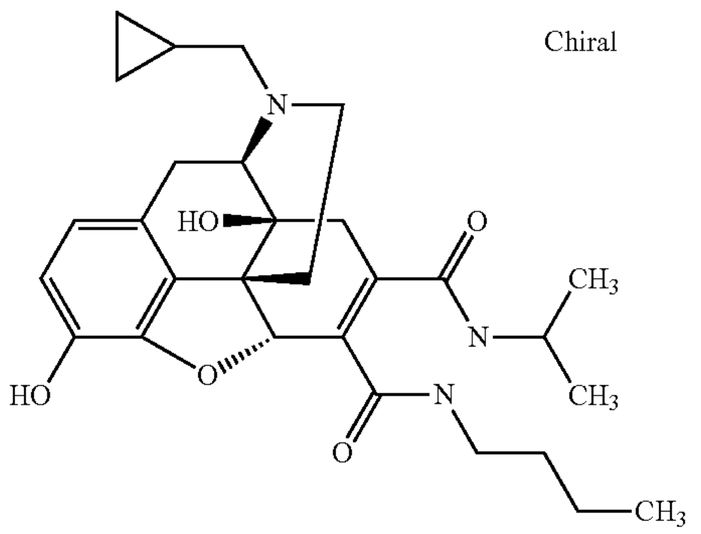
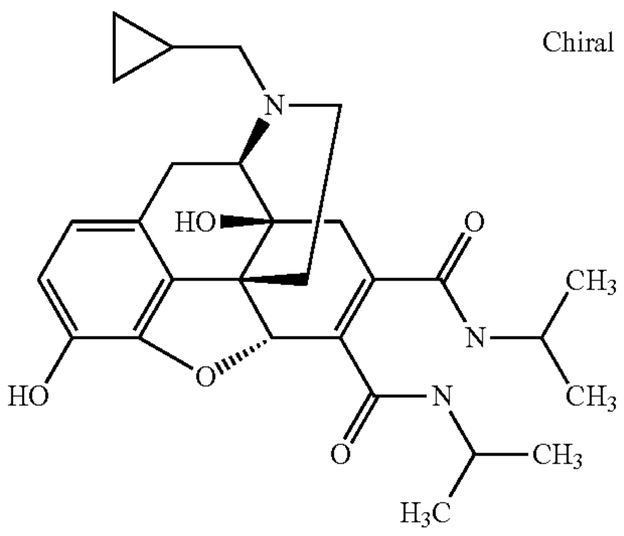
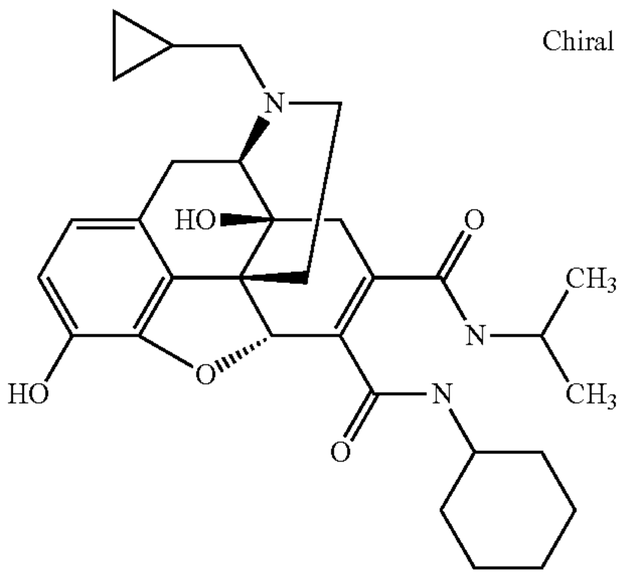
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-157	 Chiral	m/z 510 $[M + H]^+$ 0.96 min	0.11-0.14 (m, 2 H), 0.46-0.50 (m, 2 H), 0.83 (m, 1 H), 0.87 (t, J = 7.2 Hz, 1 H), 0.99 (d, J = 4.2 Hz, 3 H), 1.01 (d, J = 4.2 Hz, 3 H), 1.08-1.43 (m, 5 H), 1.95 (d, J = 17.1 Hz, 1 H), 2.11-2.65 (m, 7 H), 2.96-3.16 (m, 4 H), 3.78 (q, J = 7.5 Hz, 1 H), 4.78 (brs, 1 H), 5.21 (s, 1 H), 6.49 (d, J = 8.1 Hz, 1 H), 6.55 (d, J = 8.1 Hz, 1 H), 7.41 (t, J = 5.1 Hz, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 9.02 (brs, 1 H)
I-158	 Chiral	m/z 496 $[M + H]^+$ 0.93 min	0.11-0.13 (m, 2 H), 0.46-0.50 (m, 2 H), 0.85 (m, 1 H), 1.01 (d, J = 4.1 Hz, 3 H), 1.02 (d, J = 4.2 Hz, 3 H), 1.07 (d, J = 4.0 Hz, 3 H), 1.09 (d, J = 4.0 Hz, 3 H), 1.40 (d, J = 11.1 Hz, 1 H), 1.95 (d, J = 17.1 Hz, 1 H), 2.09-2.63 (m, 7 H), 2.98 (d J = 18.1 Hz, 1 H), 3.13 (d, J = 5.4 Hz, 1 H), 3.82 (q, J = 6.6 Hz, 1 H), 3.88 (q, J = 6.9 Hz, 1 H), 5.24 (brs, 1 H), 5.76 (s, 1 H), 6.50 (d, J = 7.5 Hz, 1 H), 6.55 (d, J = 7.5 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.54 (d, J = 6.9 Hz, 1 H), 9.01 (brs, 1 H)
I-159	 Chiral	m/z 536 $[M + H]^+$ 0.95 min	0.11-0.13 (m, 2 H), 0.46-0.50 (m, 2 H), 0.83 (m, 1 H), 0.99 (d, J = 3.0 Hz, 3 H), 1.01 (d, J = 3.0 Hz, 3 H), 1.15-1.38 (m, 6 H), 1.40 (d, J = 11.1 Hz, 1 H), 1.52-1.80 (m, 4 H), 1.97 (d, J = 17.1 Hz, 1 H), 2.09-2.65 (m, 7 H), 2.98 (d, J = 18.6 Hz, 1 H), 3.13 (d, J = 5.7 Hz, 1 H), 3.58 (m, 1 H), 3.79 (q, J = 6.9 Hz, 1 H), 5.23 (s, 1 H), 6.50 (d, J = 7.8 Hz, 1 H), 6.55 (d, J = 7.8 Hz, 1 H), 7.17 (d, J = 7.8 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 9.00 (brs, 1 H)

TABLE 41

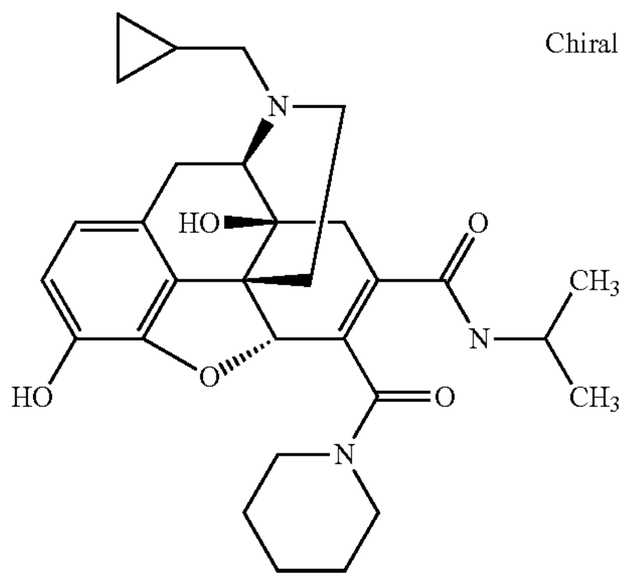
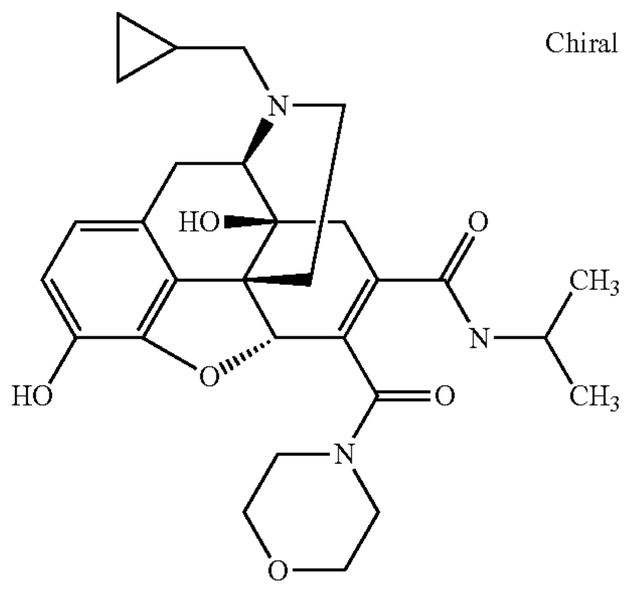
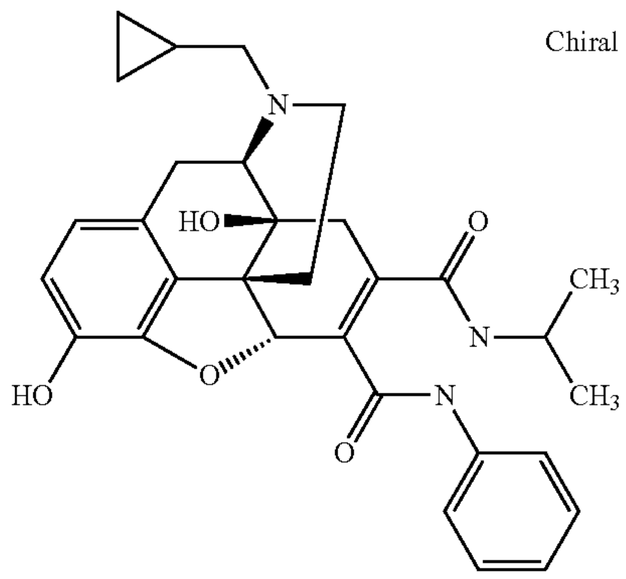
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-160	 Chiral	m/z 522 $[M + H]^+$ 1.04 min	0.12-0.13 (m, 2 H), 0.46-0.51 (m, 2 H), 0.85 (m, 1 H), 0.99 (d, J = 3.3 Hz, 3 H), 1.01 (d, J = 3.3 Hz, 3 H), 1.15-1.49 (m, 7 H), 1.91 (d, J = 16.5 Hz, 1 H), 2.08-2.65 (m, 7 H), 2.98 (d, J = 17.5 Hz, 1 H), 3.12 (d, J = 5.7 Hz, 1 H), 3.16-3.34 (m, 4 H), 3.79 (q, J = 6.9 Hz, 1 H), 4.76 (brs, 1 H), 5.01 (s, 1 H), 6.54 (d, J = 7.8 Hz, 1 H), 6.58 (d, J = 7.8 Hz, 1 H), 7.19 (d, J = 7.5 Hz, 1 H), 9.01 (brs, 1 H)
I-161	 Chiral	m/z 524 $[M + H]^+$ 0.92 min	0.12-0.14 (m, 2 H), 0.46-0.51 (m, 2 H), 0.86 (m, 1 H), 0.99 (d, J = 3.3 Hz, 3 H), 1.01 (d, J = 3.3 Hz, 3 H), 1.41 (d, J= 11.1 Hz, 1 H), 1.95 (d, J = 17.1 Hz, 1 H), 2.08-2.67 (m, 11 H), 2.98 (d, J = 17.5 Hz, 1 H), 3.12 (d, J = 5.7 Hz, 1 H), 3.49-3.60 (m, 4 H), 3.82 (q, J = 6.9 Hz, 1 H), 4.78 (brs, 1 H), 5.01 (s, 1 H), 6.54 (d, J = 8.1 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 7.38 (d, J = 7.8 Hz, 1 H), 9.13 (brs, 1 H)
I-162	 Chiral	m/z 530 $[M + H]^+$ 0.94 min	0.13-0.14 (m, 2 H), 0.47-0.51 (m, 2 H), 0.83 (m, 1 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 1.44 (d, J = 10.5 Hz, 1 H), 2.02 (d, J = 16.8 Hz, 1 H), 2.11-2.65 (m, 7 H), 3.03 (d, J = 18.6 Hz, 1 H), 3.17 (d, J= 5.7 Hz, 1 H), 3.58 (m, 1 H), 3.74 (q, J = 6.3 Hz, 1 H), 4.86 (brs, 1 H), 5.39 (s, 1 H), 6.52 (d, J = 8.1 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.8 Hz, 2 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 2 H), 9.01 (brs, 1 H), 9.70 (brs, 1 H)

TABLE 42

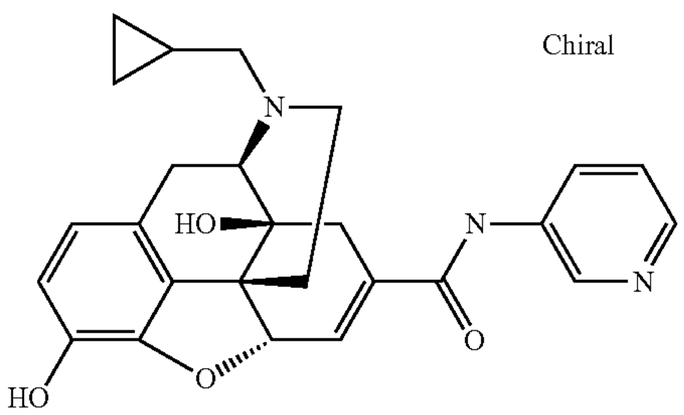
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-163	 Chiral	m/z 445 $[M + H]^+$ 0.83 min	

TABLE 42-continued

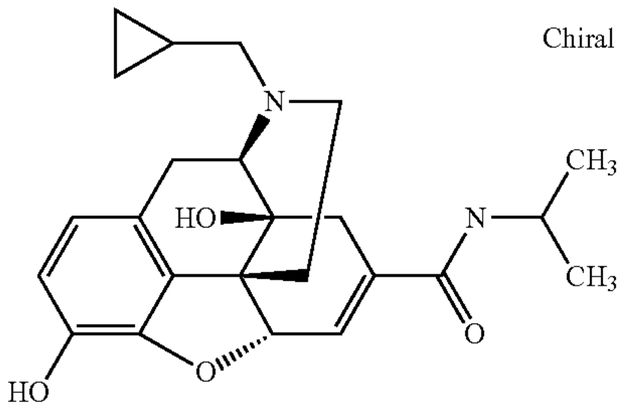
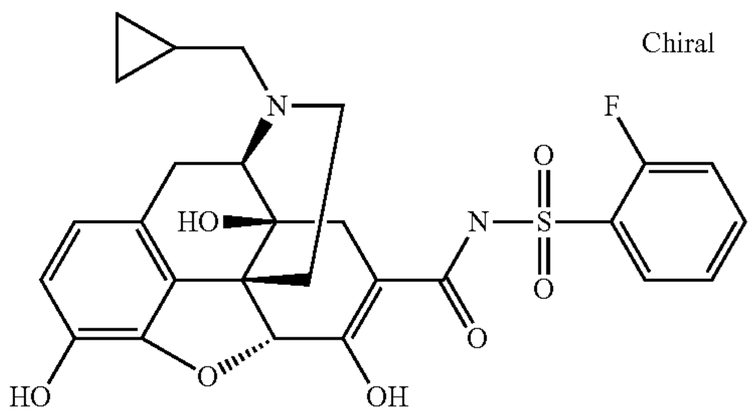
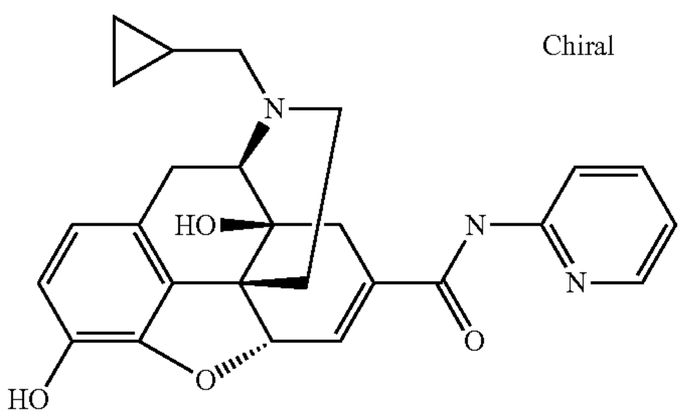
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-164	 Chiral		0.14-0.22 (m, 2 H), 0.48-0.61 (m, 2 H), 0.91 (m, 1 H), 1.12 (d, J = 6.6 Hz, 6 H), 1.53-1.66 (m, 1 H), 2.15-2.22 (m, 2 H), 2.23-2.30 (m, 2 H), 2.35-2.49 (m, 2 H), 2.70 (d.d, J = 18.9 & 6.6 Hz, 2 H), 3.13 (d, J = 18.9 Hz, 1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

TABLE 43

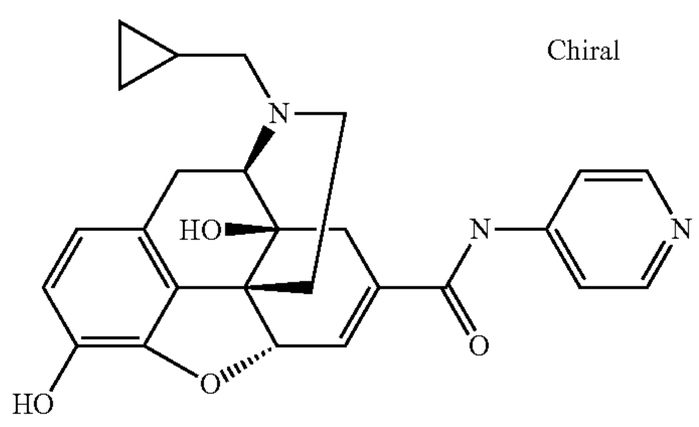
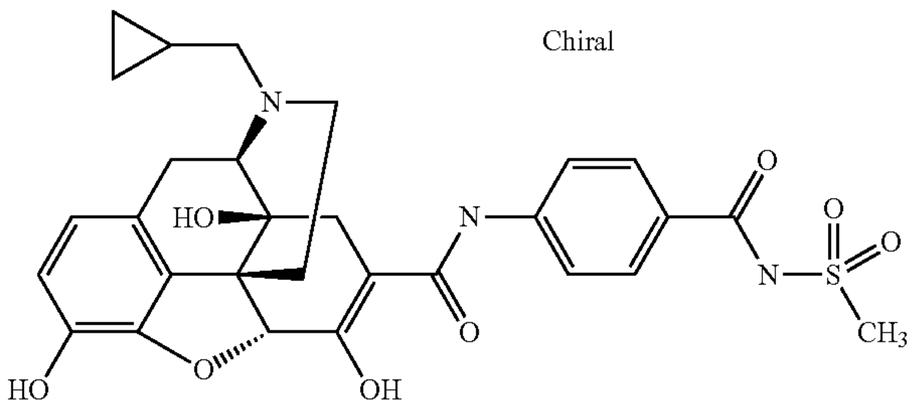
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-167	 Chiral		(CD3OD) d: 0.12-0.22 (m, 2 H), 0.48-0.63 (m, 2 H), 0.82-1.00 (m, 1 H), 1.63 (d, J= 8.1 Hz, 1 H), 2.10-2.50 (m, 7 H), 2.72 (d.d, J= 18.6 & 6.6 Hz, 2 H), 3.15 (d, J = 18.6 Hz, 1 H), 5.10 (brs, 1 H), 6.50-6.65 (m, 3 H), 7.67 (d.d, J = 4.8 & 1.5 Hz, 1 H), 8.36 (d.d, J = 4.8 & 1.5 Hz, 1 H).
I-168	 Chiral	m/z 582 [M + H]+ 0.90 min	

TABLE 43-continued

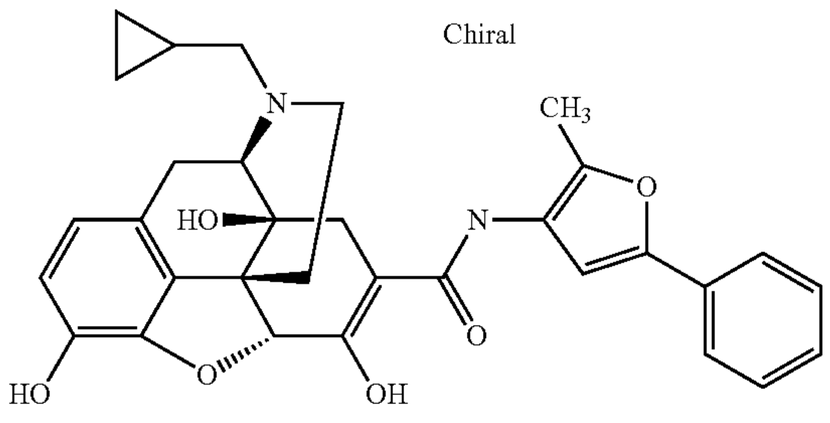
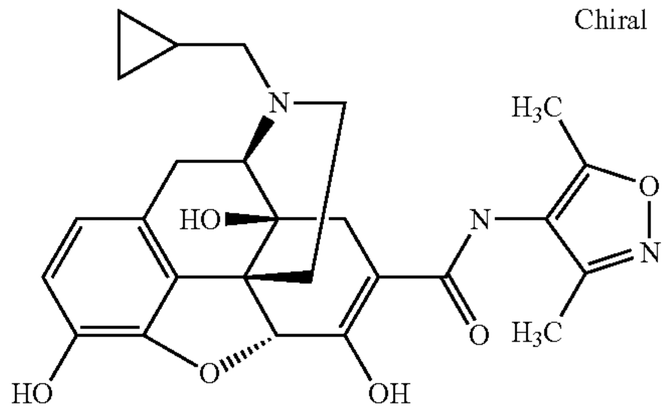
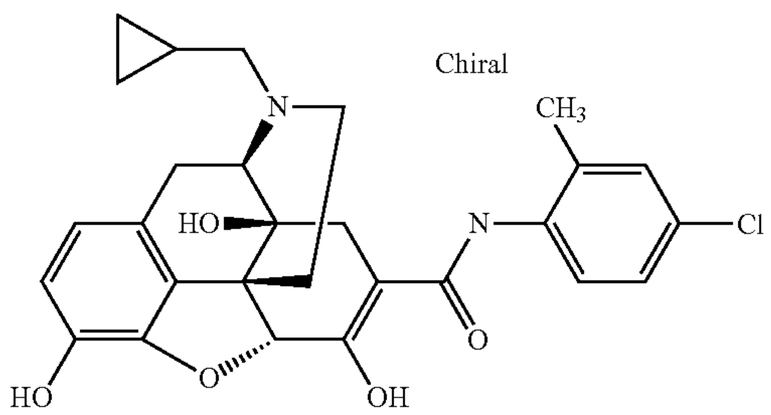
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-169	 Chiral	m/z 541 $[M + H]^+$ 1.15 min	
I-170	 Chiral	m/z 480 $[M + H]^+$ 0.37 min	
I-171	 Chiral	m/z 509 $[M + H]^+$ 0.75 min	

TABLE 44

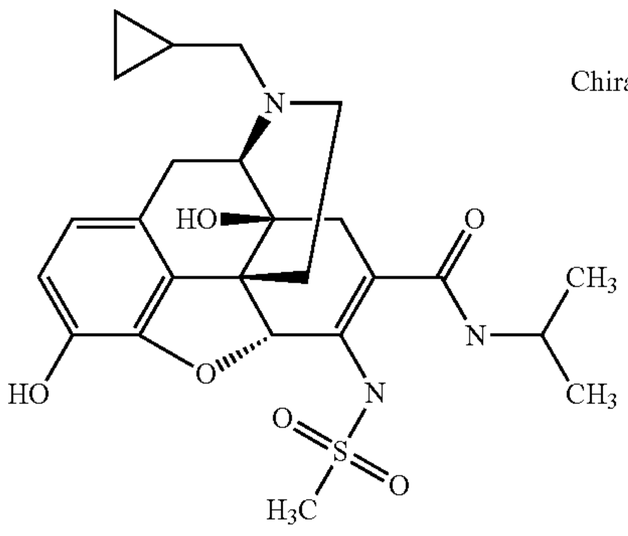
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-172	 Chiral	m/z 505 $[M + H]^+$ 0.97 min	0.11-0.13 (m, 2 H), 0.46-0.50 (m, 2 H), 0.84 (m, 1 H), 0.98 (d, J = 3.1 Hz, 3 H), 1.01 (d, J = 3.1 Hz, 3 H), 1.37 (d, J = 10.8 Hz, 1 H), 2.08 (d, J = 17.4 Hz, 1 H), 2.11-2.24 (m, 2 H), 2.35 (d, J = 6.6 Hz, 1 H), 2.51-2.63 (m, 2 H), 3.01 (d, J = 18.3 Hz, 1 H), 3.13 (d, J = 5.7 Hz, 1 H), 3.54 (s, 3 H), 3.86 (q, J = 7.2 Hz, 1 H), 4.79 (brs, 1 H), 4.98 (brs, 1 H), 5.76 (s, 1 H), 6.54 (d, J = 7.8 Hz, 1 H), 6.59 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.5 Hz, 1 H), 9.16 (brs, 1 H)

TABLE 44-continued

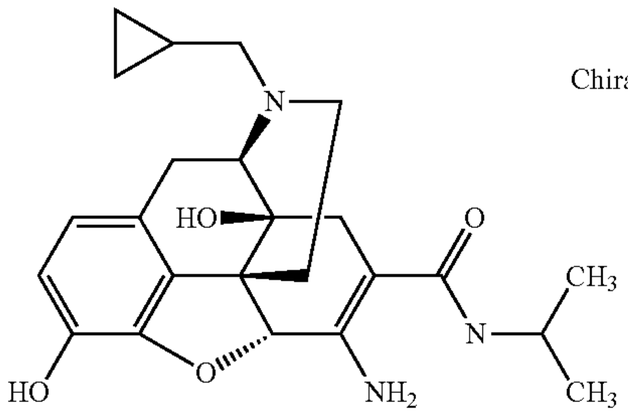
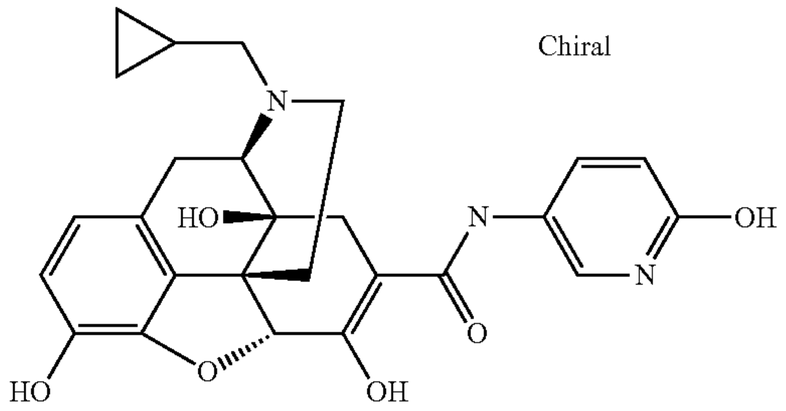
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-173	 Chiral	m/z 426 $[M + H]^+$ 0.90 min	0.12-0.14 (m, 2 H), 0.46-0.52 (m, 2 H), 0.85 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 1.38 (d, J = 10.2 Hz, 1 H), 1.86 (d, J = 15.0 Hz, 1 H), 2.02 (d, J = 15.0 Hz, 1 H), 2.10-2.17 (m, 2 H), 2.28 (dd, J = 6.9, 6.9 Hz, 1 H), 2.43 (dd, J = 6.9, 8.4 Hz, 1 H), 2.54-2.62 (m, 2 H), 3.01 (d, J = 18.3 Hz, 1 H), 3.17 (d, J = 5.7 Hz, 1H), 3.58 (m, 1 H), 3.88 (q, J = 7.2 Hz, 1 H), 4.62 (brs, 1 H), 4.68 (s, 1 H), 6.47 (d, J = 8.1 Hz, 1 H), 6.55 (d, J = 8.1 Hz, 1 H), 6.94 (brs, 1 H), 9.06 (brs, 1 H)
I-174	 Chiral		(CD3OD) d: 0.10-0.25 (m, 2 H), 0.48-0.63 (m, 2 H), 0.83-1.00 (m, 1 H), 1.55 (d, J = 8.1 Hz, 1 H), 2.01 (d, J = 15.6 Hz, 1 H), 2.22-2.57 (m, 6 H), 2.70 (d.d, J = 18.3 & 7.2 Hz, 2 H), 3.12 (d, J = 18.3 Hz, 1 H), 4.67 (s, 1 H), 6.44-6.62 (m, 3 H), 7.54 (d.d, J = 9.6 & 3.6 Hz, 1 H), 8.00 (d, J = 3.6 Hz, 1 H).

TABLE 45

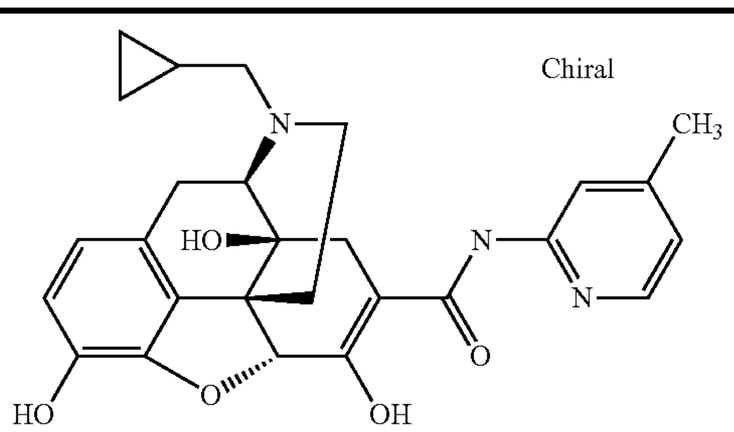
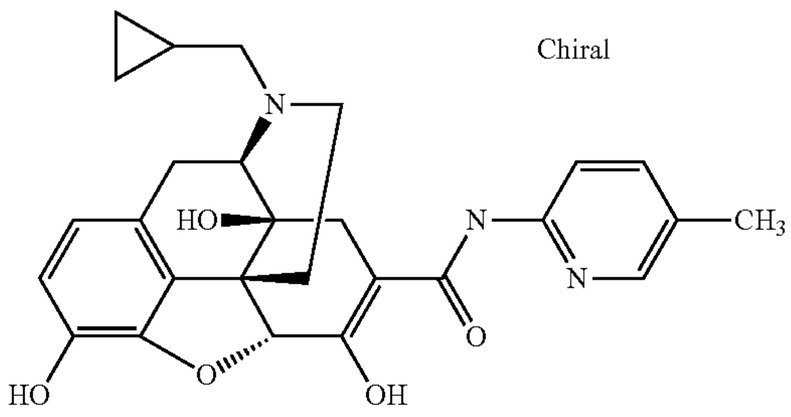
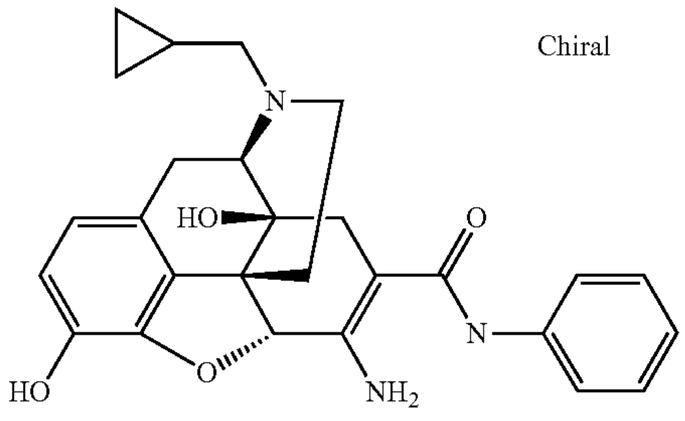
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-175	 Chiral	m/z 458 [M + H]+ 0.86 min	
I-176	 Chiral	ESI: m/z 458 $[M + H]^+$	
I-177	 Chiral	m/z 460 $[M + H]^+$ 1.20 min	0.13-0.17 (m, 2 H), 0.47-0.50 (m, 2 H), 0.87 (m, 1 H), 1.41 (d, J = 10.5 Hz, 1 H), 2.07 (d, J = 15.0 Hz, 1 H), 2.10-2.25 (m, 2 H), 2.32 (dd, J = 5.7, 6.9 Hz, 1 H), 2.45 (dd, J = 5.7, 6.0 Hz, 1 H), 2.63 (dt, J = 6.3, 11.7, 2 H), 3.05 (d, J = 18.3 Hz, 1 H), 3.19 (d, J= 6.0 Hz, 1 H), 4.67 (brs, 1 H), 4.75 (s, 1 H), 6.51 (d, J = 8.1 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 8.4 Hz, 1 H), 7.25 (d, J = 3.6 Hz, 2 H), 7.52 (d, J = 7.5 Hz, 2 H), 8.38 (brs, 1 H), 9.07 (brs, 1 H)

TABLE 46

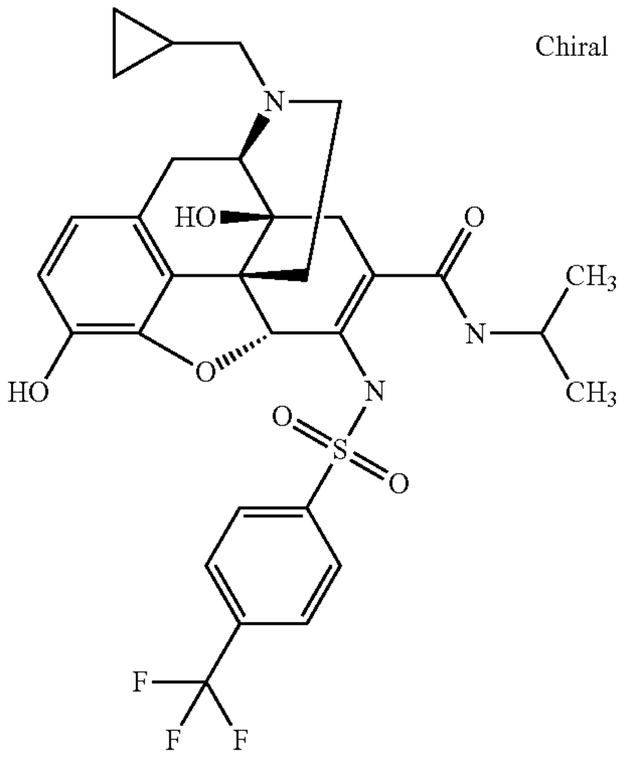
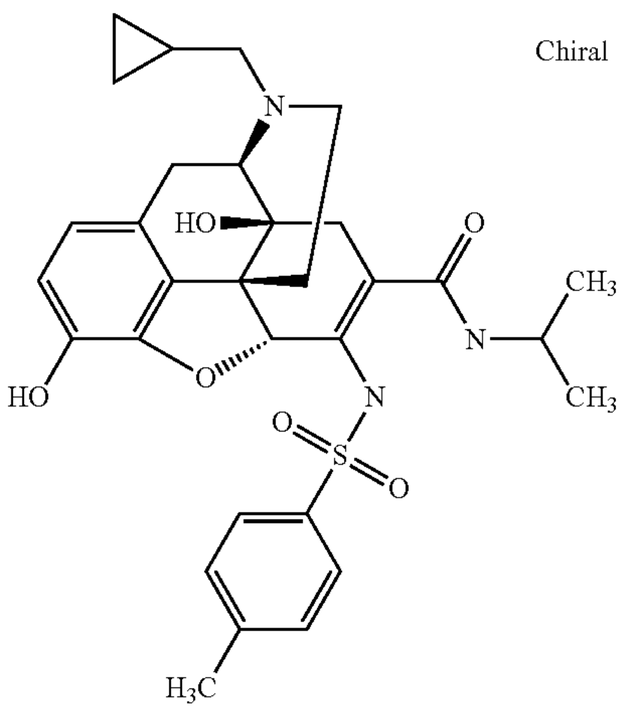
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-178	 Chiral	m/z 636 $[M + H]^+$ 1.11 min	0.11-0.13 (m, 2 H), 0.46-0.51 (m, 2 H), 0.86 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H), 1.46 (d, J = 11.1 Hz, 1 H), 1.87 (d, J = 18.0 Hz, 1 H), 2.11-2.63 (m, 7 H), 2.25 (s, 3 H), 3.03 (d, J = 17.4 Hz, 1 H), 3.18 (brs, 1 H), 3.84 (q, J = 7.2 Hz, 1 H), 4.71 (brs, 1 H), 5.45 (brs, 1 H), 6.50 (brs, 1 H), 6.57 (brs, 1 H), 7.61-8.19 (m, 4 H), 9.03 (brs, 1 H), 10.7 (brs, 1 H), 12.7 (brs, 1 H)
I-179	 Chiral	m/z 581 $[M + H]^+$ 1.06 min	0.11-0.13 (m, 2 H), 0.46-0.51 (m, 2 H), 0.86 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H), 1.46 (d, J = 11.1 Hz, 1 H), 1.87 (d, J = 18.0 Hz, 1 H), 2.09 (s, 3 H), 2.11-2.63 (m, 7 H), 3.03 (d, J = 17.4 Hz, 1 H), 3.18 (brs, 1 H), 3.84 (q, J = 7.2 Hz, 1 H), 4.69 (brs, 1 H), 5.45 (brs, 1 H), 6.48 (d, J = 7.2 Hz, 1 H), 6.55 (d, J = 7.2 Hz, 1 H), 7.33 (brd, J = 5.4 Hz, 2 H), 7.54 (brs, 1 H), 7.74 (d, J = 7.5 Hz, 2 H), 9.11 (brs, 1 H), 12.3 (brs, 1 H)

TABLE 47

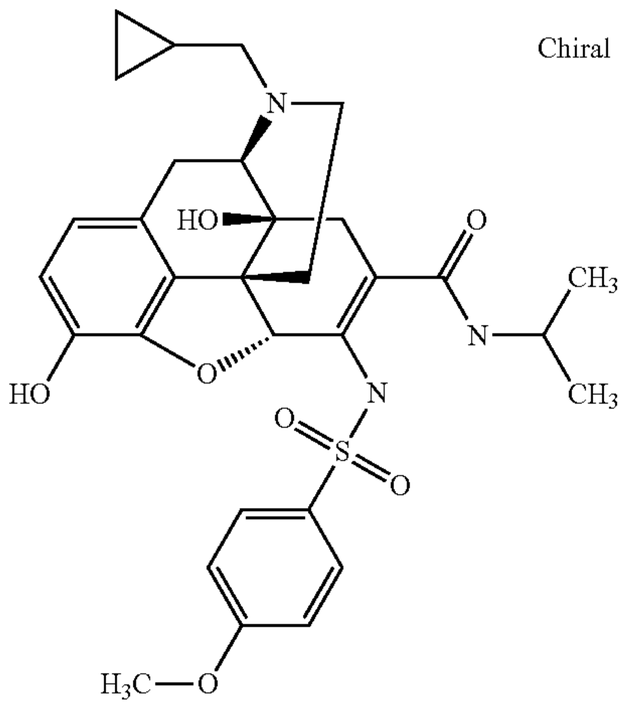
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-180	 Chiral	m/z 597 $[M + H]^+$ 1.03 min	0.11-0.13 (m, 2 H), 0.46-0.51 (m, 2 H), 0.85 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H), 1.46 (d, J = 9.9 Hz, 1 H), 1.87 (d, J = 17.4 Hz, 1 H), 2.11-2.62 (m, 7 H), 3.01 (d, J = 17.7 Hz, 1 H), 3.15 (d, J = 4.6 Hz, 1 H), 3.82 (s, 3 H), 3.83 (q, J = 5.4 Hz, 1 H), 4.67 (brs, 1 H), 5.44 (s, 1 H), 6.49 (d, J = 8.1 Hz, 1 H), 6.55 (d, J = 8.1 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 2 H), 7.52 (brd, J = 9.3 Hz, 1 H), 7.79 (d, J = 8.4 Hz, 2 H), 9.12 (brs, 1 H), 12.2 (brs, 1 H)

TABLE 47-continued

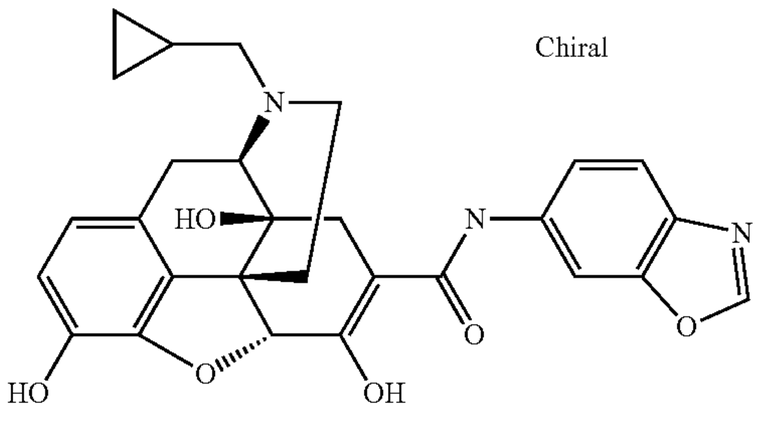
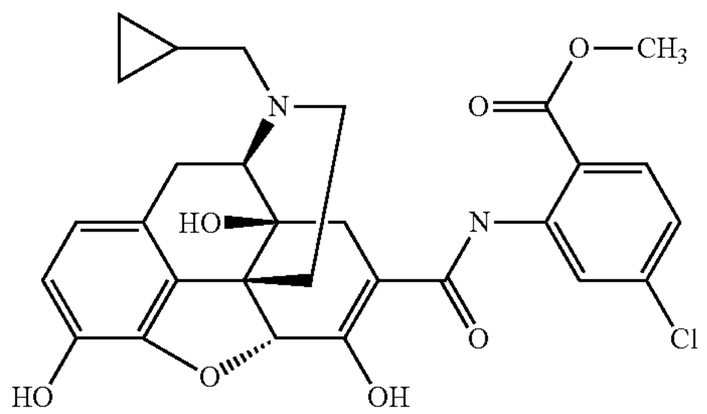
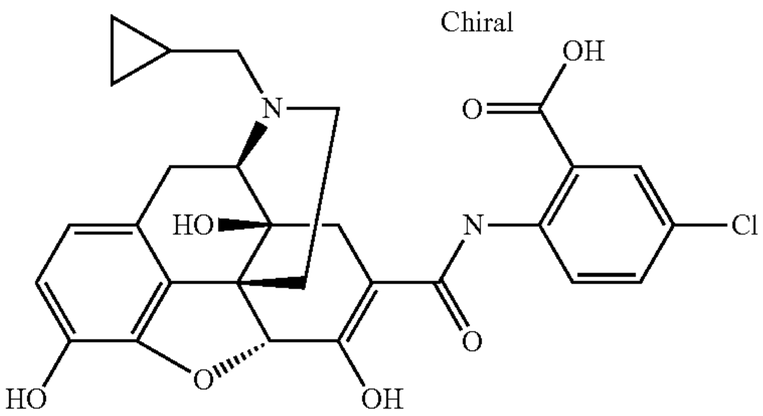
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-181	 Chiral	m/z 502 $[M + H]^+$ 0.35 min	
I-182	 Chiral	m/z 553 $[M + H]^+$ 0.68 min	
I-183	 Chiral	m/z 539 $[M + H]^+$ FAB-MS	

TABLE 48

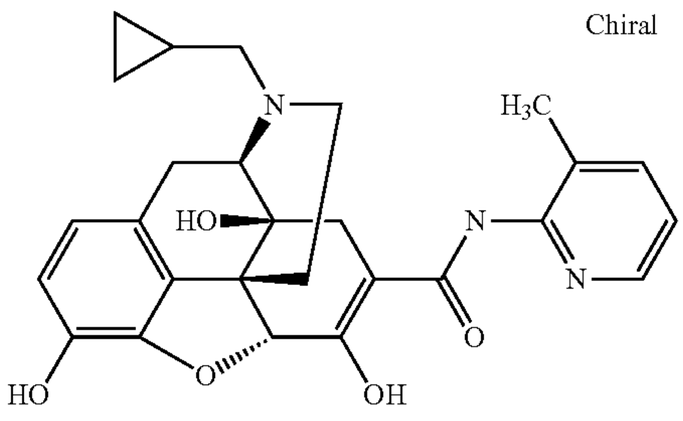
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-184	 Chiral	m/z 458 $[M + H]^+$ 0.97 min	

TABLE 48-continued

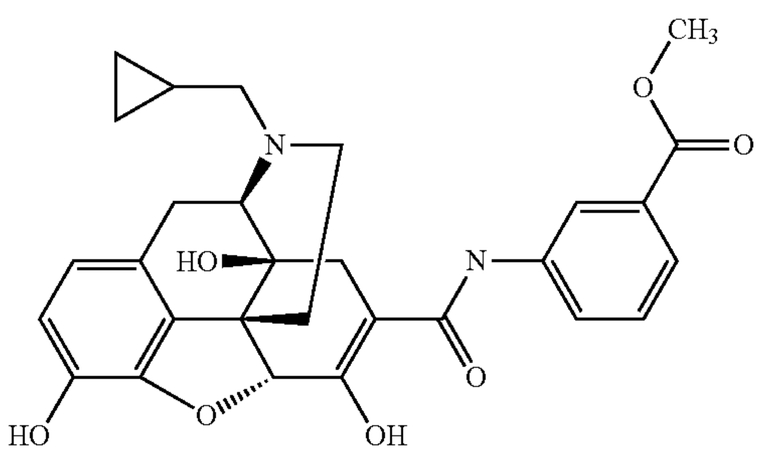
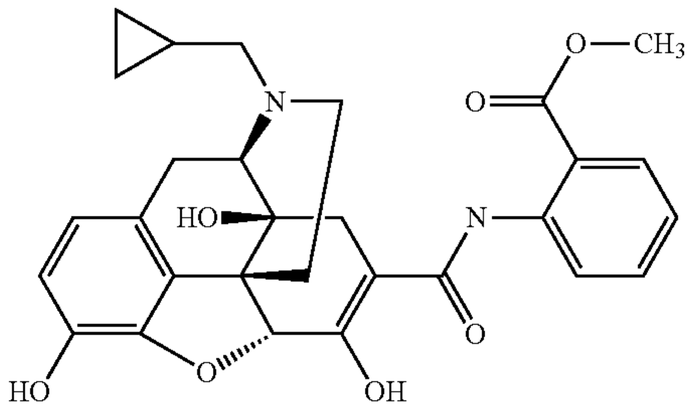
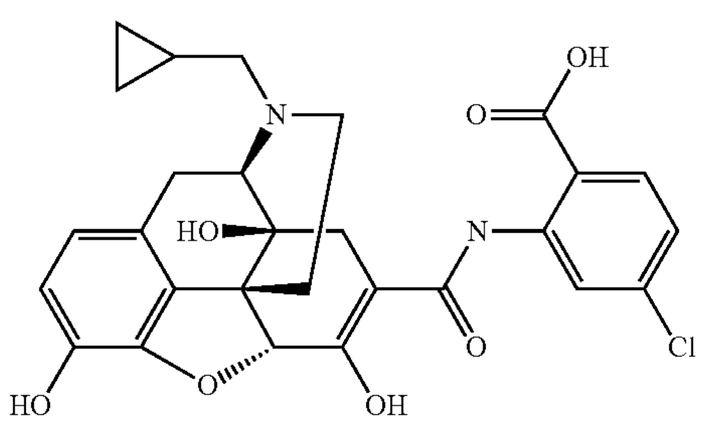
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-185		Chiral m/z 519 $[M + H]^+$ 0.43 min	
I-186		Chiral m/z 519 $[M + H]^+$ 1.67 min**	
I-187		Chiral m/z 539 $[M + H]^+$ 0.50 min	

TABLE 49

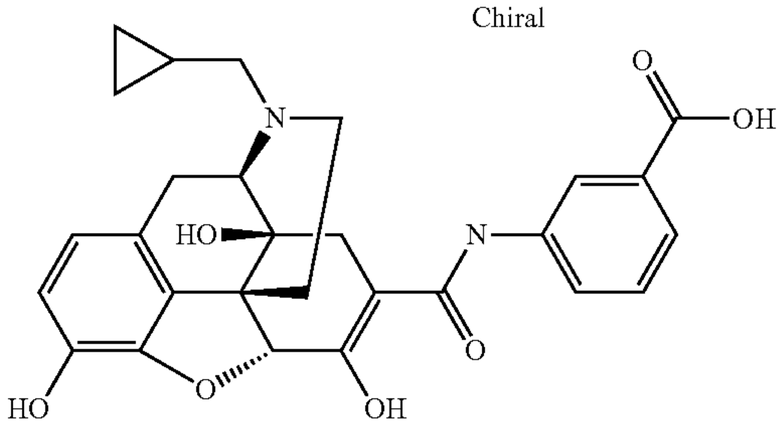
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-188		Chiral m/z 505 $[M + H]^+$ 0.35 min	

TABLE 49-continued

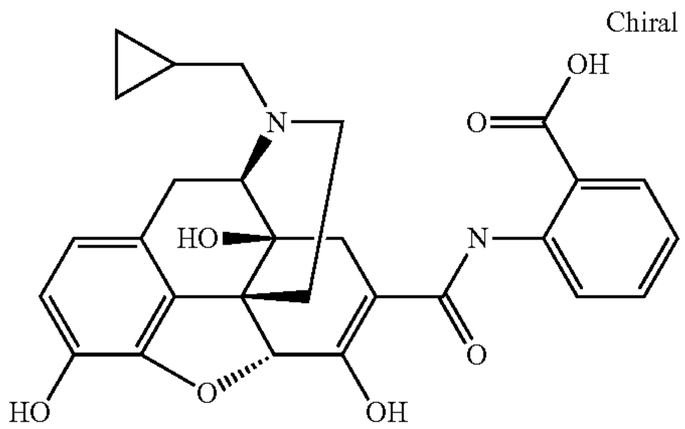
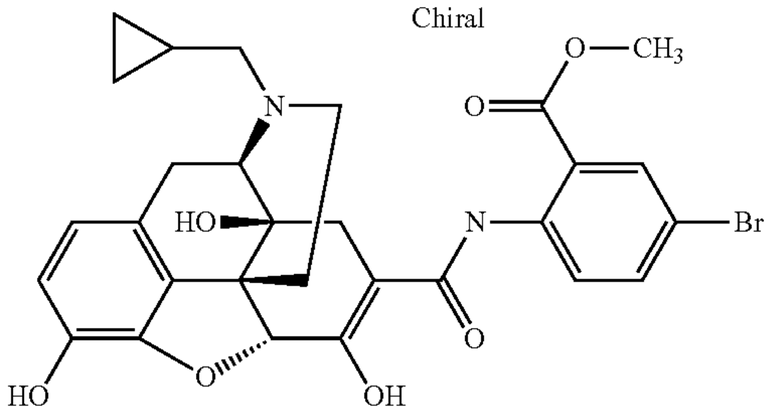
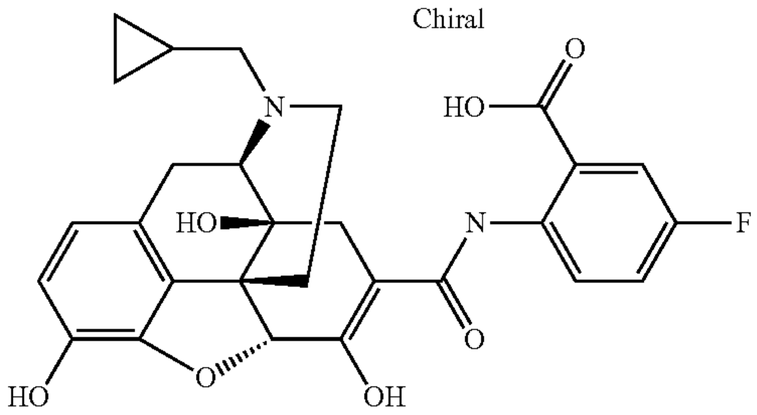
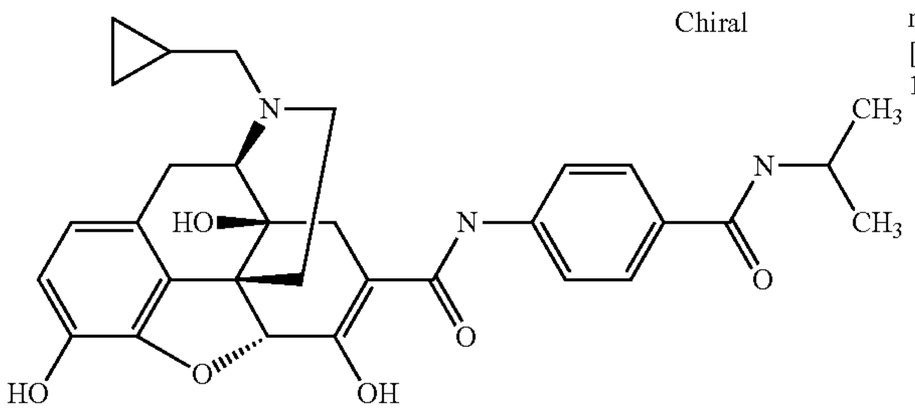
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-189	 Chiral	m/z 505 $[M + H]^+$ 0.42 min	
I-190	 Chiral	m/z 597 $[M + H]^+$ 0.77 min	
I-191	 Chiral	m/z 523 $[M + H]^+$ 1.20 min	
I-192	 Chiral	m/z 546 $[M + H]^+$ 1.00 min	

TABLE 50

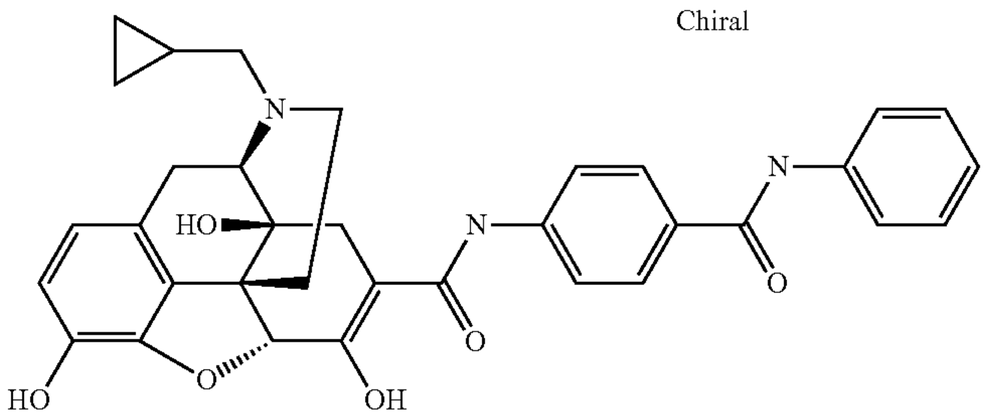
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-193	 Chiral	m/z 580 $[M + H]^+$ 1.09 min	

TABLE 50-continued

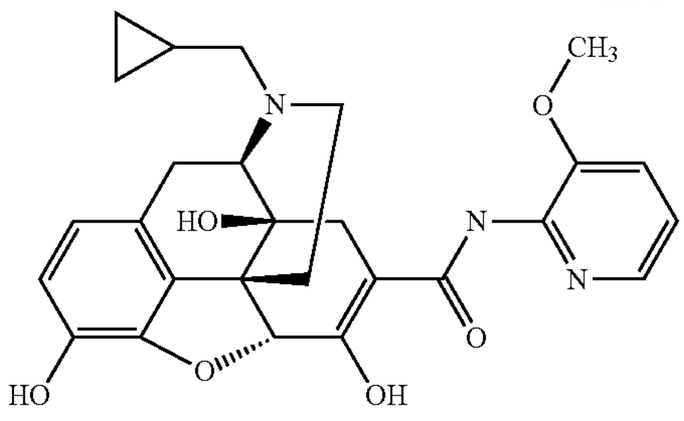
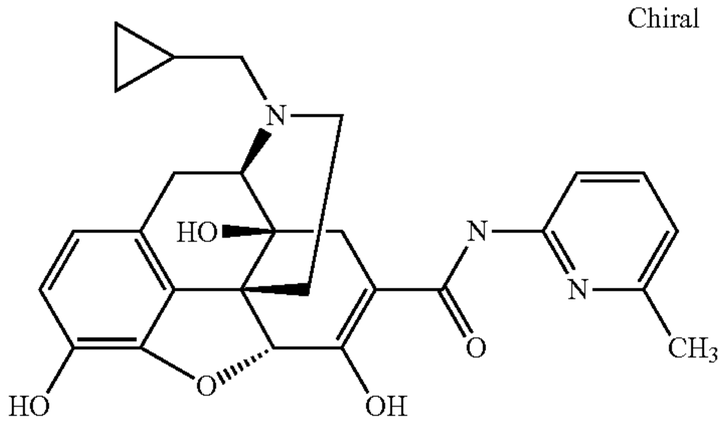
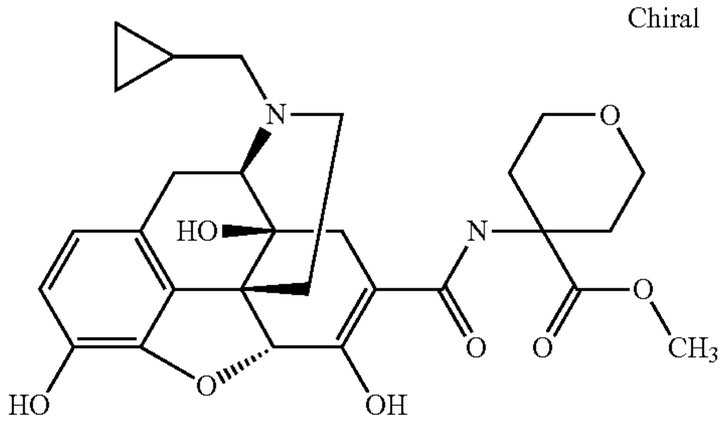
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-194	 Chiral	m/z 474 $[M + H]^+$ 0.88 min	
I-195	 Chiral	m/z 458 $[M + H]^+$ 1.08 min	
I-196	 Chiral		0.12-0.16 (m, 2 H), 0.46-0.55 (m, 2 H), 0.88 (m, 1 H), 1.43 (d, J = 12.4 Hz, 1 H), 1.65-2.65 (m, 12 H), 2.97-3.70 (m, 6 H), 3.59 (s, 3 H), 4.74 (s 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 6.59 (d, J = 8.0 Hz, 1 H), 7.68 (brs, 1 H), 9.16 (brs, 1 H), 13.5 (brs, 1 H)

TABLE 51

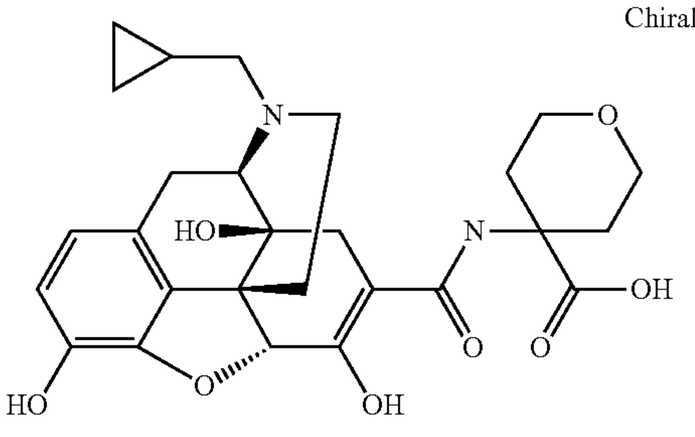
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-197	 Chiral		0.20-0.40 (m, 2 H), 0.46-0.65 (m, 2 H), 0.97 (m, 1 H), 1.54 (d, J = 6.8 Hz, 1 H), 1.80-2.10 (m, 3 H), 2.31-3.69 (m, 15 H), 4.83 (s 1 H), 6.59 (d, J = 8.0 Hz, 1 H), 6.65 (d, J = 8.0 Hz, 1 H), 7.56 (brs, 1 H), 9.29 (brs, 1 H), 13.6 (brs, 1 H)

TABLE 51-continued

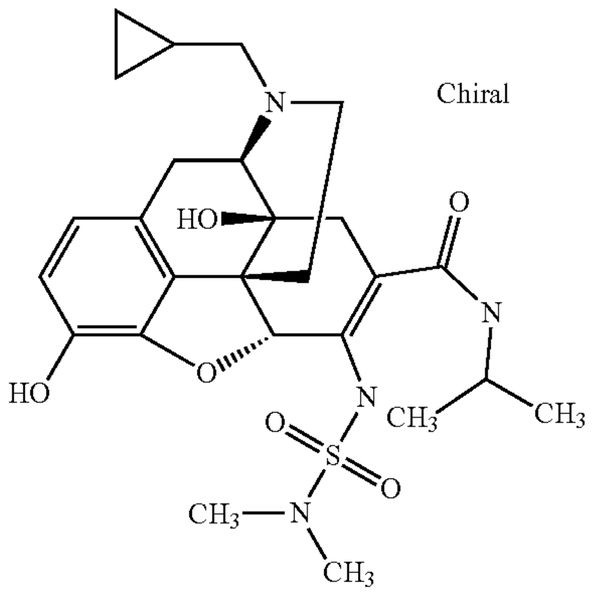
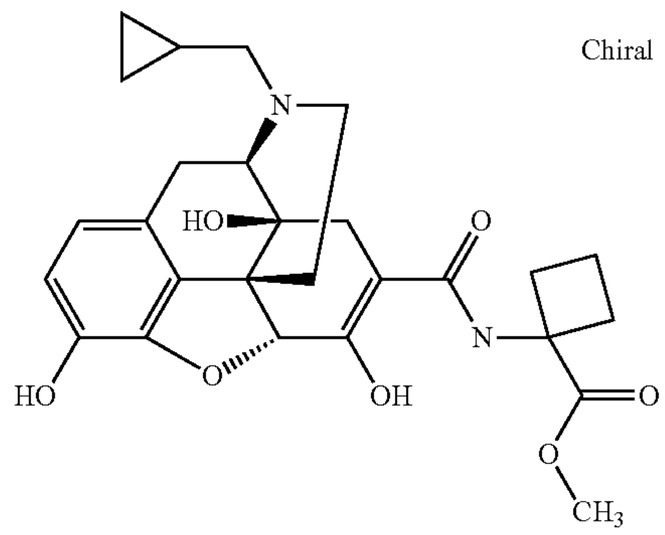
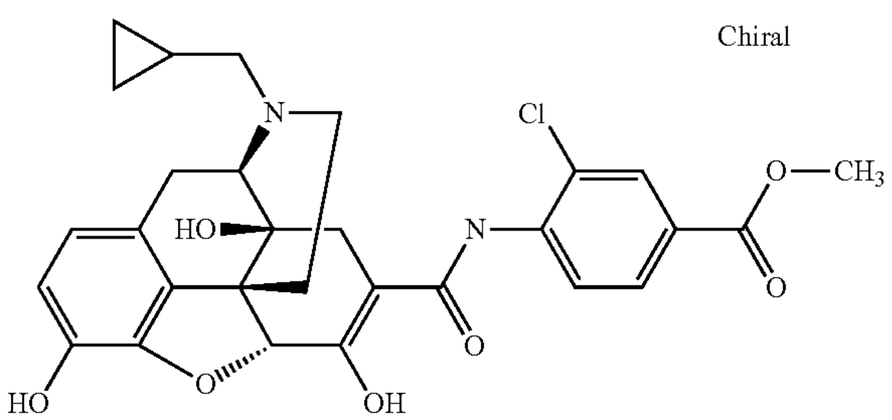
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-198	 Chiral	m/z 533 $[M + H]^+$ 0.95 min	0.11-0.13 (m, 2 H), 0.46-0.52 (m, 2 H), 0.86 (m, 1 H), 1.03 (d, J = 6.3 Hz, 3 H), 1.08 (d, J = 6.3 Hz, 3 H), 1.46 (brd, J = 8.4 Hz, 1 H), 1.94 (d, J = 17.7 Hz, 1 H), 2.71-2.60 (m, 7 H), 2.81 (s, 6 H), 3.04 (d, J = 17.1 Hz, 1 H), 3.18 (brs, 1 H), 3.95 (q, J = 5.4 Hz, 1 H), 4.77 (brs, 1 H), 5.45 (s, 1 H), 6.51 (d, J = 7.5 Hz, 1 H), 6.57 (d, J = 7.5 Hz, 1 H), 7.64 (brs, 1 H), 9.14 (brs, 1 H), 12.2 (brs, 1 H)
I-199	 Chiral	m/z 497 $[M + H]^+$ 0.97 min	0.13-0.15 (m, 2 H), 0.48-0.52 (m, 2 H), 0.86 (m, 1 H), 1.41 (d, J = 11.4 Hz, 1 H), 1.85 (t, J = 7.8 Hz, 2 H), 1.93 (d, J = 16.5 Hz, 1 H), 2.07-2.62 (m, 11 H), 3.05 (d, J = 18.3 Hz, 1 H), 3.21 (d, J = 6.0 Hz, 1 H), 3.59 (s, 3 H), 4.72 (s, 1 H), 4.77 (brs, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 8.26 (brs, 1 H), 9.15 (brs, 1 H), 14.1 (brs, 1 H)
I-200	 Chiral	m/z 553 $[M + H]^+$ 0.47 min	

TABLE 52

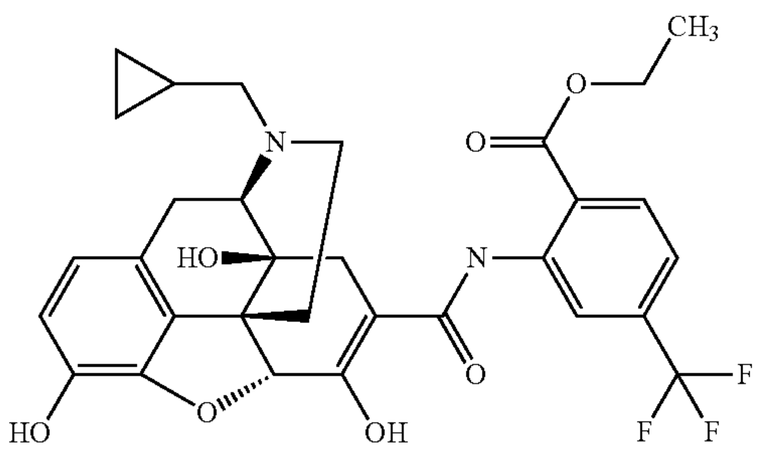
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-201	 Chiral	m/z 601 $[M + H]^+$ 1.01 min	

TABLE 52-continued

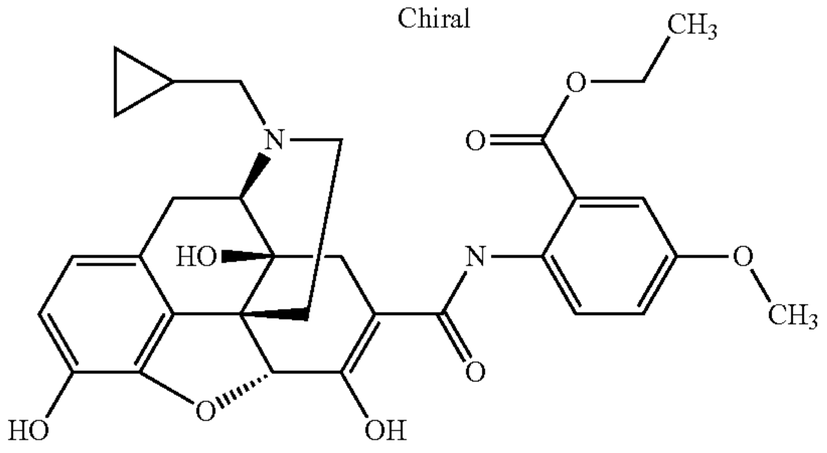
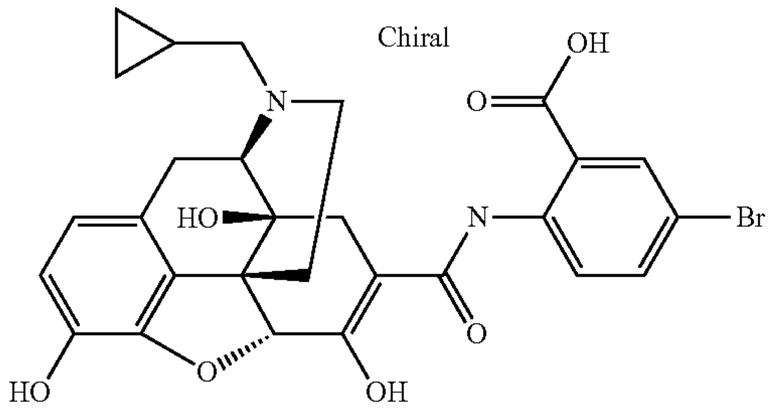
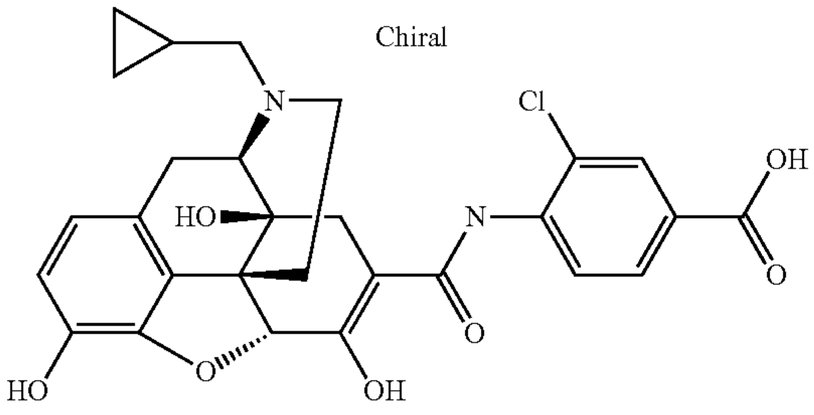
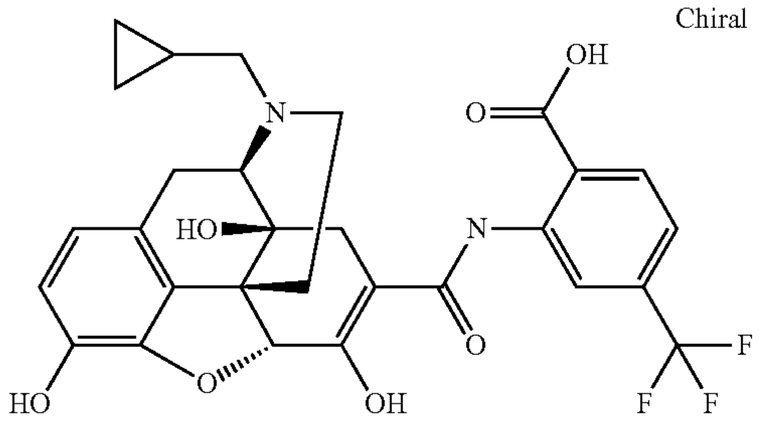
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-202	Chiral 	m/z 563 $[M + H]^+$ 0.58 min	
I-203	Chiral 	m/z 583 $[M + H]^+$ 0.54 min	
I-204	Chiral 	m/z 539 $[M + H]^+$ 0.33 min	
I-205	Chiral 	m/z 573 $[M + H]^+$ 0.62 min	

TABLE 53

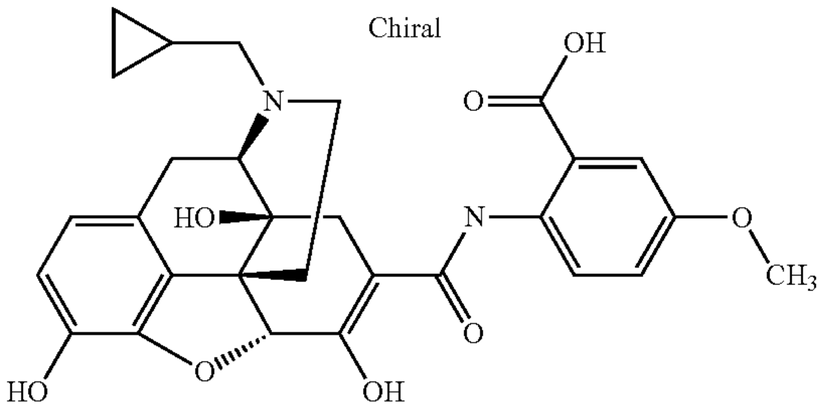
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-206	Chiral 	m/z 535 $[M + H]^+$ 0.41 min	

TABLE 53-continued

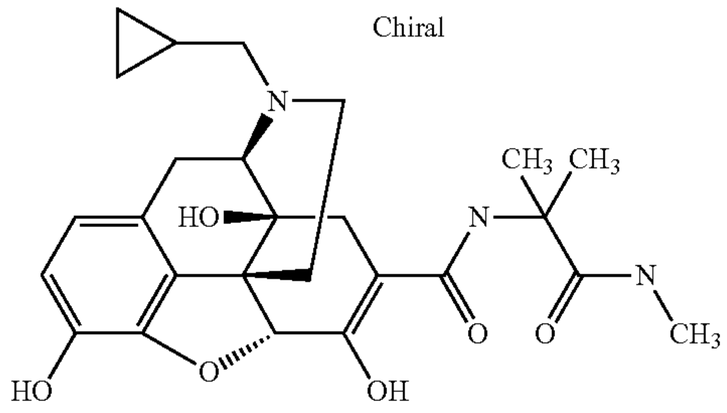
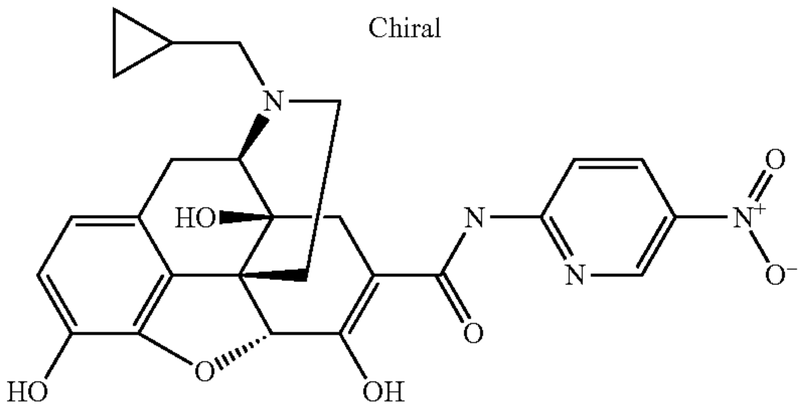
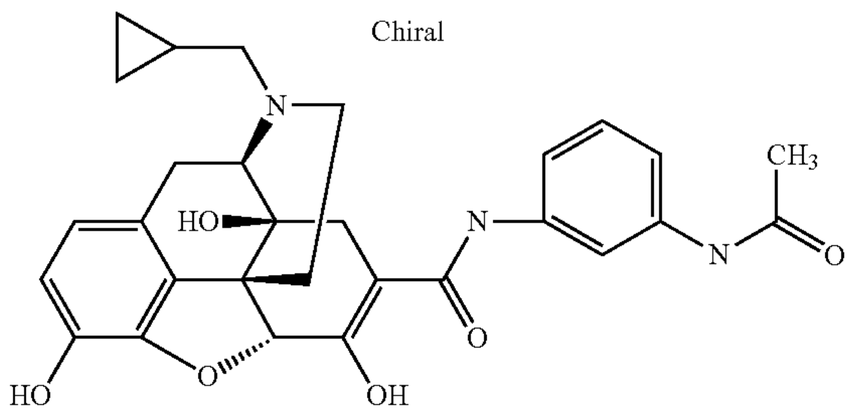
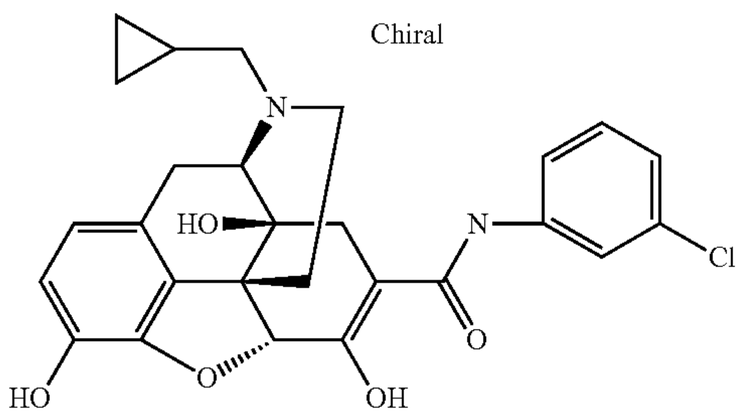
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-207	 Chiral	m/z 484 $[M + H]^+$ 0.32 min	
I-208	 Chiral	m/z 507 $[M + H]^+$ 1.05 min	
I-209	 Chiral	m/z 518 $[M + H]^+$ 1.14 min**	
I-210	 Chiral	m/z 495 $[M + H]^+$ 1.64 min**	

TABLE 54

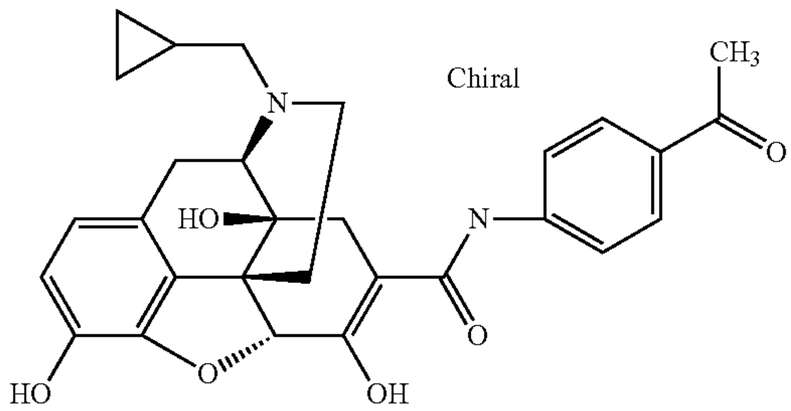
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-211	 Chiral	m/z 503 $[M + H]^+$ 1.33 min**	

TABLE 54-continued

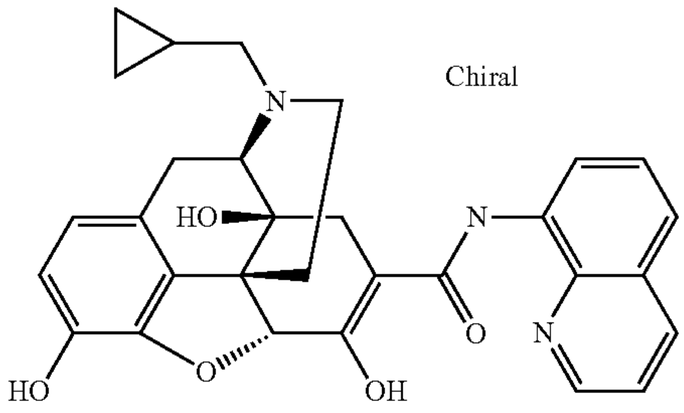
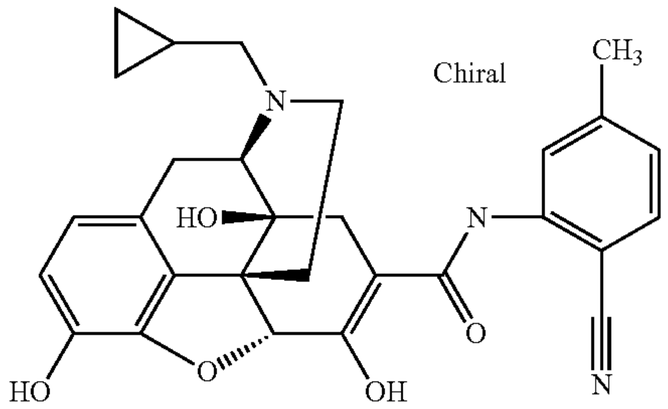
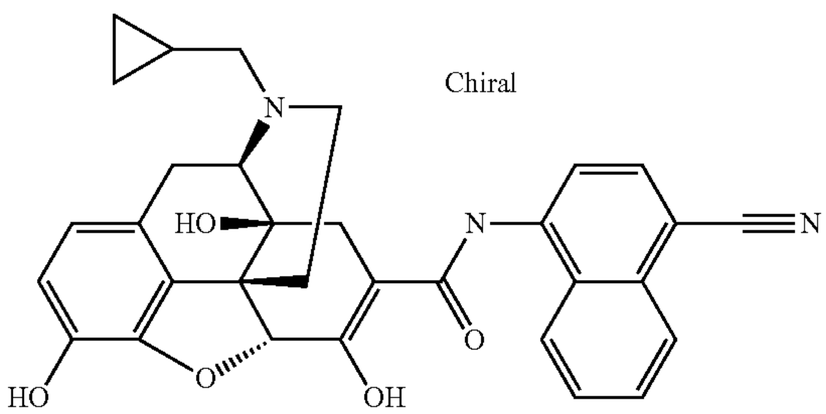
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-212	 Chiral	m/z 512 $[M + H]^+$ 1.67 min**	
I-213	 Chiral	m/z 500 $[M + H]^+$ 1.41 min**	
I-214	 Chiral	m/z 536 $[M + H]^+$ 1.69 min**	

TABLE 55

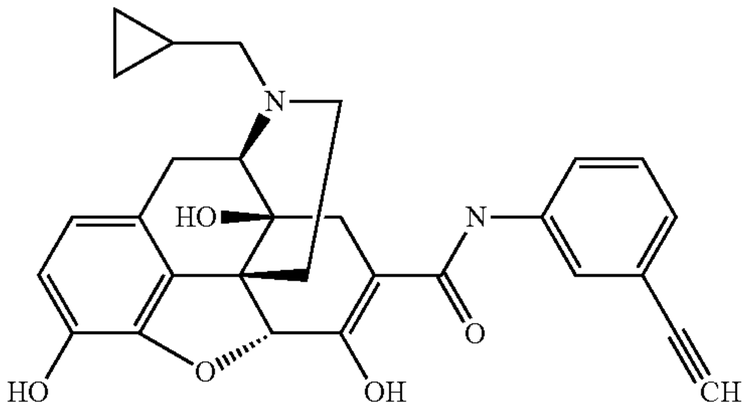
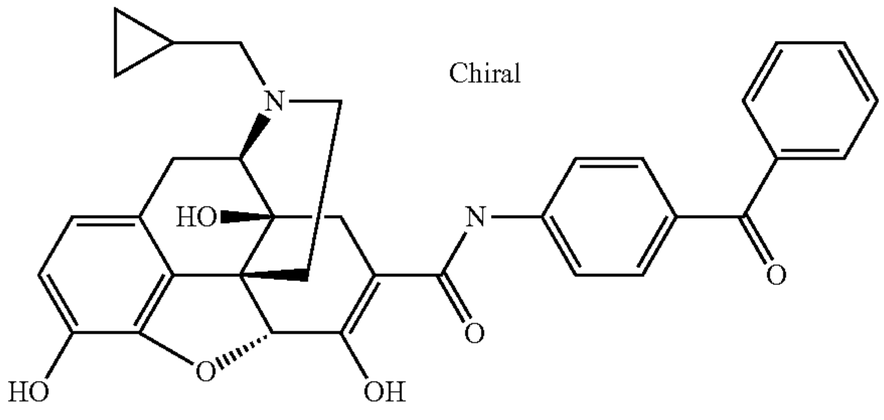
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-215		m/z 485 $[M + H]^+$ 1.60 min**	
I-216	 Chiral	m/z 565 $[M + H]^+$ 1.82 min**	

TABLE 55-continued

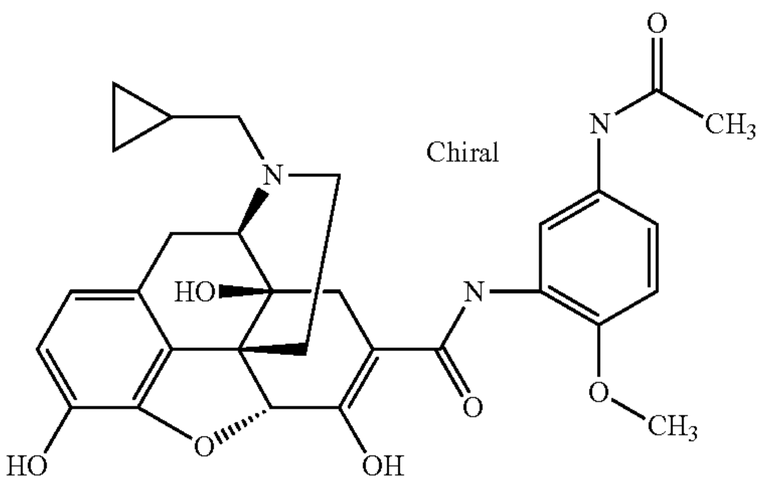
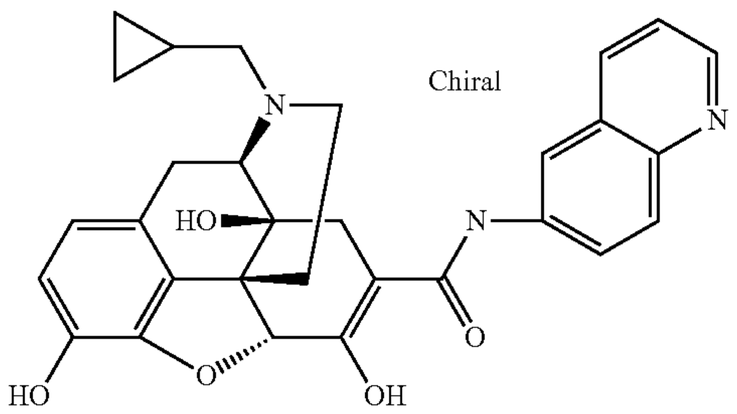
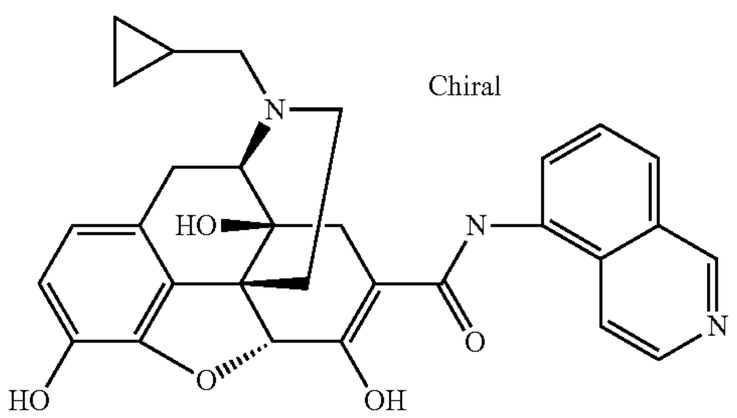
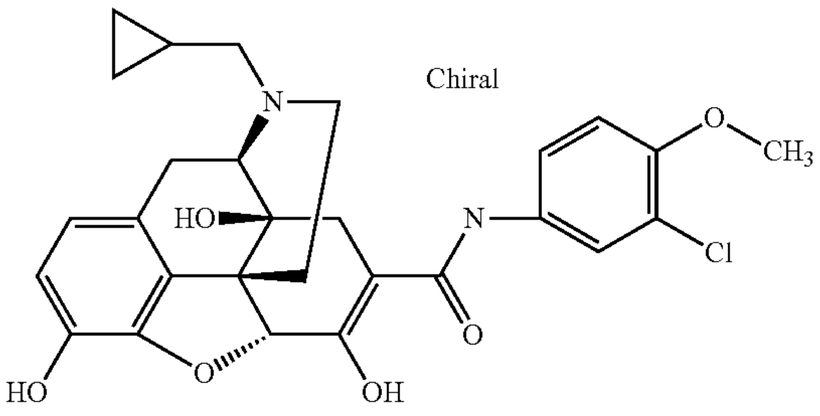
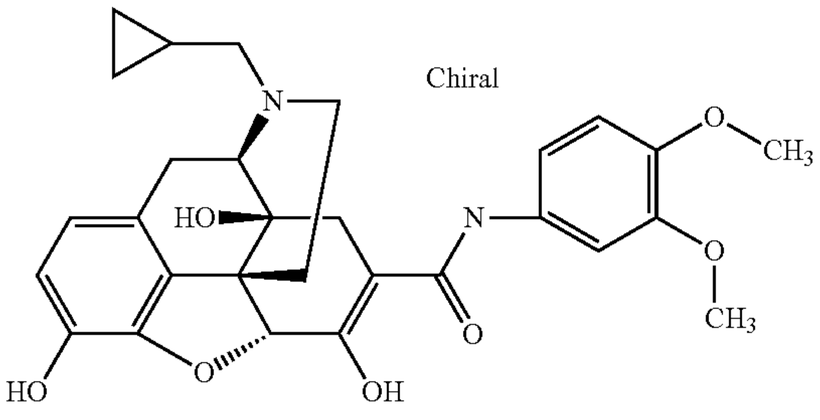
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-217		m/z 548 [M + H]+ 1.17 min**	
I-218		m/z 512 [M + H]+ 0.95 min**	
I-219		m/z 512 [M + H]+ 1.66 min**	
I-220		m/z 525 [M + H]+ 1.60 min**	
I-221		m/z 521 [M + H]+ 1.35 min**	

TABLE 56

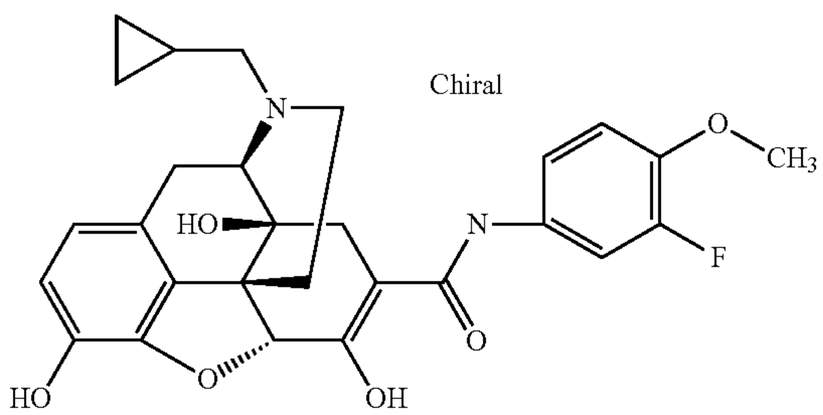
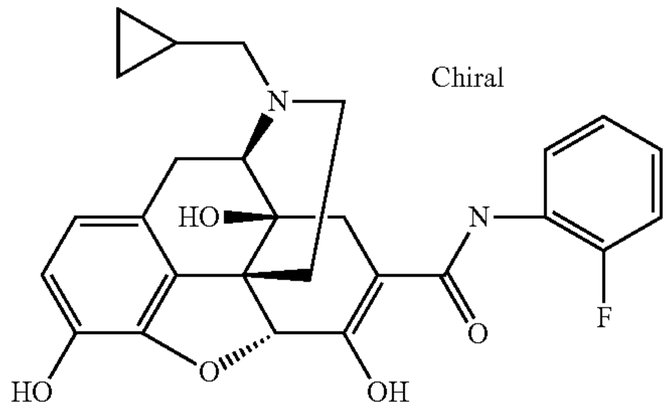
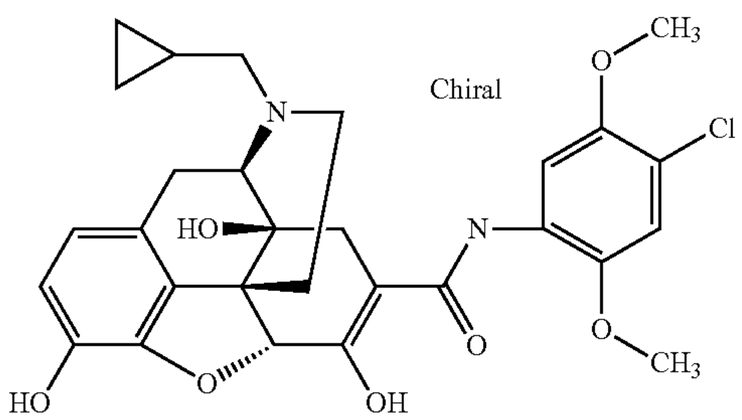
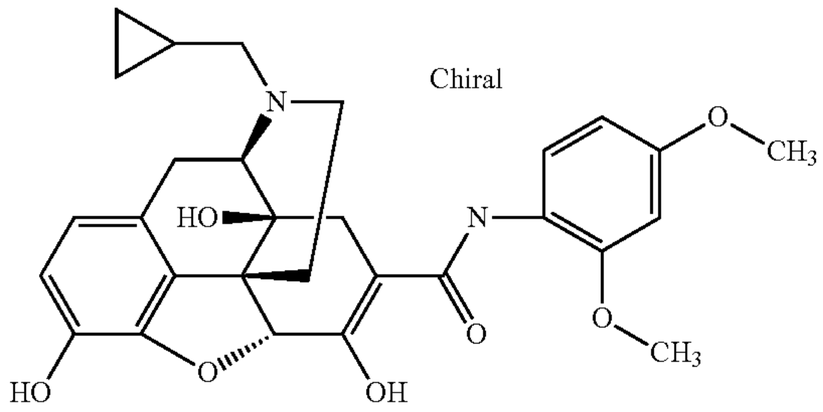
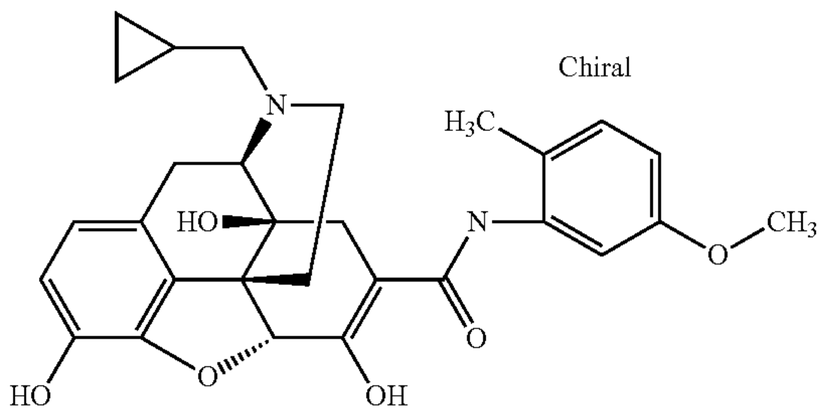
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-222	 Chiral	m/z 509 $[M + H]^+$ 1.57 min**	
I-223	 Chiral	m/z 479 $[M + H]^+$ 1.50 min**	
I-224	 Chiral	m/z 555 $[M + H]^+$ 1.76 min**	
I-225	 Chiral	m/z 519 $[M + H]^+$ 1.67 min**	
I-226	 Chiral	m/z 505 $[M + H]^+$ 1.53 min**	

TABLE 56-continued

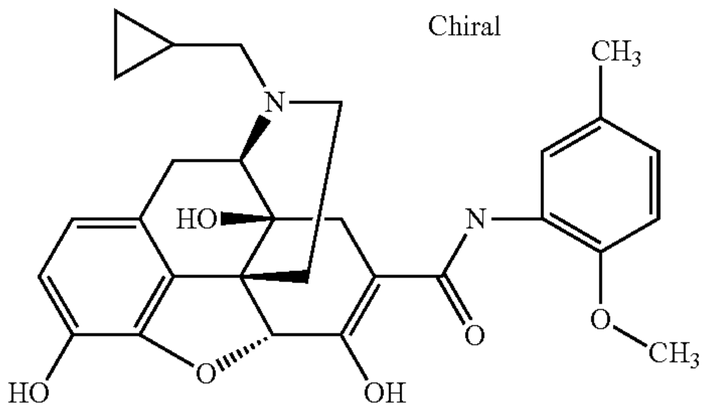
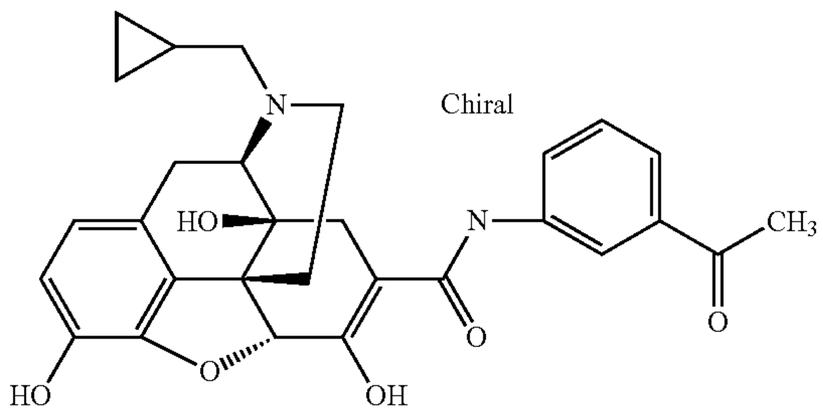
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-227	 Chiral	m/z 505 $[M + H]^+$ 1.64 min**	
I-228	 Chiral	m/z 503 $[M + H]^+$ 1.38 min****	

TABLE 57

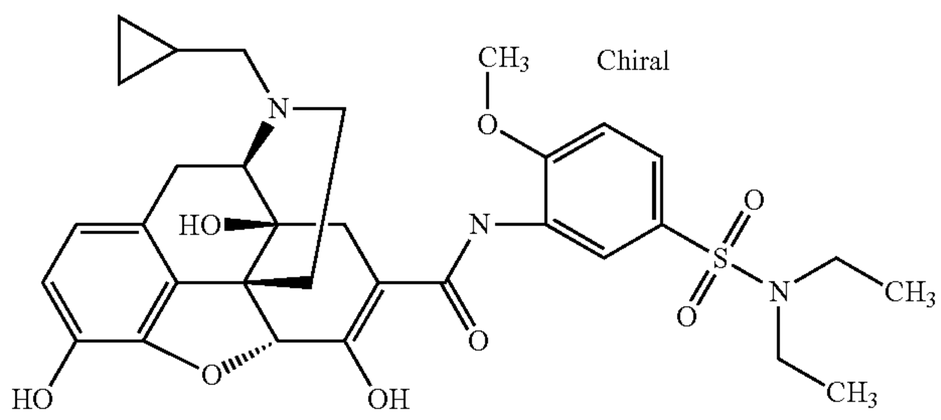
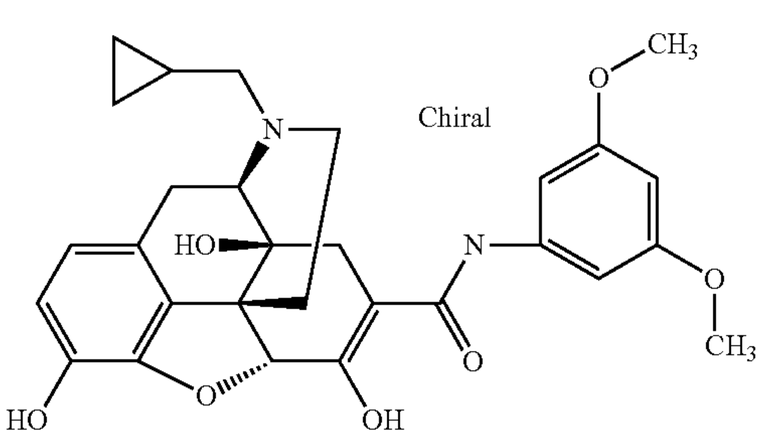
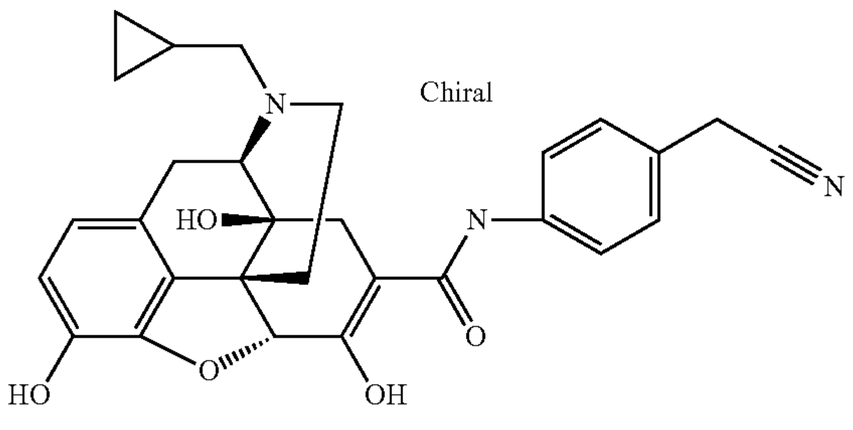
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-229	 Chiral	m/z 626 $[M + H]^+$ 1.74 min**	
I-230	 Chiral	m/z 521 $[M + H]^+$ 1.56 min**	
I-231	 Chiral	m/z 500 $[M + H]^+$ 1.40 min**	

TABLE 57-continued

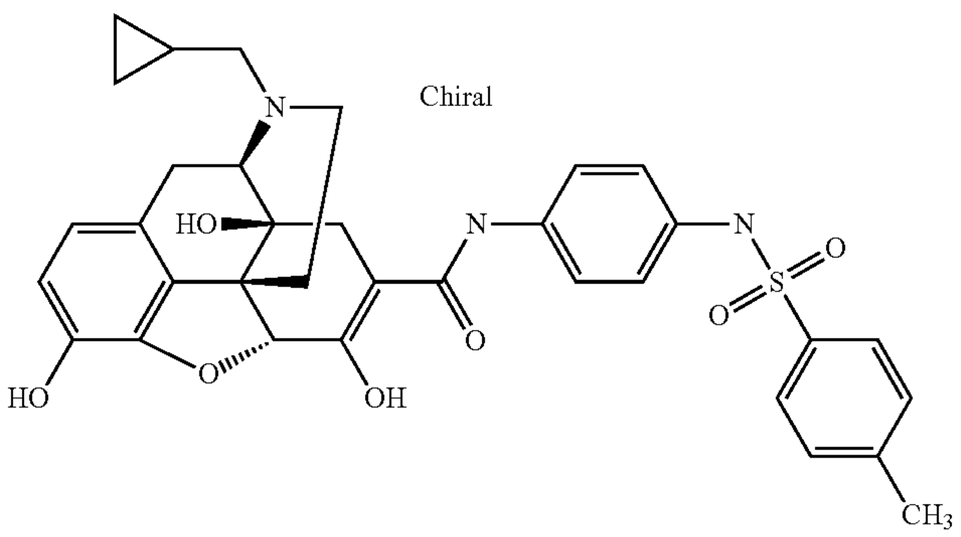
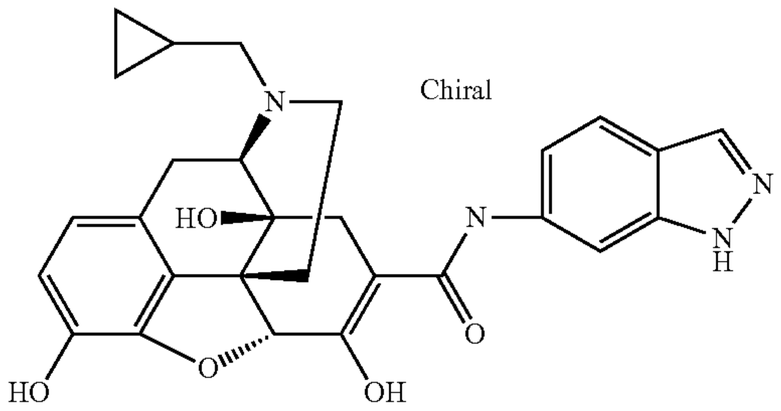
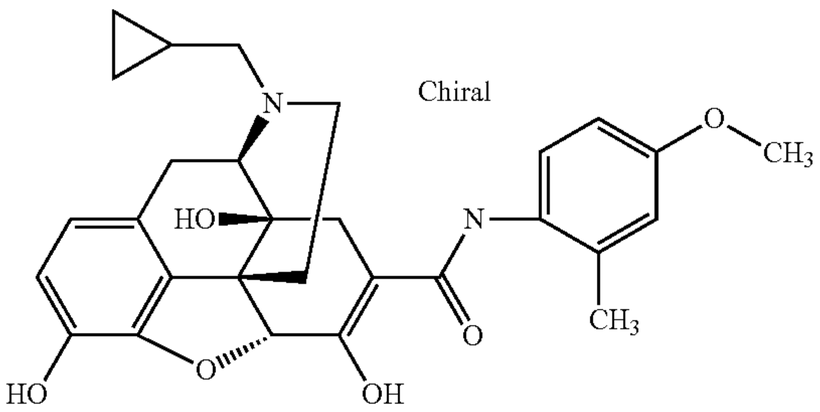
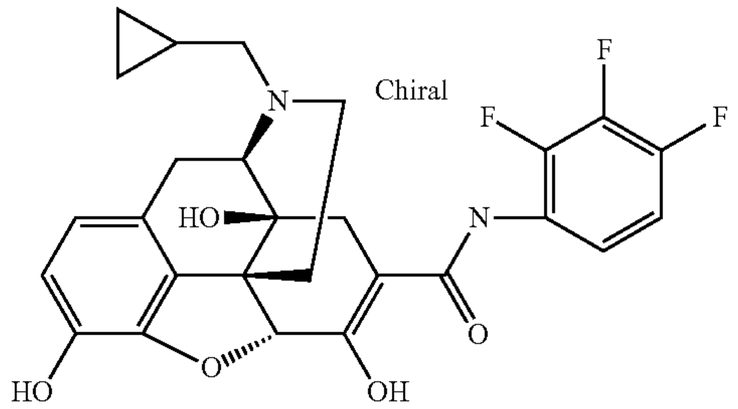
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-232	 Chiral	m/z 630 $[M + H]^+$ 1.72 min**	
I-233	 Chiral	m/z 501 $[M + H]^+$ 1.25 min**	
I-234	 Chiral	m/z 505 $[M + H]^+$ 1.46 min**	
I-235	 Chiral	m/z 515 $[M + H]^+$ 1.56 min**	

TABLE 58

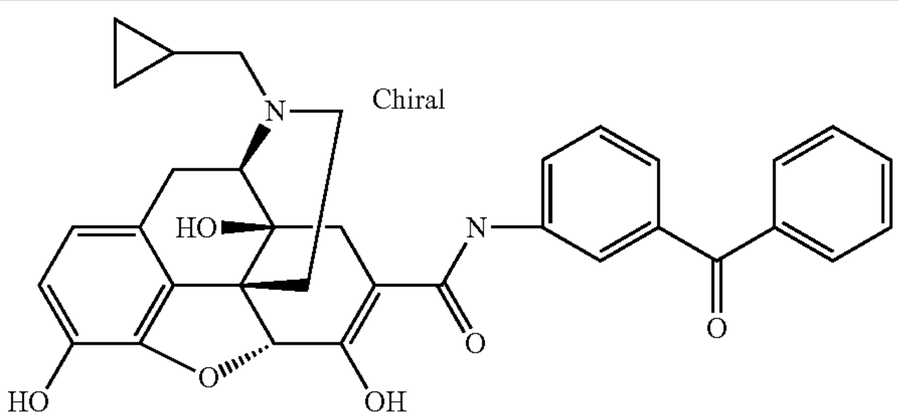
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-236	 Chiral	m/z 565 $[M + H]^+$ 1.77 min**	

TABLE 58-continued

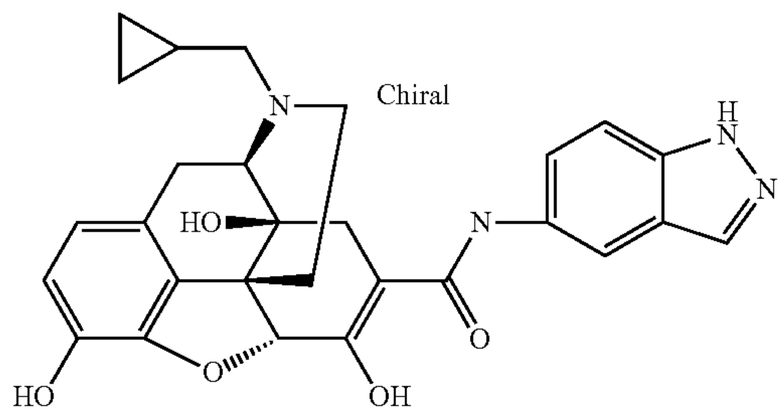
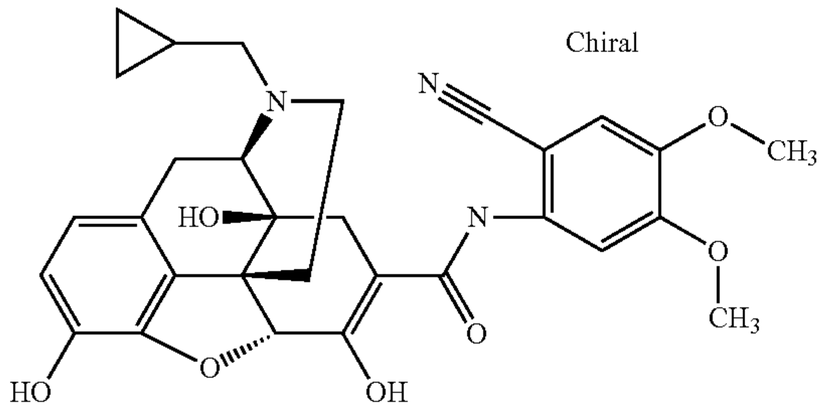
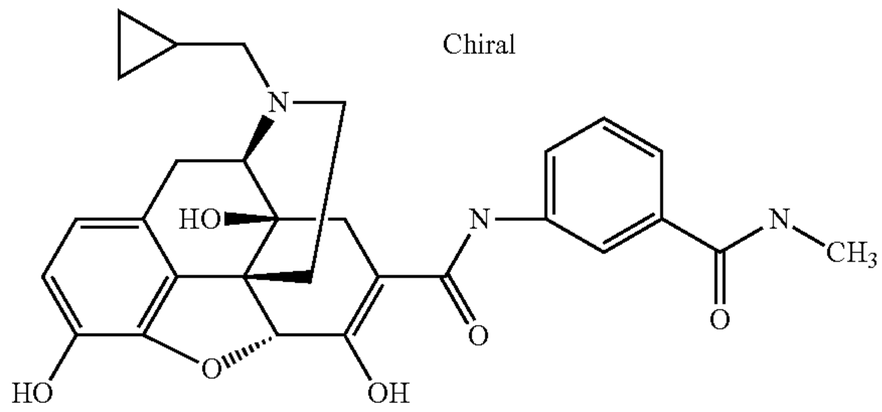
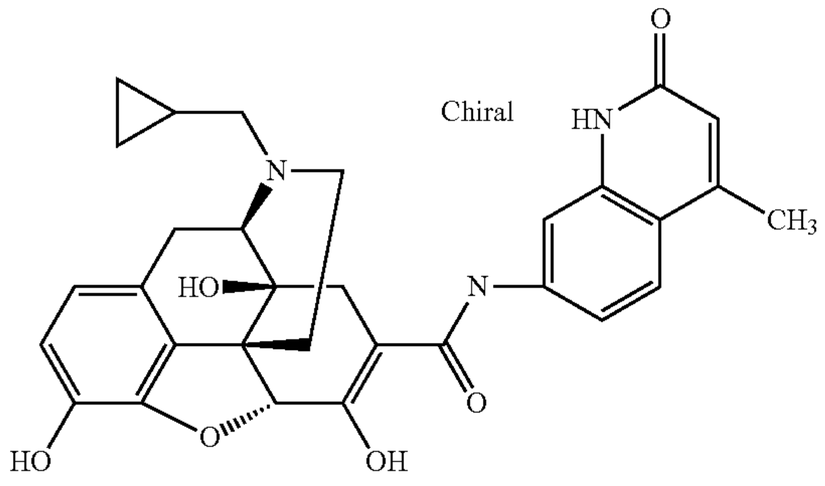
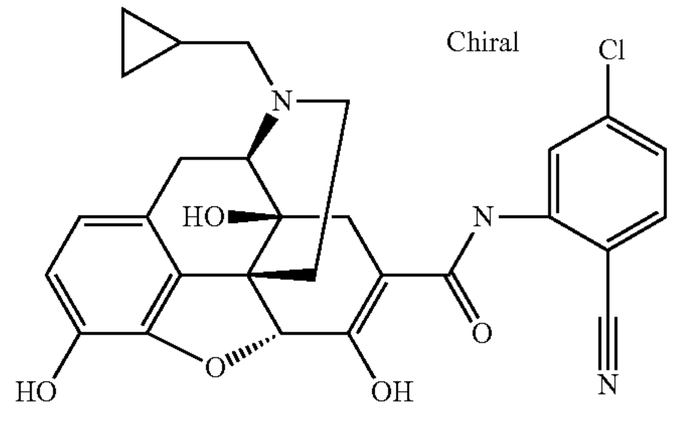
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-237		m/z 501 [M + H]+ 1.17 min**	
I-238		m/z 546 [M + H]+ 1.29 min**	
I-239		m/z 518 [M + H]+ 1.21 min**	
I-240		m/z 542 [M + H]+ 1.31 min**	
I-241		m/z 520 [M + H]+ 1.50 min**	

TABLE 58-continued

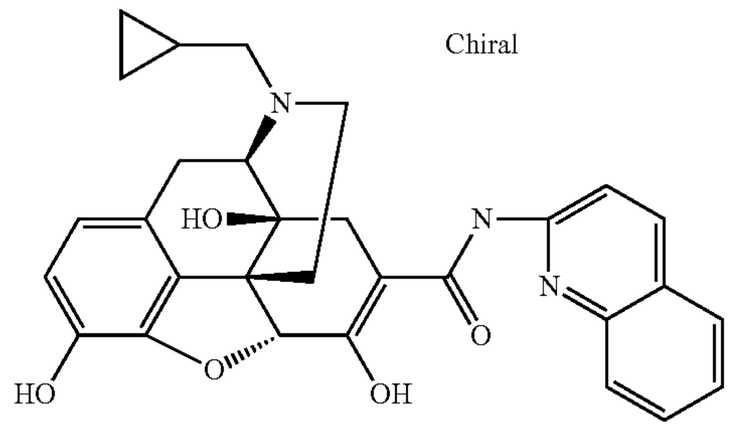
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-242	 Chiral		

TABLE 59

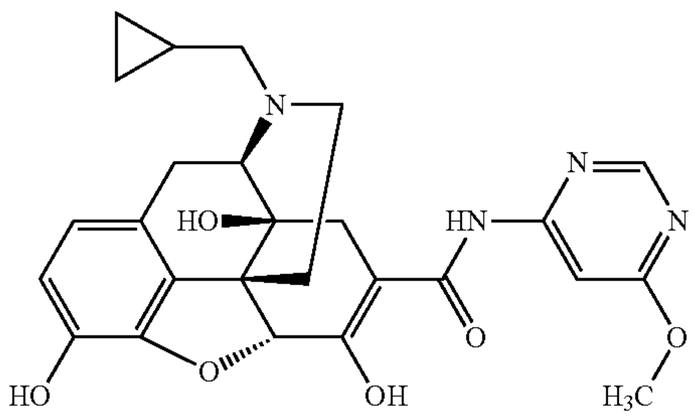
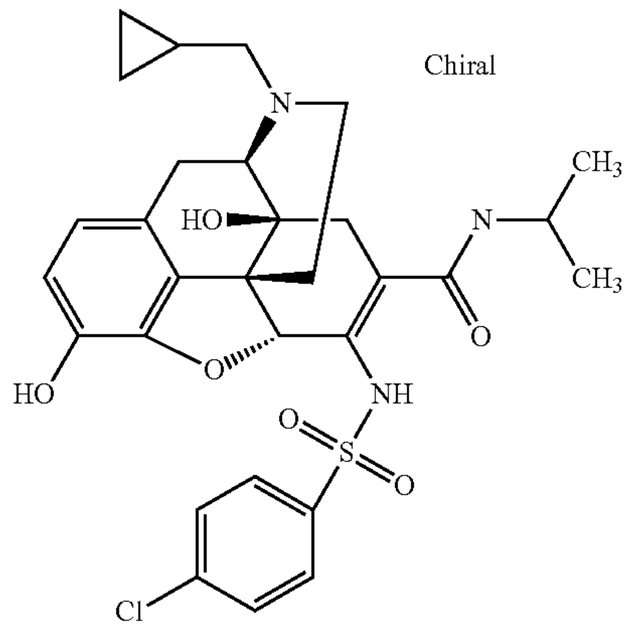
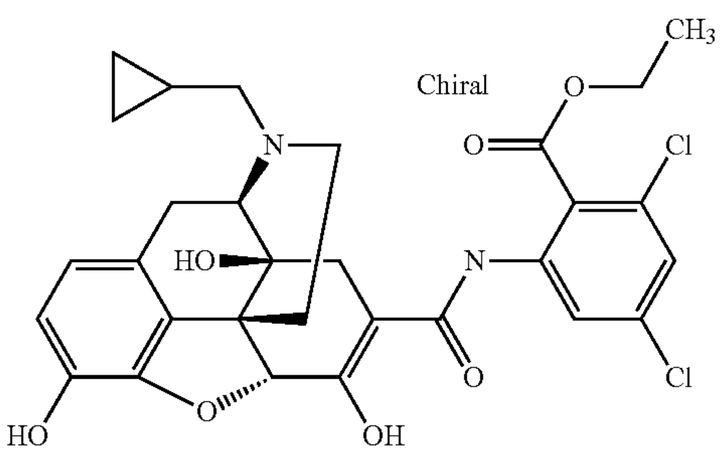
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-243		m/z 493 $[M + H]^+$ 1.05 min	
I-244	 Chiral	m/z 460 $[M + H]^+$ 1.02 min	0.11-0.13 (m, 2 H), 0.48-0.51 (m, 2 H), 0.87 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H), 1.48 (d, J = 11.1 Hz, 1 H), 1.88 (d, J = 18.0 Hz, 1 H), 2.10 (s, 3 H), 2.18-2.57 (m, 7 H), 3.04 (d, J = 16.8 Hz, 1 H), 3.19 (brs, 1 H), 3.78 (q, J = 6.9 Hz, 1 H), 4.68 (brs, 1 H), 5.43 (brs, 1 H), 6.49 (d, J = 6.6 Hz, 1 H), 6.51 (d, J = 6.6 Hz, 1 H), 7.35-7.37 (m, 2 H), 7.54 (brs, 1 H), 7.85 (d, J = 6.9 Hz, 2 H), 9.09 (brs, 1 H), 12.4 (brs, 1 H)
I-245	 Chiral	m/z 601 $[M + H]^+$ 0.76 min	

TABLE 59-continued

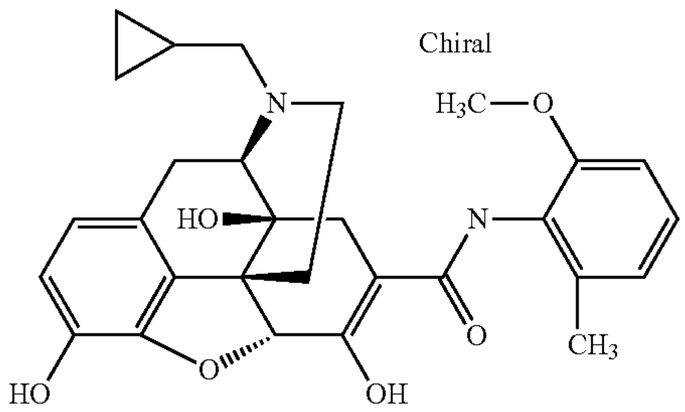
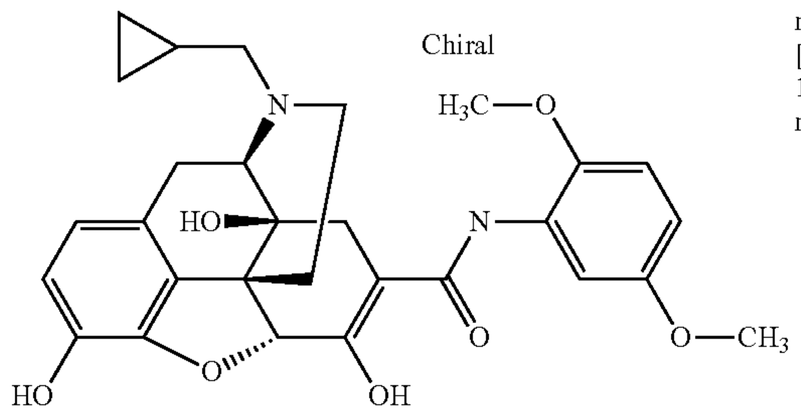
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-246		m/z 505 [M + H]+ 1.38 min**	
I-247		m/z 521 [M + H]+ 1.58 min**	

TABLE 60

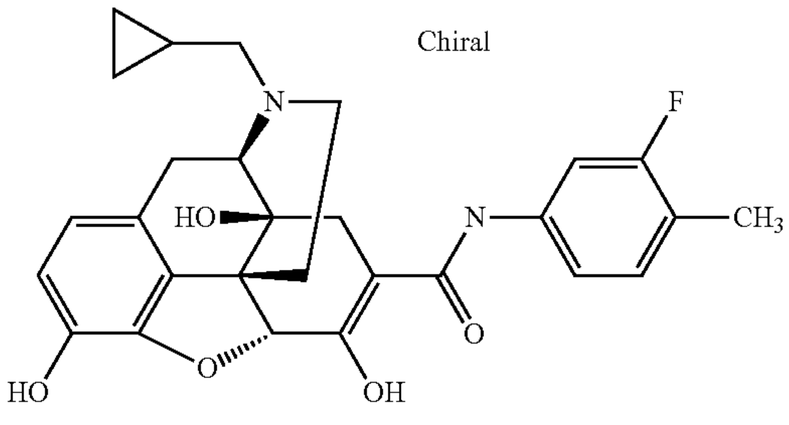
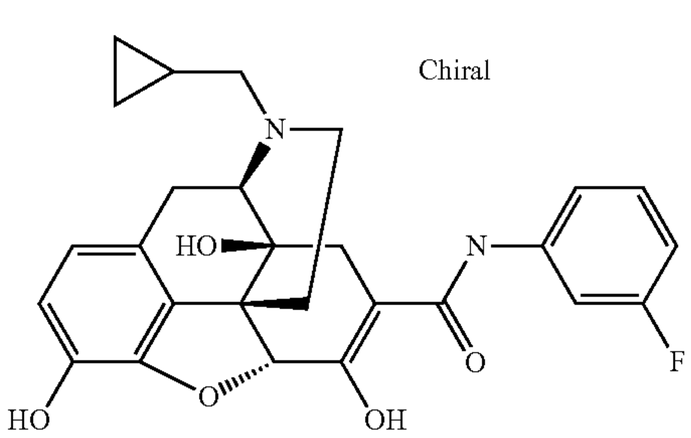
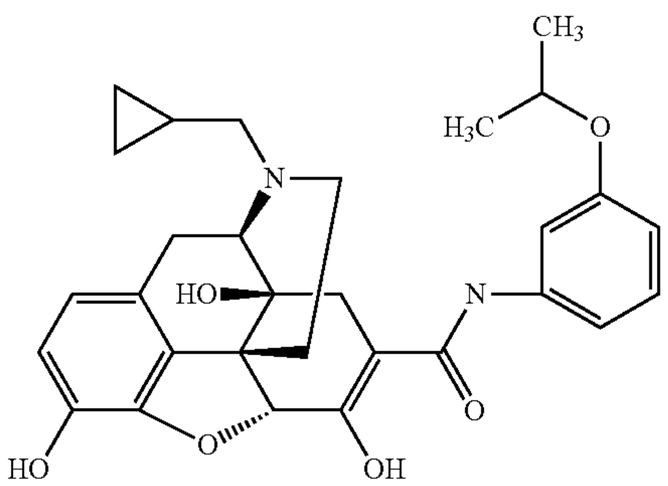
Compound No.	Chemical structure	LC/MS*[1]	NMR (1H-NMR (d6-DMSO) δ)
I-248		m/z 493 [M + H]+ 1.69 min**	
I-249		m/z 479 [M + H]+ 1.55 min**	
I-250		m/z 519 [M + H]+ 1.74 min**	

TABLE 60-continued

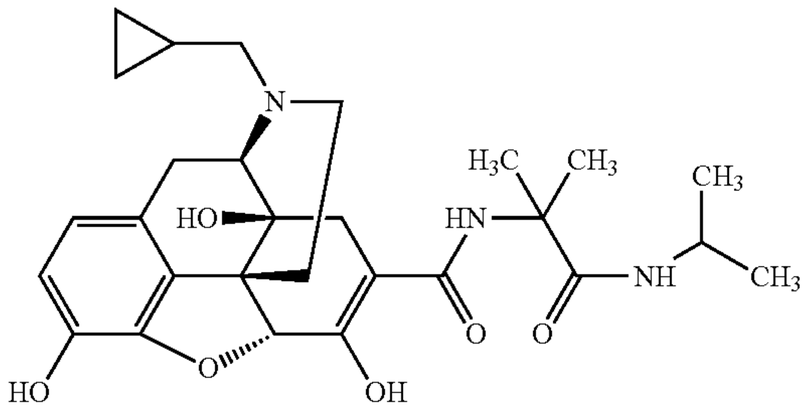
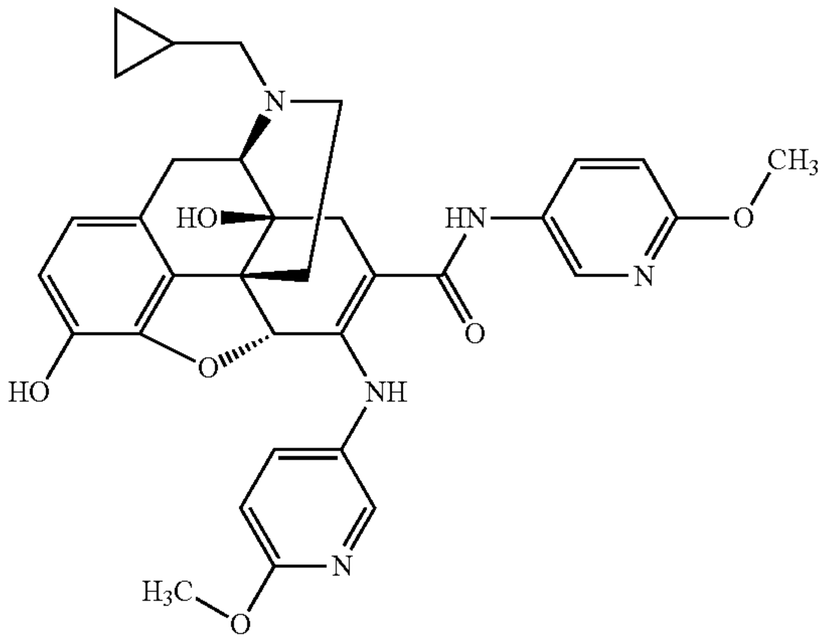
Compound No.	Chemical structure	LC/MS*1	NMR (1H-NMR (d6-DMSO) δ)
I-251		m/z 512 [M + H]+ 0.38 min	
I-252			0.10-0.15 (m, 2 H), 0.34-0.38 (m, 2 H), 0.73 (m, 1 H), 1.26 (d, J = 9.6 Hz, 1 H), 1.93-2.54 (m, 10 H), 2.94 (d, J = 18.4 Hz, 1 H), 3.10 (d, J = 6.0 Hz, 1 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 4.58 (s, 1 H), 4.84 (s,1 H), 6.42 (d, J = 8.0 Hz, 2 H), 6.48 (d, J = 8.0 Hz, 2 H), 6.61 (d, J = 9.3 Hz, 2 H), 6.69 (d, J = 9.2 Hz, 2 H), 7.56 (dd, J = 2.8, 8.8 Hz, 1 H), 7.66 (dd, J = 2.8, 8.8 Hz, 1 H), 8.00 (d, J = 2.4 Hz, 1 H), 8.08 (d, J = 2.0 Hz, 1 H), 8.76 (s, 1 H), 8.97 (s, 1 H), 10.78 (s, 1 H).

TABLE 61

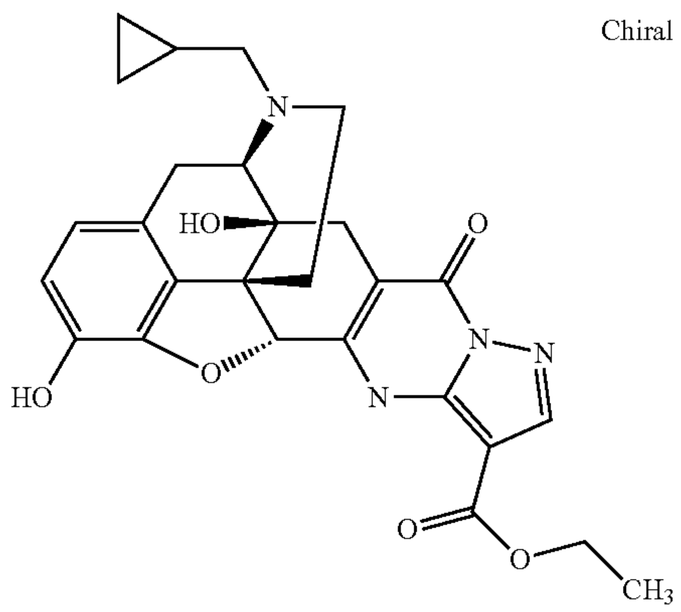
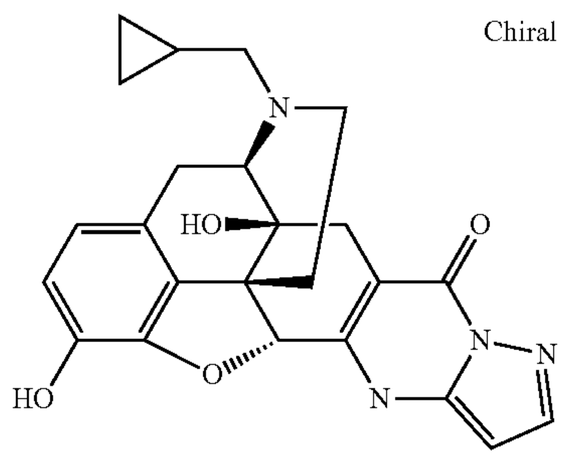
Compound No.	Chemical structure
I-253	 Chiral
I-254	 Chiral

TABLE 61-continued

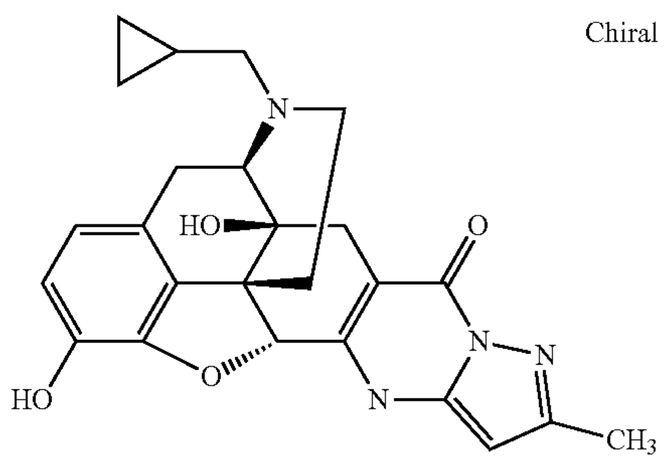
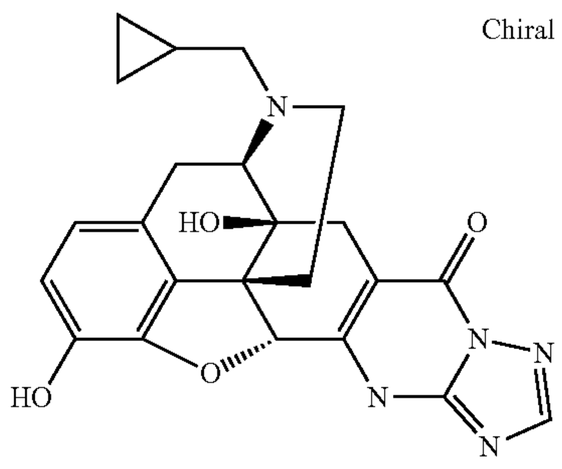
Compound No.	Chemical structure
I-255	 Chiral
I-256	 Chiral

TABLE 61-continued

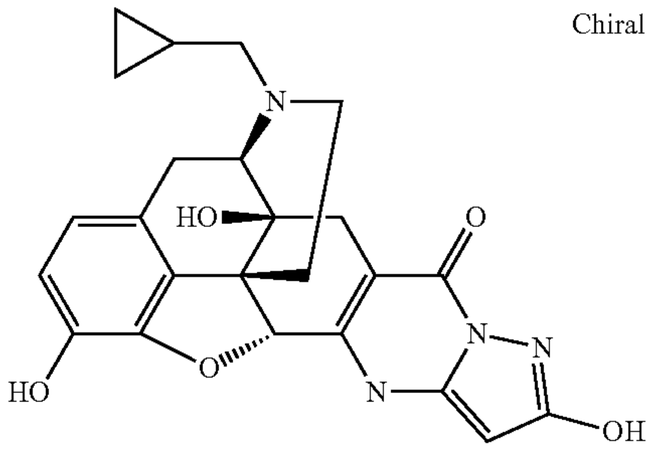
Compound No.	Chemical structure
I-257	Chiral 

TABLE 62

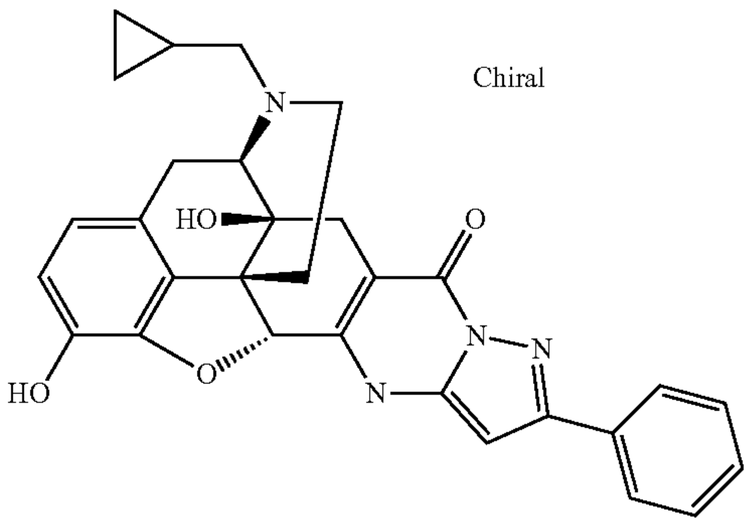
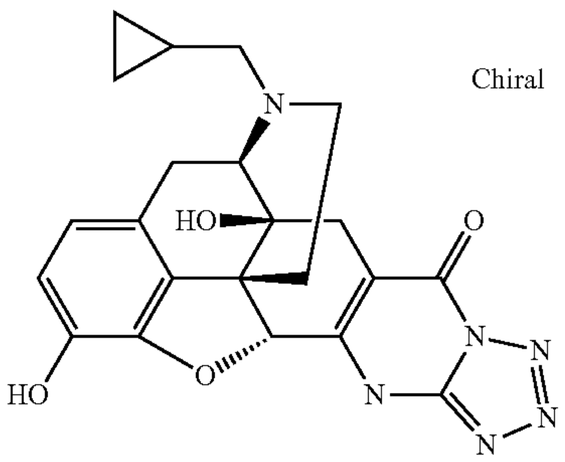
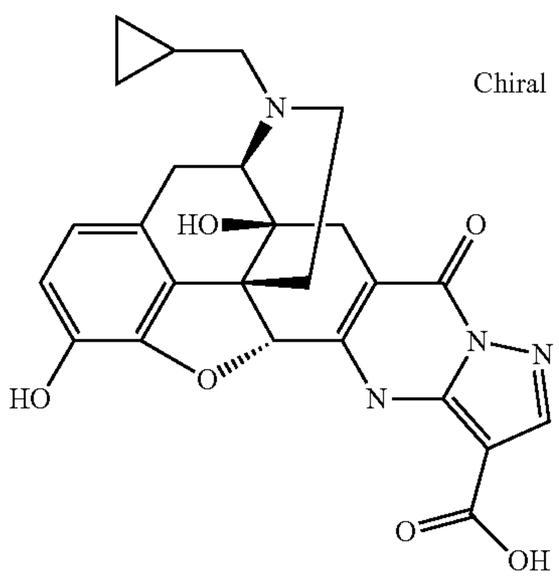
Compound No.	Chemical structure
I-258	Chiral 
I-259	Chiral 
I-260	Chiral 

TABLE 62-continued

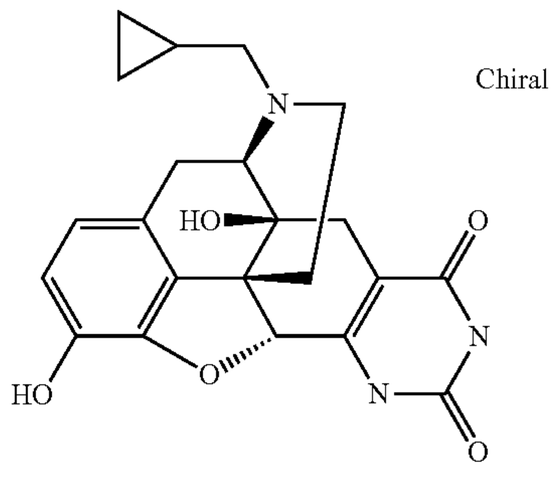
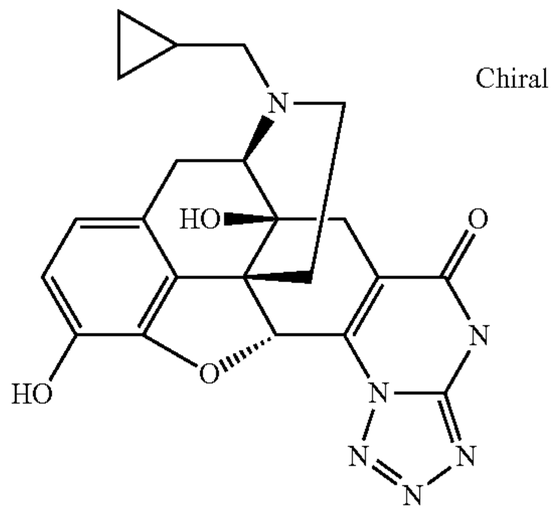
Compound No.	Chemical structure
I-261	Chiral 
I-262	Chiral 

TABLE 63

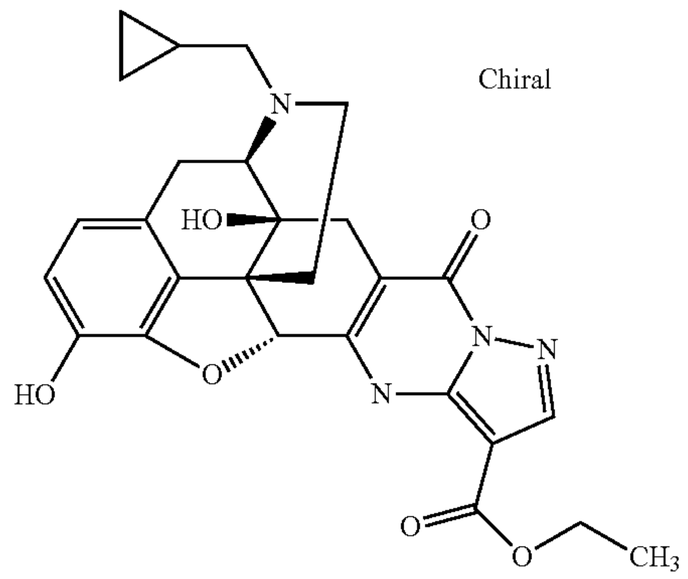
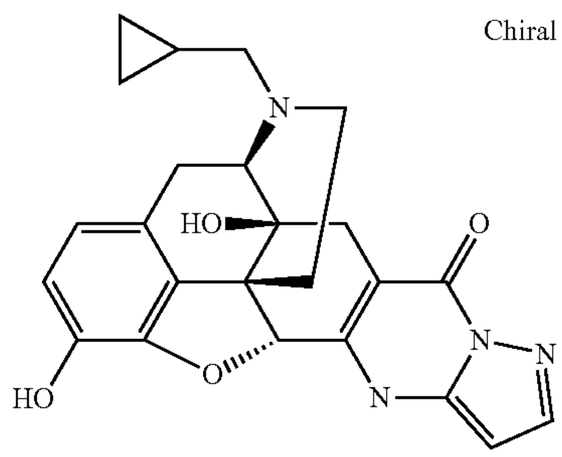
Compound No.	Chemical structure
I-253	Chiral 
I-254	Chiral 

TABLE 63-continued

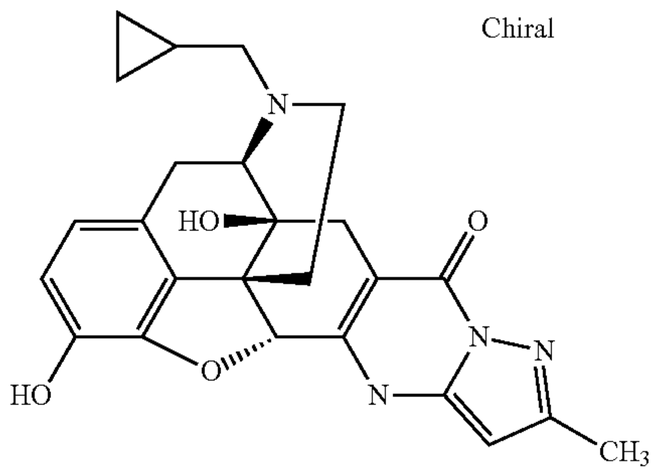
Compound No.	Chemical structure
I-255	Chiral 

TABLE 64

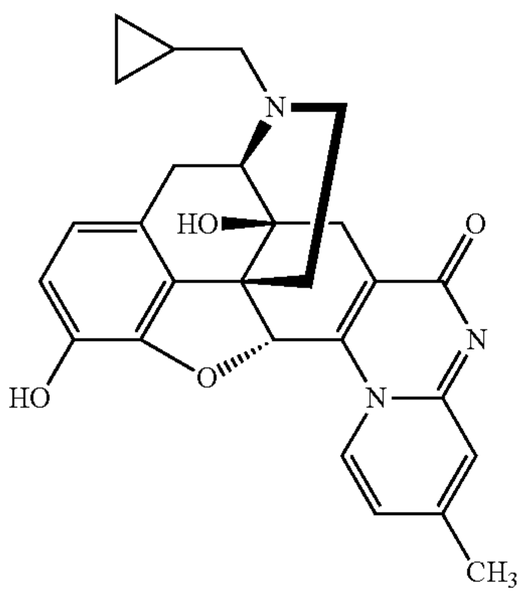
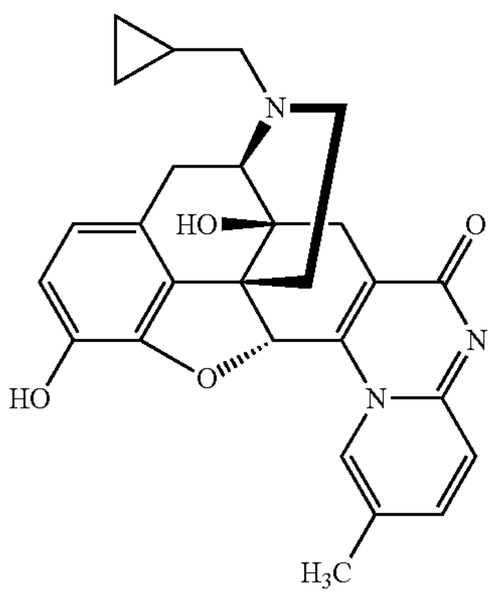
Compound No.	Chemical structure
I-266	 m/z 457.91 $[M + H]^+$ 0.97 min
I-267	 m/z 457.91 $[M + H]^+$ 0.62 min

TABLE 64-continued

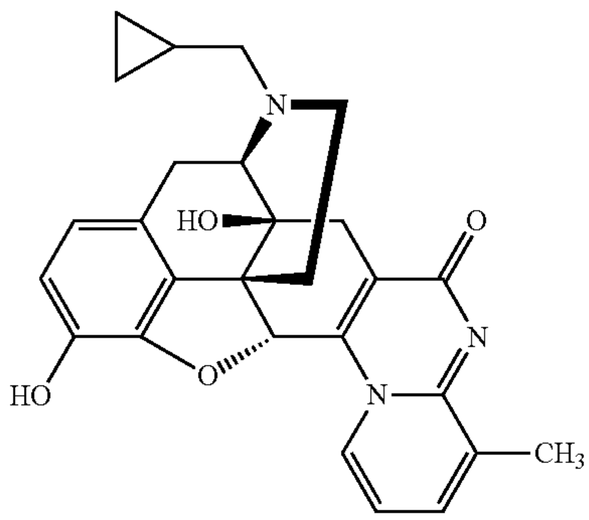
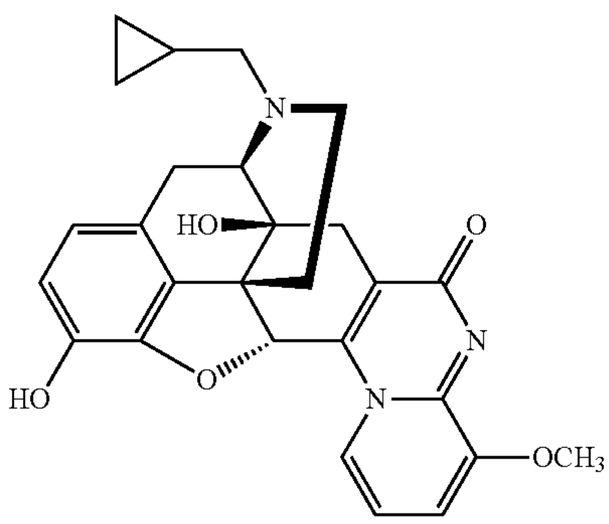
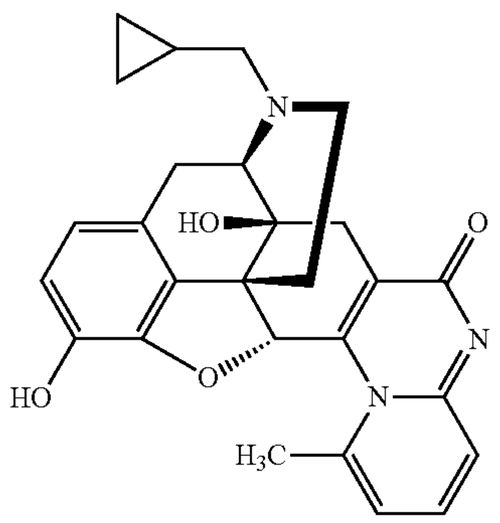
Compound No.	Chemical structure
I-268	 m/z 457.91 $[M + H]^+$ 0.87 min
I-269	 m/z 473.91 $[M + H]^+$ 0.69
I-270	 m/z 457.91 $[M + H]^+$ 0.97 min

TABLE 65

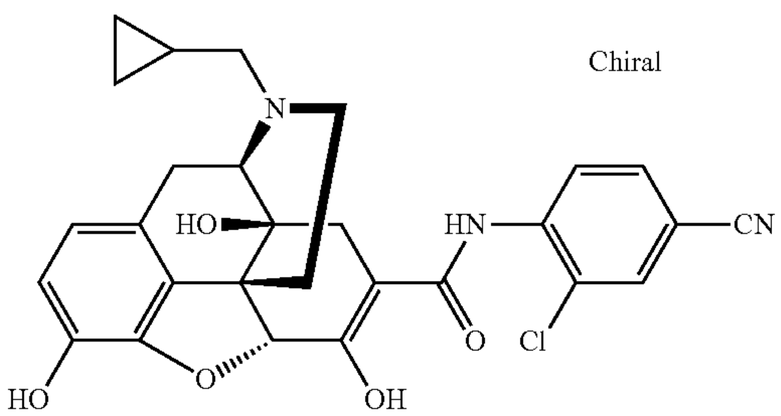
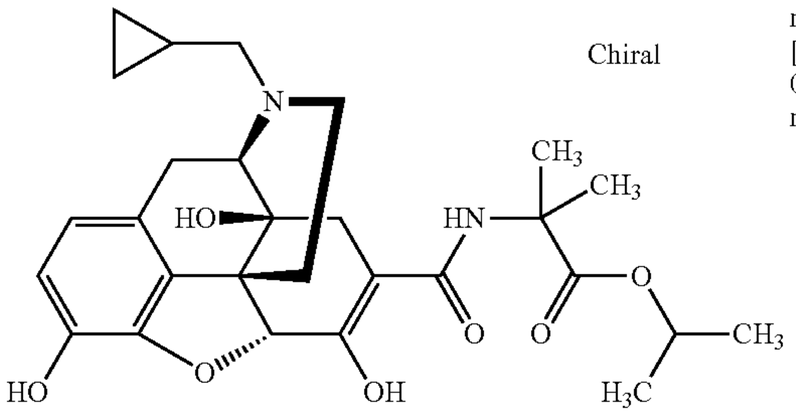
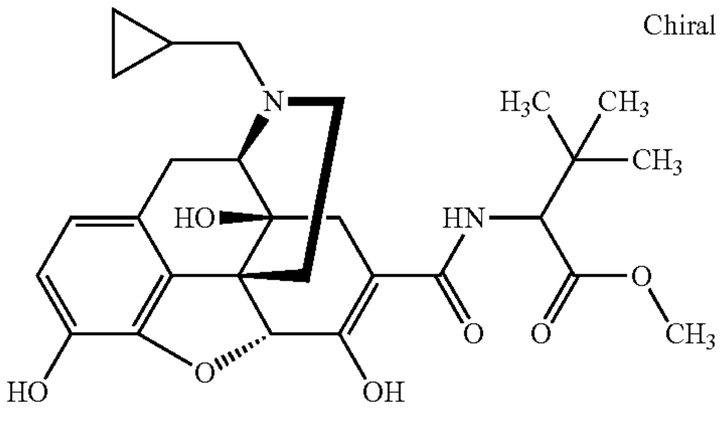
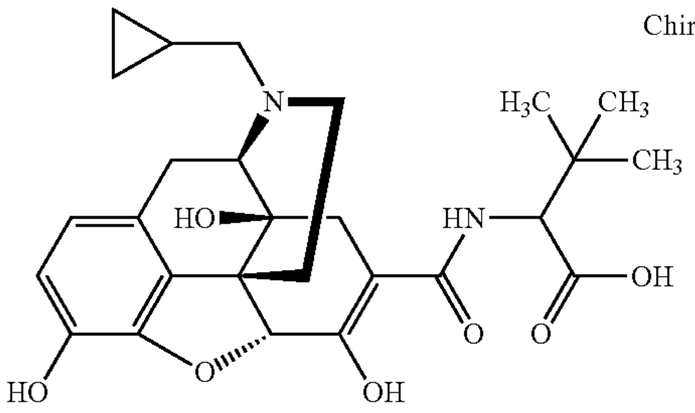
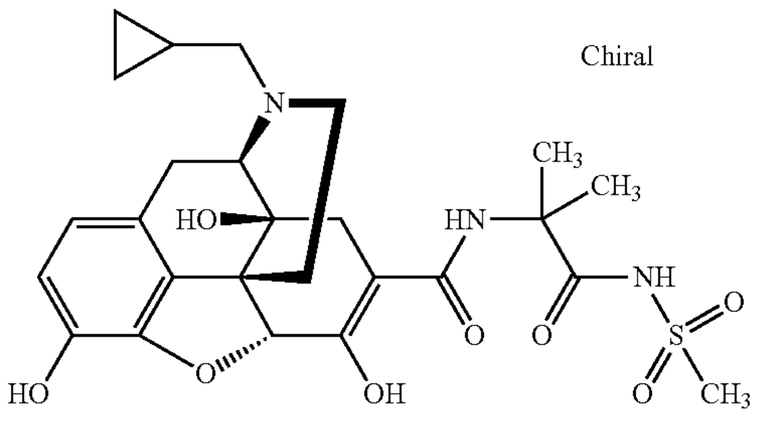
Compound No.	Chemical structure	LC/MS*[1]
I-271	 Chiral	m/z 520 $[M + H]^+$ 1.63 min**
I-272	 Chiral	m/z 513 $[M + H]^+$ 0.45 min
I-273	 Chiral	m/z 513 $[M + H]^+$ 0.38 min
I-274	 Chiral	m/z 499 $[M + H]^+$ 0.38 min
I-275	 Chiral	m/z 548 $[M + H]^+$ 0.38 min

TABLE 66

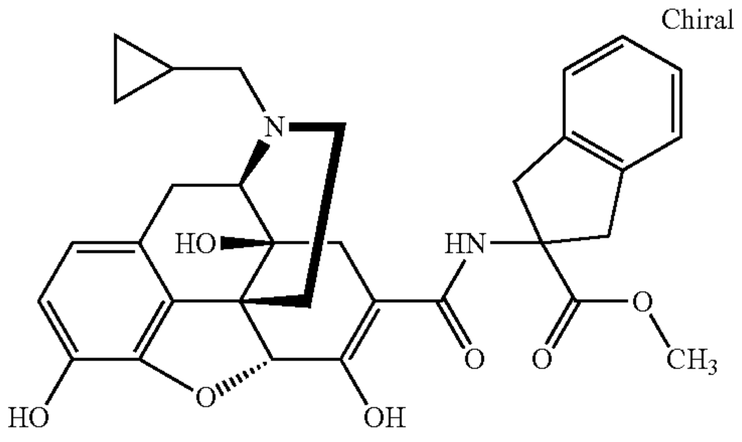
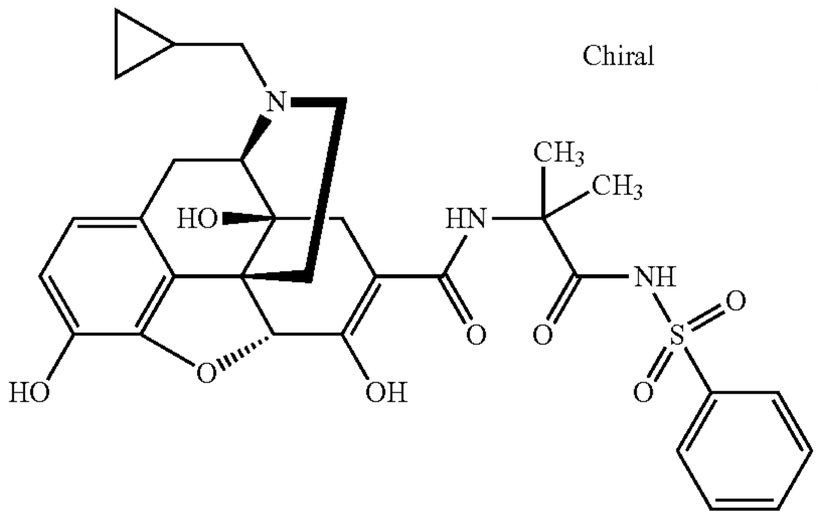
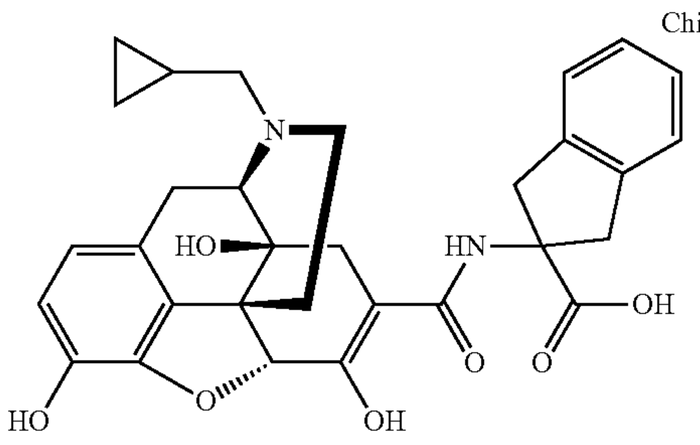
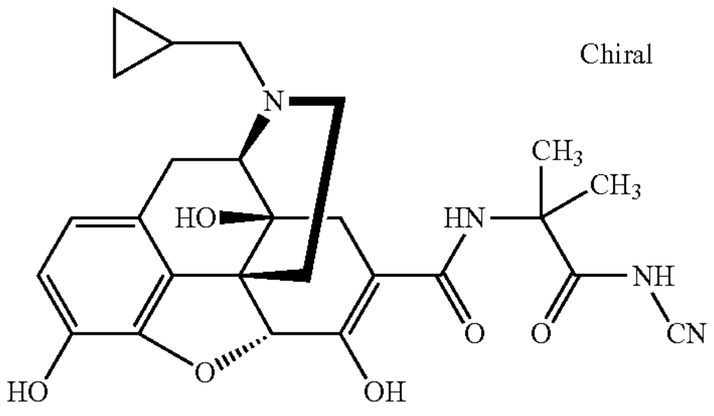
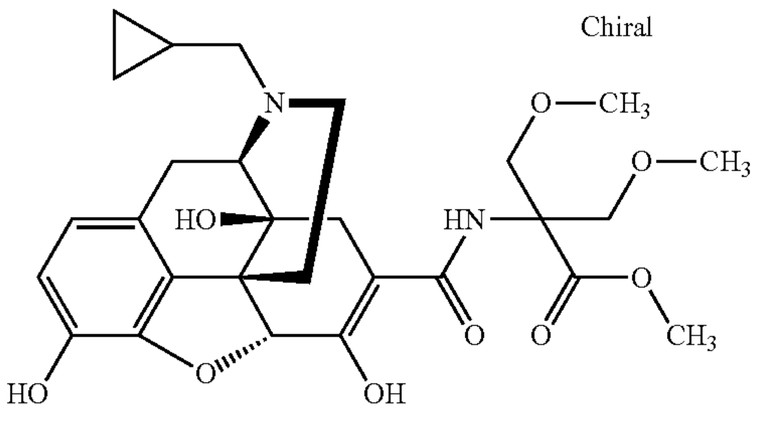
Compound No.	Chemical structure	LC/MS*[1]
I-276	 Chiral	m/z 559 $[M + H]^+$ 0.53 min
I-277	 Chiral	m/z 610 $[M + H]^+$ 0.46 min
I-278	 Chiral	m/z 545 $[M + H]^+$ 0.38 min
I-279	 Chiral	m/z 495 $[M + H]^+$ 0.31 min
I-280	 Chiral	m/z 545 $[M + H]^+$ 0.97 min

TABLE 67

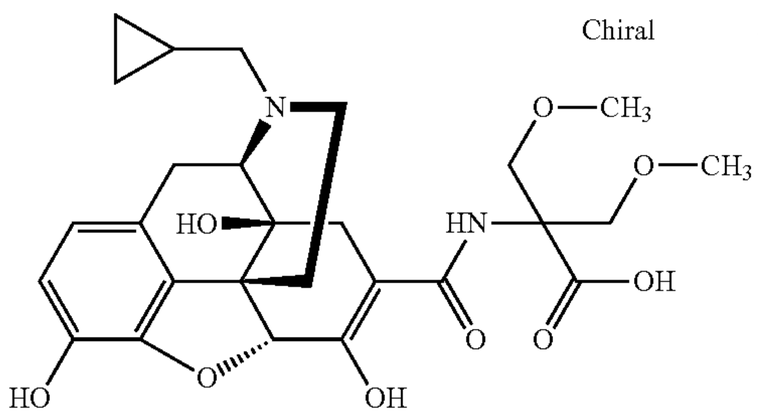
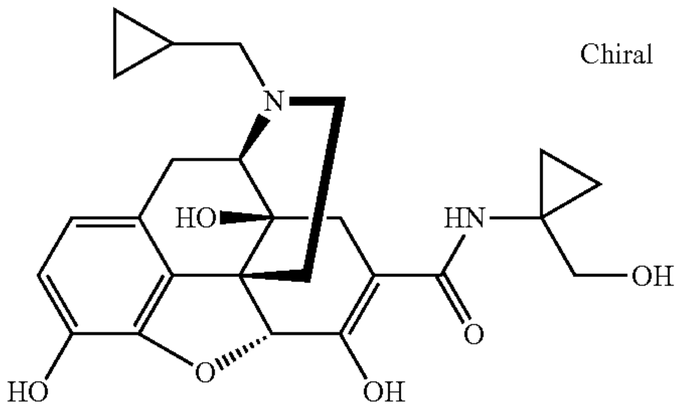
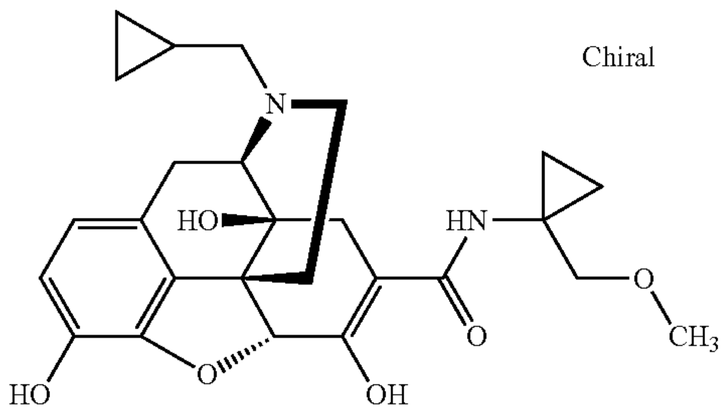
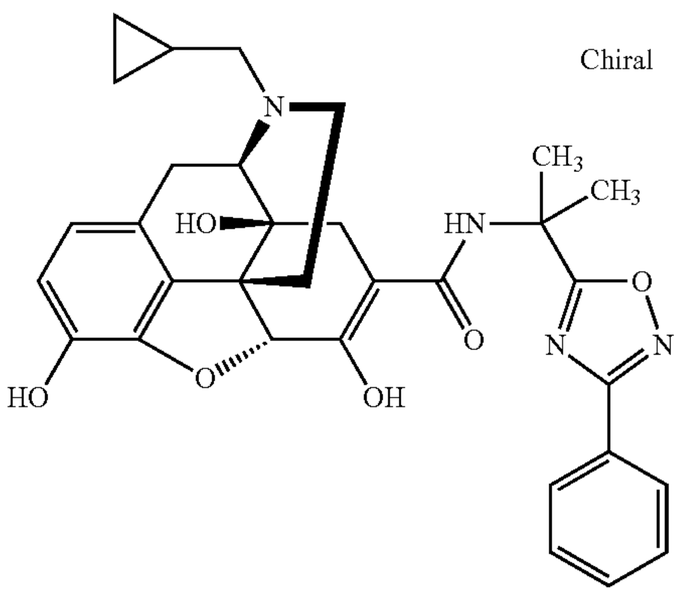
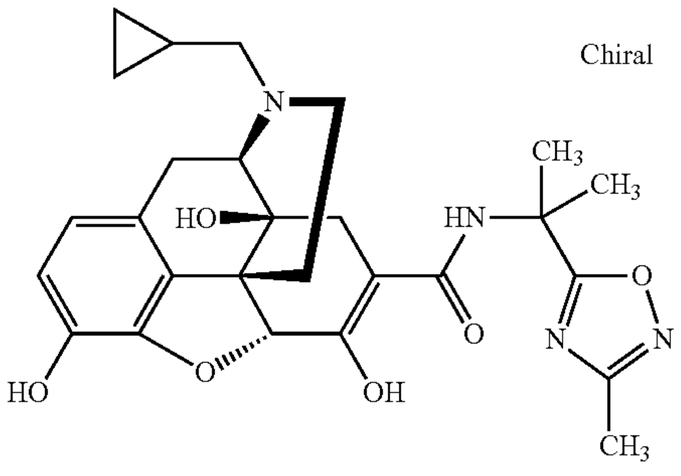
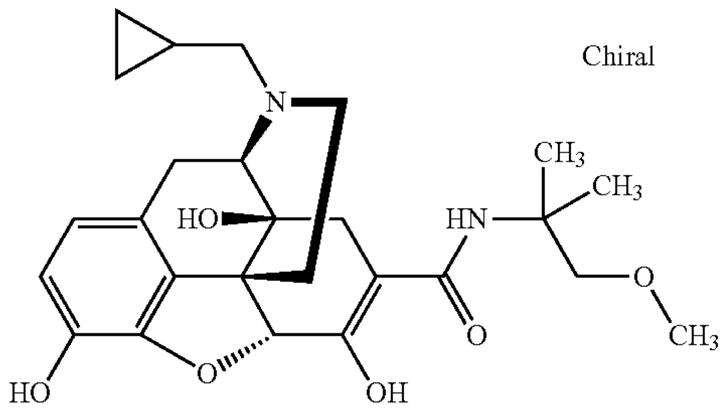
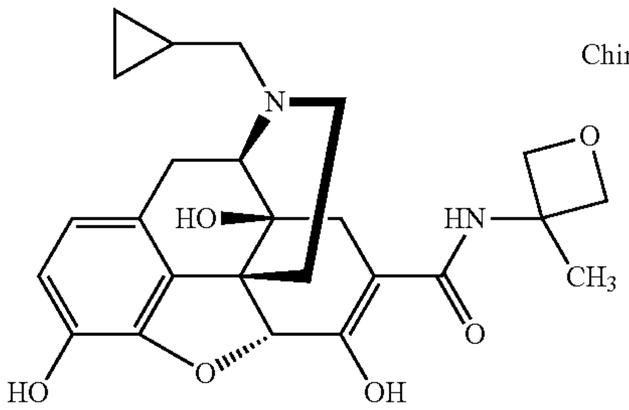
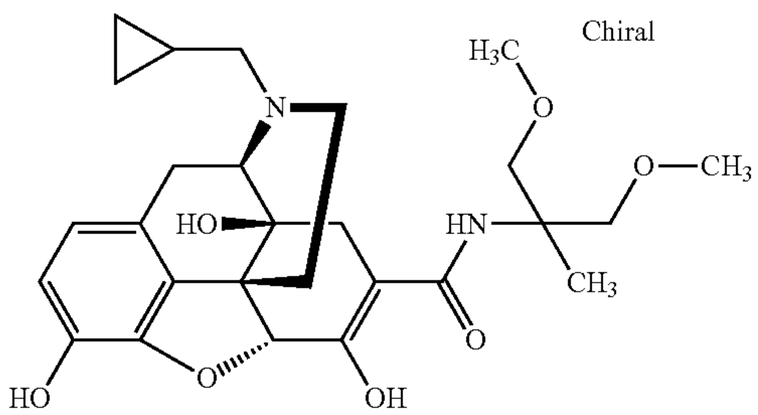
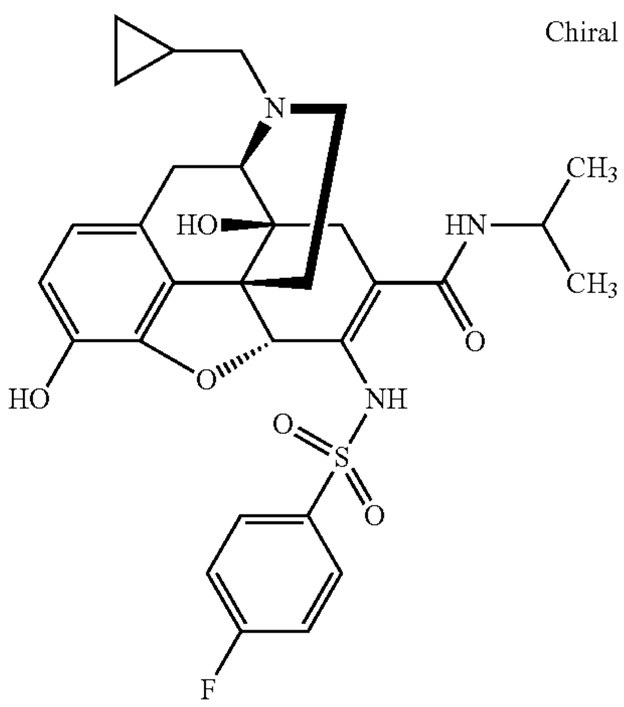
Compound No.	Chemical structure	LC/MS*[1]
I-281	 Chiral	m/z 531 $[M + H]^+$ 0.92 min
I-282	 Chiral	m/z 455 $[M + H]^+$ 0.87 min
I-283	 Chiral	m/z 469 $[M + H]^+$ 0.94 min
I-284	 Chiral	m/z 571 $[M + H]^+$ 0.68 min
I-285	 Chiral	m/z 509 $[M + H]^+$ 0.32 min

TABLE 68

Compound No.	Chemical structure	LC/MS*[1]
I-286	 Chiral	m/z 471 $[M + H]^+$ 0.32 min
I-287	 Chiral	m/z 455 $[M + H]^+$ 0.90 min
I-288	 Chiral	m/z 501 $[M + H]^+$ 0.32 min
I-289	 Chiral	m/z 584 $[M + H]^+$ 0.46 min

(LC/MS conditions of measurements)*[1]:

Column: Chromolith Flash ROD RP-18e, 25 × 4.6 mm LD.

Flow Rate: 2 ml/min

UV Detector: 280 nm

Solvent System: [A] = H2O_0.05% HCOOH

[B] = MeOH_0.05% HCOOH

Gradient: 0 min; 90% [A]_10% [B]

0.2 mm; 90% [A]_10% [B]

1.0 mm; 10% [A]_90% [B]

1.80 mm; 10% [A]_90% [B]

Proviso, values with symbol ** follow below conditions of measurement

Column: Phenomenex Luna 5μ C18(2) 100 A, size 50 × 4.60 mm

Gradient: 10%-100% Acetnitrile linear during 3.0 mm at 3.0 mL/min

TEST EXAMPLE 1

Binding Assay of Opioid 8 Receptor

1) Method of Preparing Membrane Specimen for Binding Assay

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×g for 20 minutes. To the resulting pellet was added 15 ml 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 buffer (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 Binding Assay and Data Analysis

To a solution of 10 μl of the test compound diluted at 10-fold stage was added 10 μl of final 3 nM [^{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 10 mM 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.

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

From the above results, it is seen that compound (1) has an affinity for an opioid δ receptor.

TEST EXAMPLE 2

Bindind Assay to Opioid μ Receptor

1) Method of Preparing Membrane Specimen for Binding Assay

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×g for 20 minutes. To the resulting pellet was added 15 ml of the same buffer, and the mixture was treated with Histocoln 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 buffer (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 Receptor Binding Assay and Data Analysis

To a solution of 10 μl of the test compound diluted at 10-fold stage diluted test compound was added 10 μl of final 2 nM [^{3}H]-DAMGO (51.5 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 been pre-treated with 0.5% polyethyleneimine, and washed with 2.5 mL of an ice-cooled 10 mM Tris-HCl buffer (pH 7.4) 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, 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 (1.72 nM) obtained in advance by Scatchard plot analysis (Anal.Biochem. 107(1), 220-239, 1980).

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)

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

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

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

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

The test compound 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.

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.

Transport rate (%)=(carbon powder movement distance)/full length of small intestine (cm))×100

M.P.E.(%)={(small intestine transport rate (%) of each individual of test compound administration group−average small intestine transport rate (%) of solvent administration group)/(average small intestine transport rate (%) of control group−average small intestine transport rate (%) of solvent administration group)}×100

TABLE 71

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

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

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

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

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

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

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

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

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

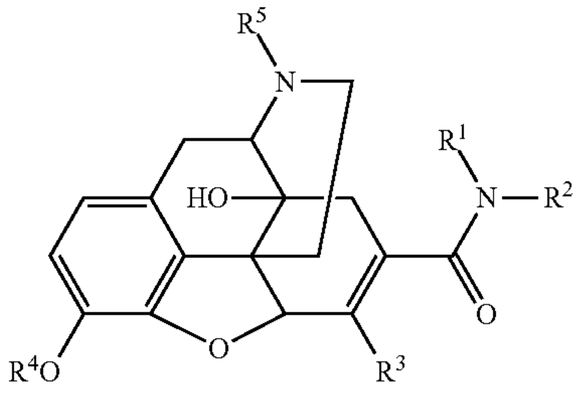
INDUSTRIAL APPLICABILITY

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

The invention claimed is:

1. A compound represented by the formula (I):

[Chemical Formula 1]

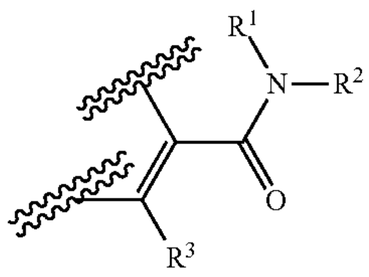


(I)

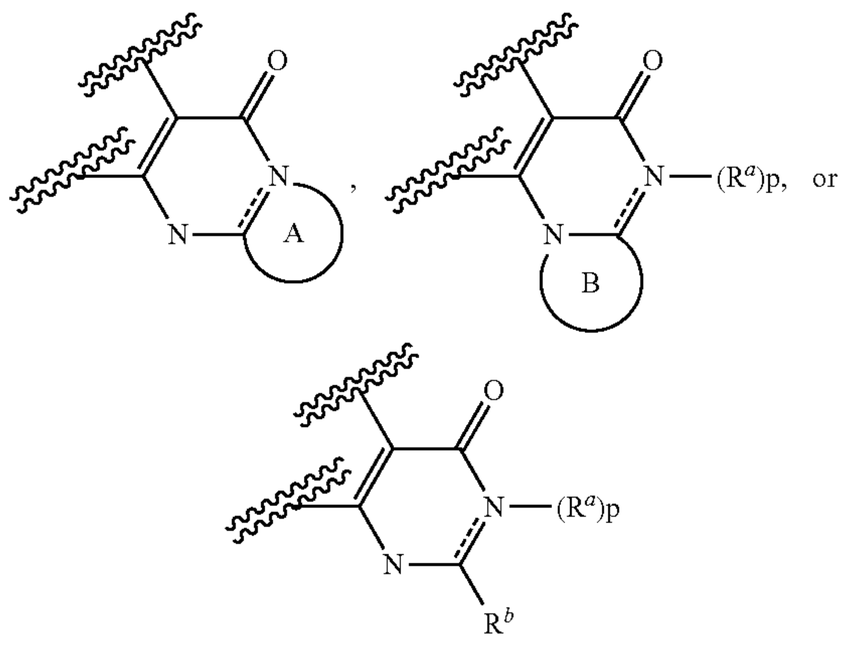
wherein R^1 and R^2 are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkylsulfonyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, an optionally substituted heterocyclic group, 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, 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; *or* [a] *the* group represented by the formula:

[Chemical Formula 2]



[may be] *is selected from:*



wherein ring A and ring B are each independently optionally substituted nitrogen-containing heterocycle optionally containing additional nitrogen atom, oxygen atom, and/or sulfur atom in the ring;

broken line indicates the presence or the absence of a bond;

when 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; *and*

R^5 is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^3 is hydroxy, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, wherein R^3 is optionally substituted amino, or a pharmaceutically acceptable salt thereof.

4. The compound in any one of claims 1 to 3, 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 thereof.

5. A pharmaceutical composition containing a compound in any one of claims 1 to **[4]** *3*, or a pharmaceutically acceptable salt thereof.

6. A composition having an opioid receptor antagonistic activity containing a compound in any one of claims 1 to **[4]** *3*, or a pharmaceutically acceptable salt thereof.

7. A composition for treating and/or preventing emesis, vomiting and/or constipation containing a compound in any one of claims 1 to **[4]** *3*, or a pharmaceutically acceptable salt thereof.

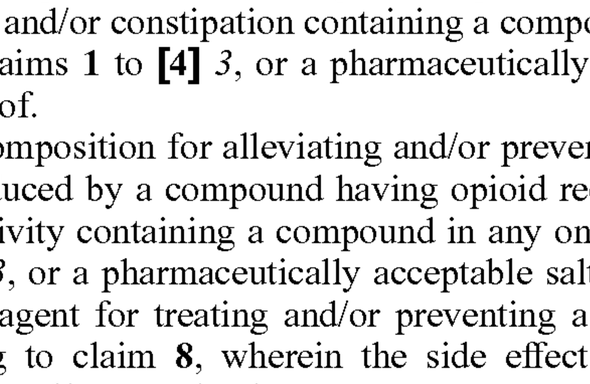
8. A composition for alleviating and/or preventing a side effect induced by a compound having opioid receptor agonistic activity containing a compound in any one of claims 1 to **[4]** *3*, or a pharmaceutically acceptable salt thereof.

9. An agent for treating and/or preventing a side effect according to claim 8, wherein the side effect is emesis, vomiting and/or constipation.

10. A composition for treatment and/or prevention according to claim 8 **[**or 9**]**, wherein the compound having the opioid receptor agonistic activity is morphine, oxycodone, or a pharmaceutically acceptable salt thereof.

11. A composition for analgesic containing a compound having an opioid receptor agonistic activity, and an effective amount of compound according to any one of claims 1 to **[4]** *3*, or a pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side effect induced by administrating of the compound having an opioid receptor agonistic activity.

12. A compound represented by the formula (I):



(I)

wherein

R^1 is hydrogen; R^2 is selected from lower alkyl optionally substituted with lower alkoxy, lower alkoxycarbonyl, or a heterocyclic group optionally substituted with lower alkyl or phenyl; phenyl optionally substituted with lower alkyl, lower alkoxy, halogen, or cyano lower alkyl; cycloalkyl optionally substituted with lower alkoxycarbonyl or lower alkoxy lower alkyl; or a heterocyclic group optionally substituted with lower alkoxy or oxo;

R^3 is hydroxyl;

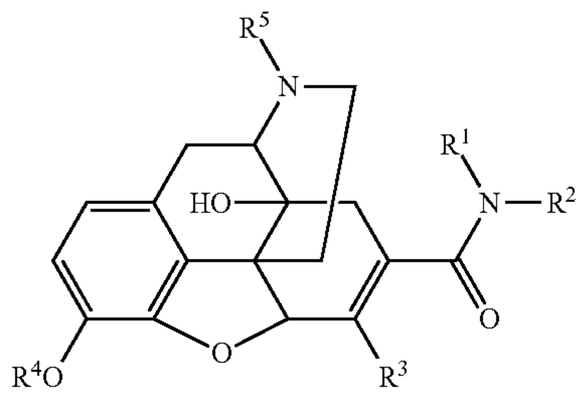
R^4 is hydrogen; and

R^5 is cyclopropylmethyl;

or a pharmaceutically acceptable salt thereof.

13. A compound represented by the formula (I):

[Chemical Formula 1]



(I)

wherein

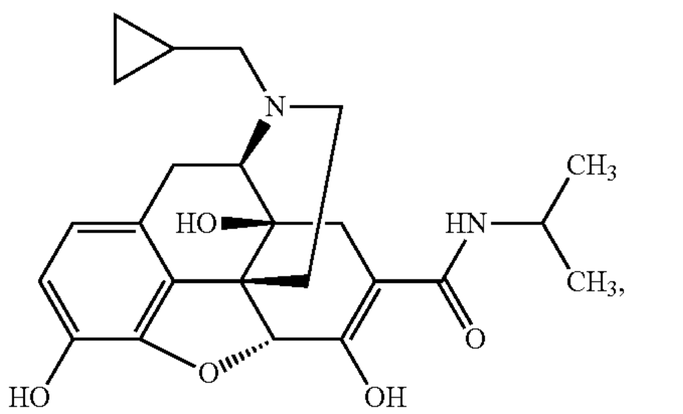
R^1 is hydrogen;

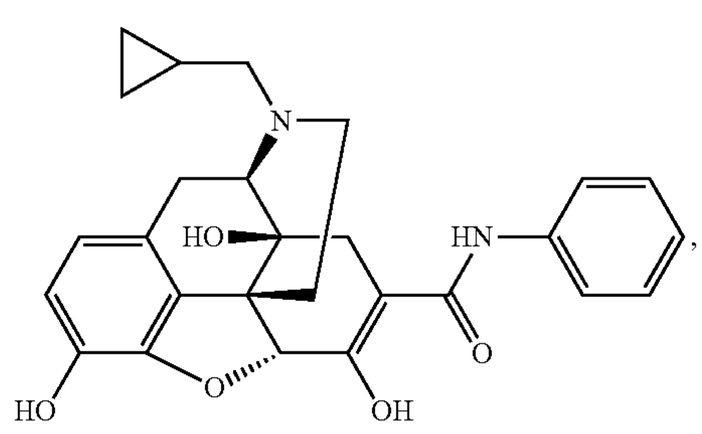
R^2 is lower alkyl optionally substituted with lower alkoxy or with a heterocyclic group that is optionally substituted with aryl; phenyl optionally substituted with lower alkyl or with lower alkoxy; cycloalkyl substituted with lower alkylcarbonyl; or a heterocyclic group substituted with lower alkoxy or with aryl;

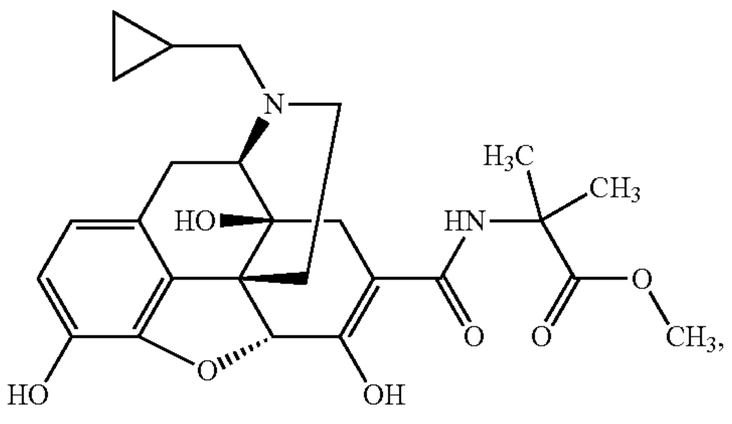
R^3 is hydroxyl; R^4 is hydrogen; and

R^5 is cyclopropylmethyl; or a pharmaceutically acceptable salt thereof.

14. A compound, wherein the compound is







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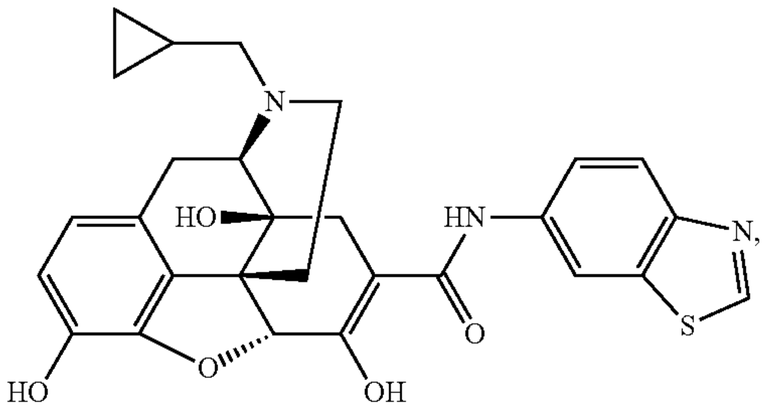

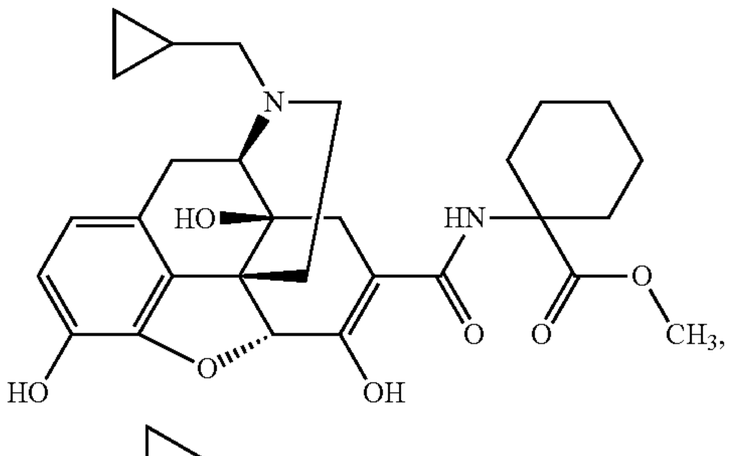

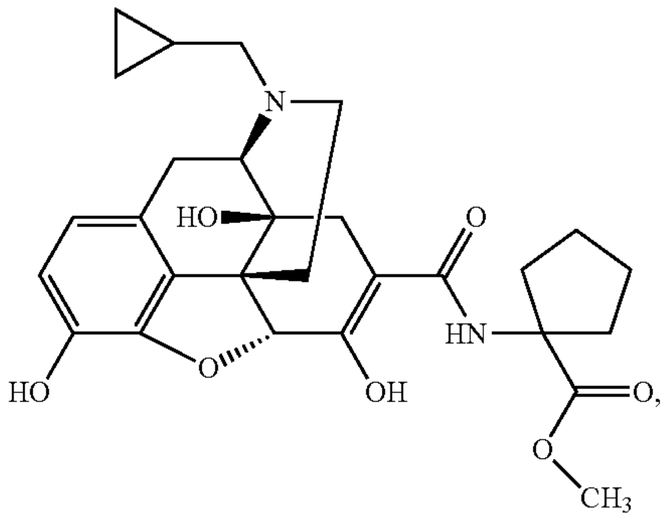

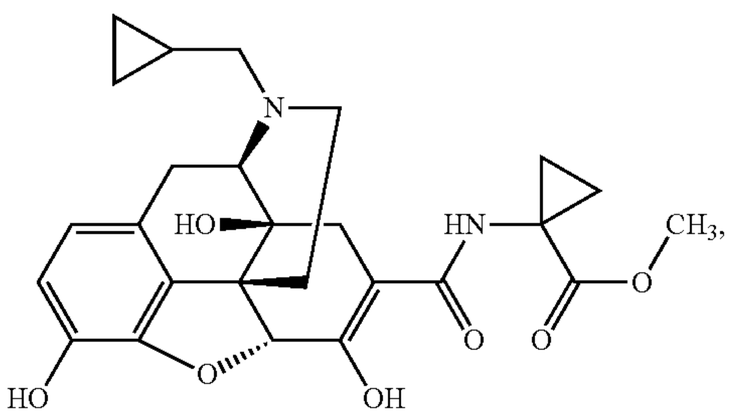

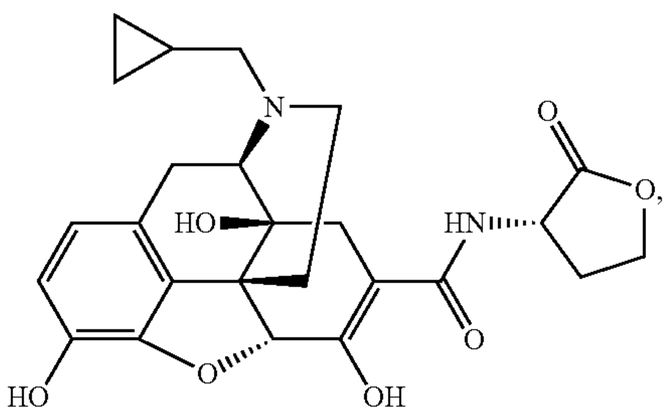

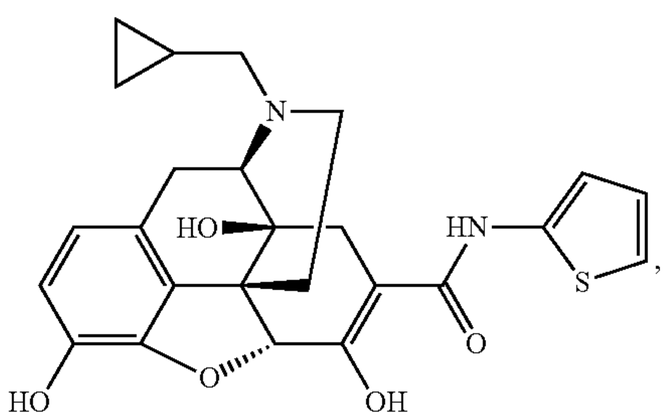

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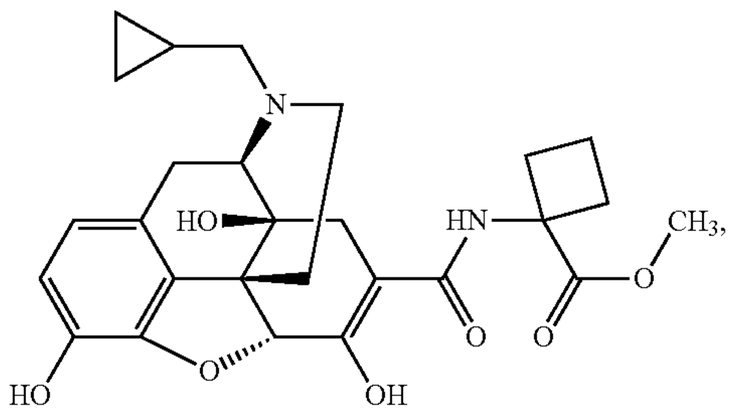

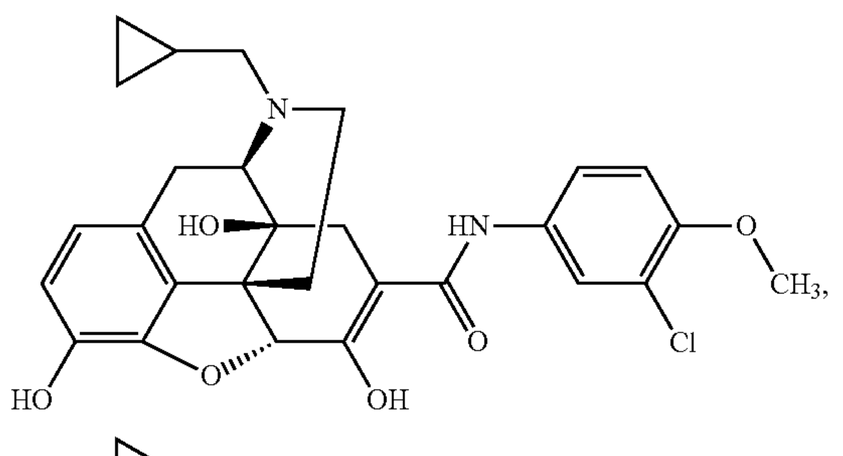

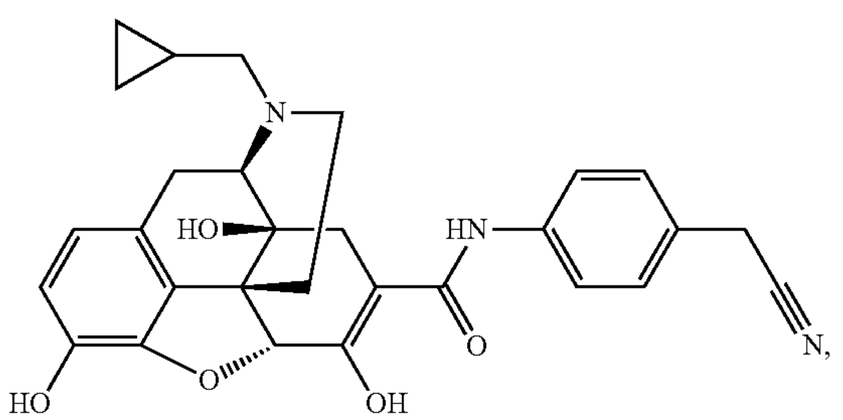

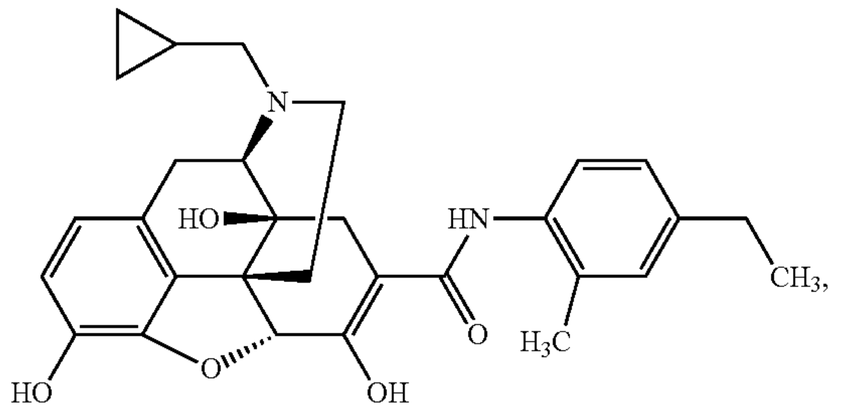

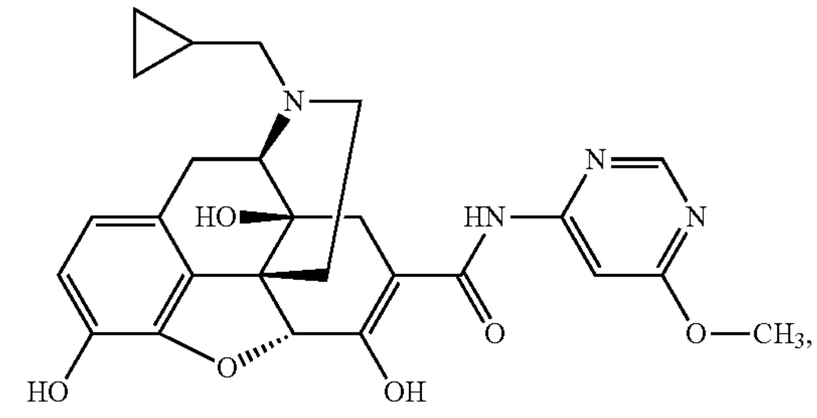

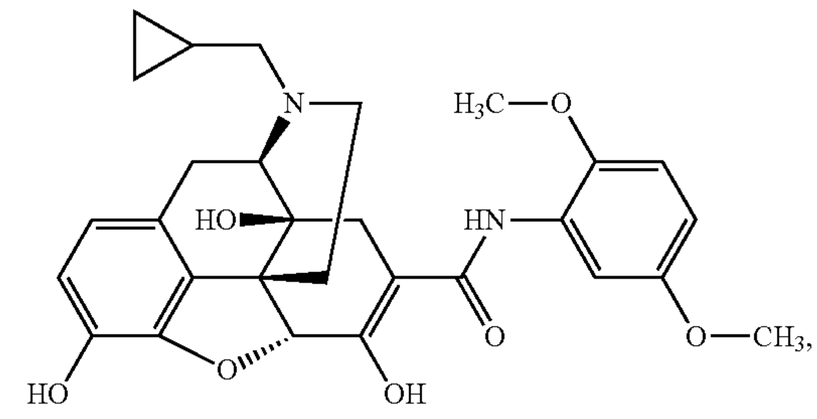

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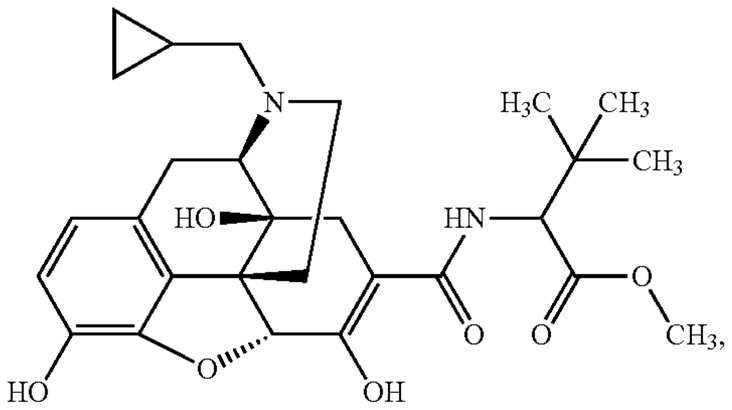
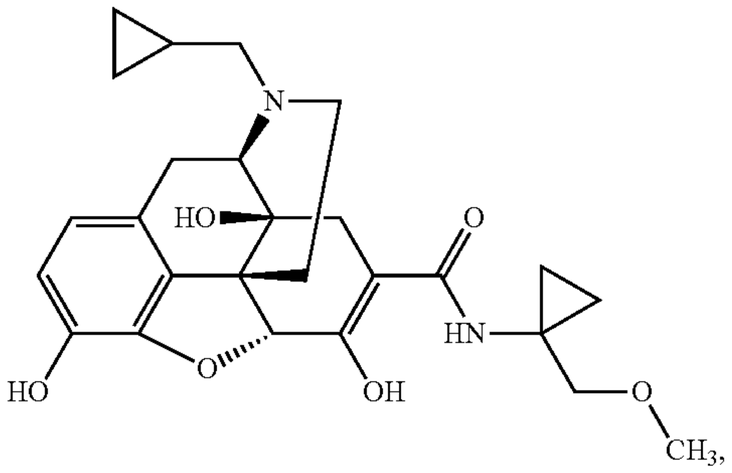
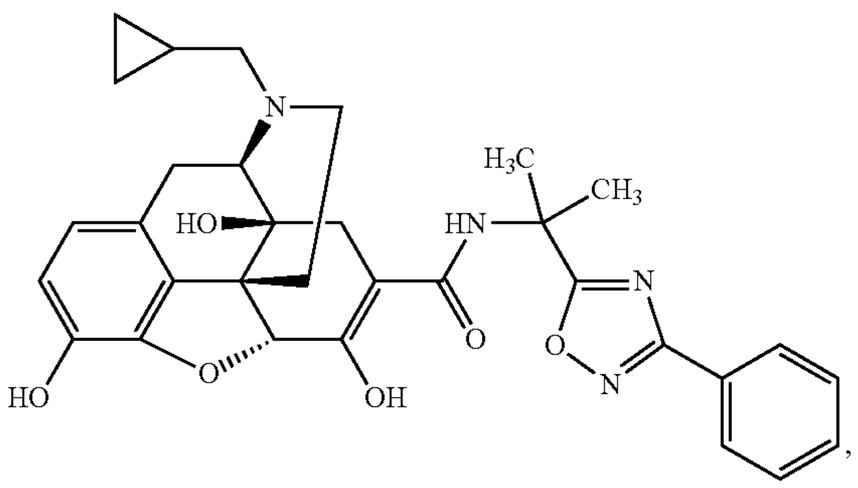
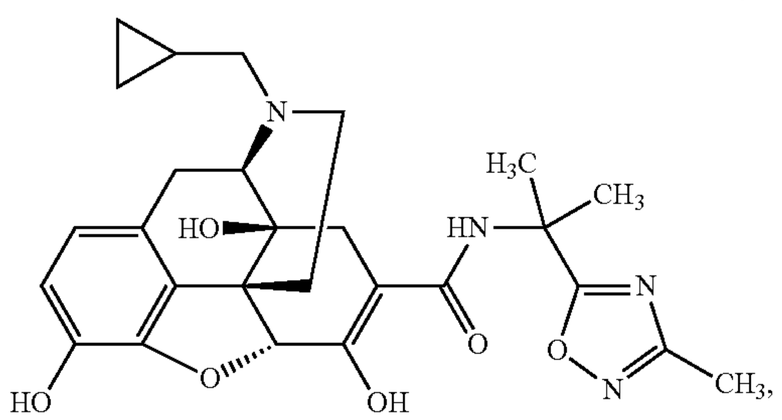
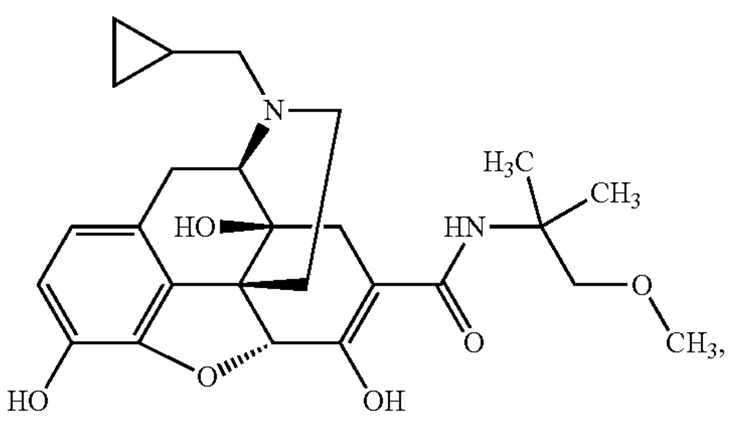
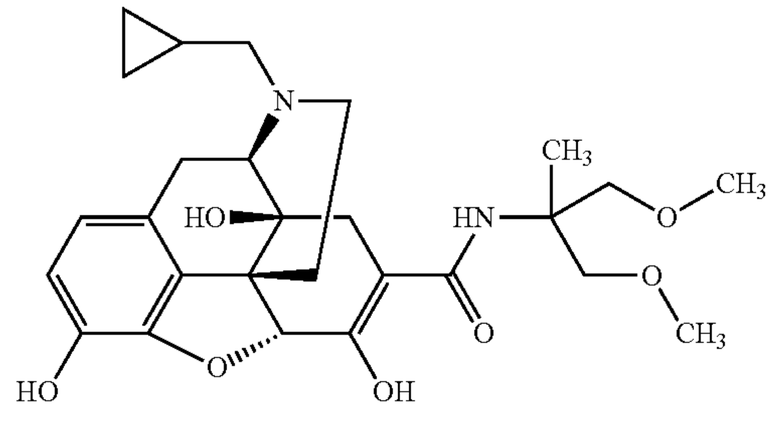




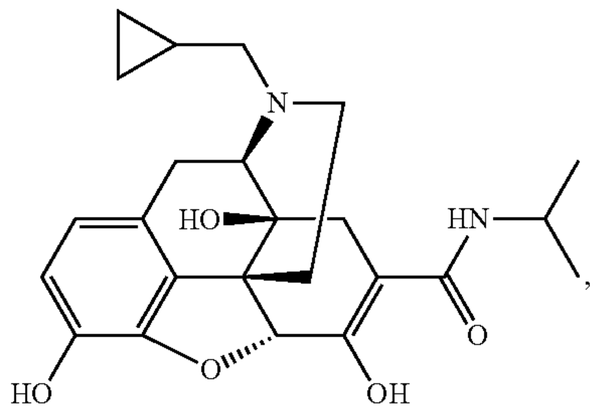


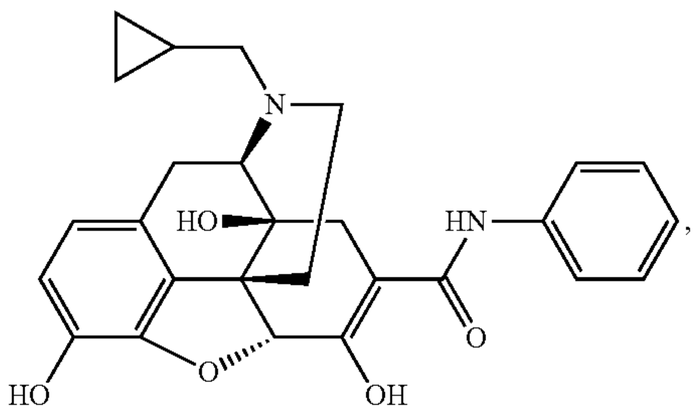


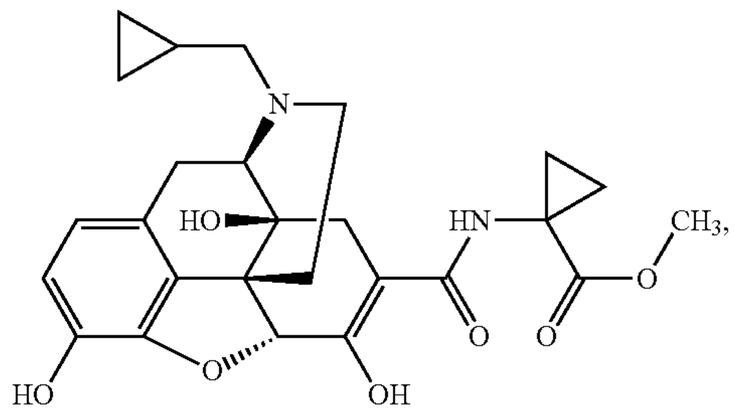


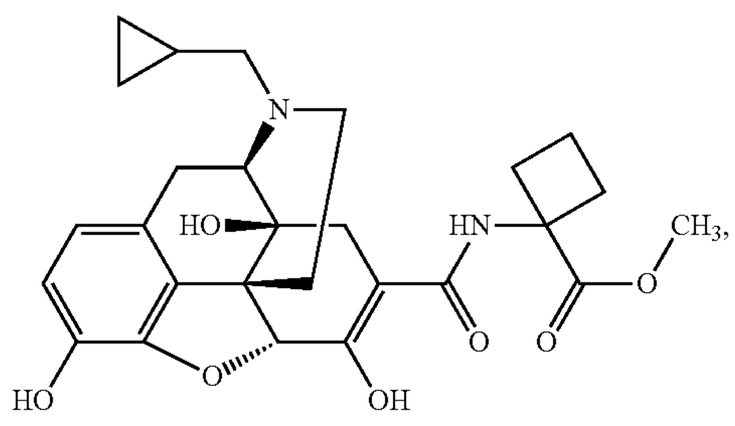


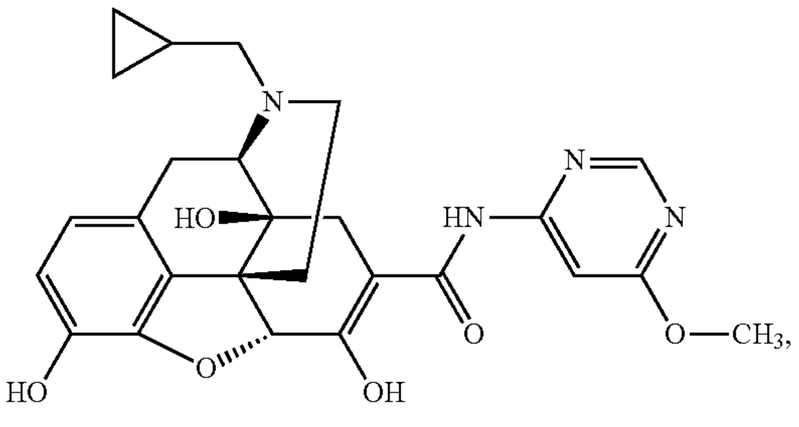
15. A compound, wherein the compound is

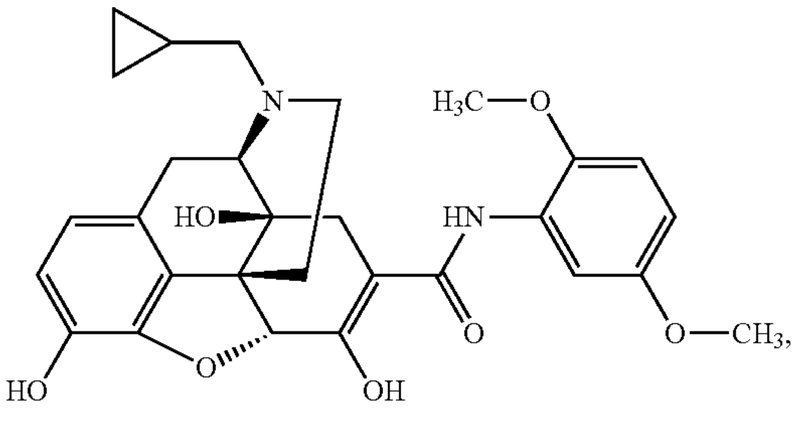












or a pharmaceutically acceptable salt thereof.

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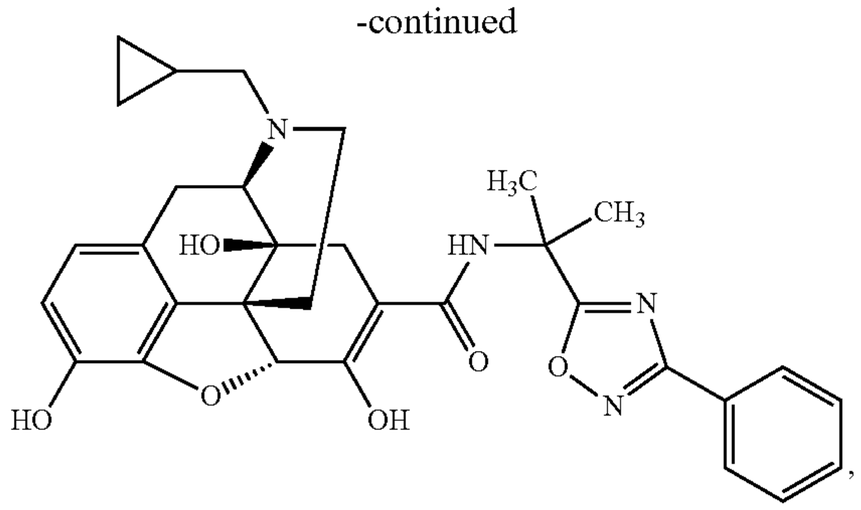
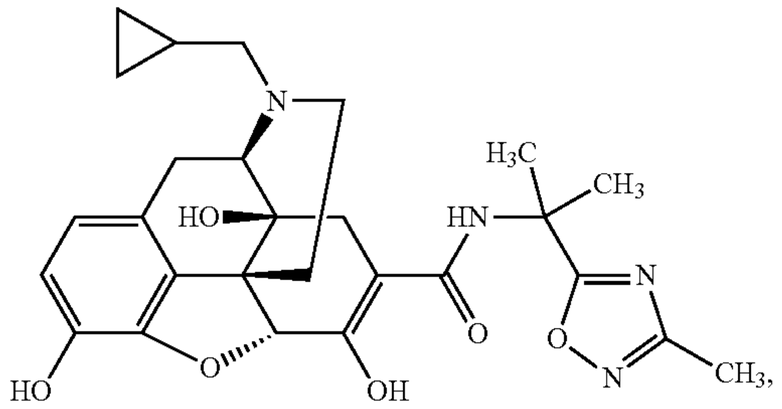
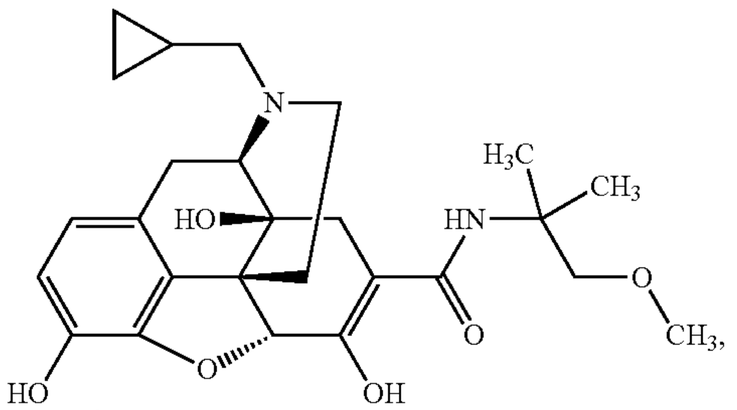
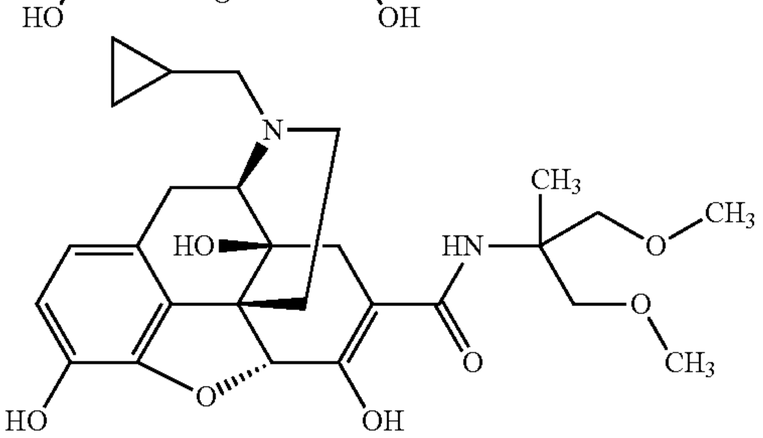








or a pharmaceutically acceptable salt thereof.

16. A composition for analgesic containing:

a compound having an opioid receptor agonistic activity, and an effective amount of compound according to claim **12** or a pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side effect induced by administrating of the compound having an opioid receptor agonistic activity.

17. A composition for analgesic containing:

a compound having an opioid receptor agonistic activity, and an effective amount of compound according to claim **13** or a pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side effect induced by administrating of the compound having an opioid receptor agonistic activity.

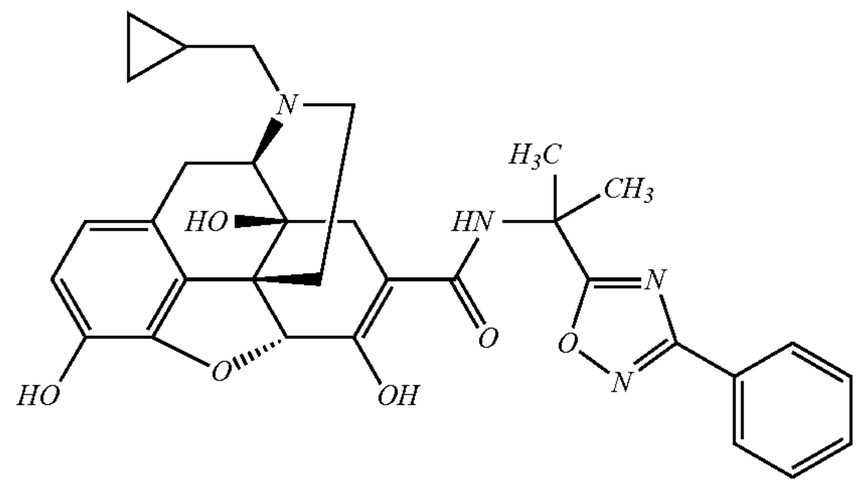
18. A composition for analgesic containing:

a compound having an opioid receptor agonistic activity, and an effective amount of compound according to claim **14** or a pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side effect induced by administrating of the compound having an opioid receptor agonistic activity.

19. A composition for analgesic containing:

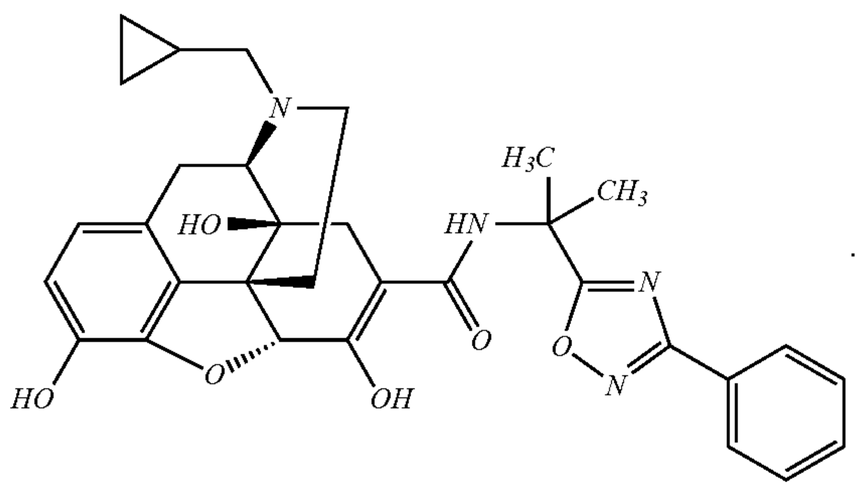
a compound having an opioid receptor agonistic activity, and an effective amount of compound according to claim **15** or a pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side effect induced by administrating of the compound having an opioid receptor agonistic activity.

20. A compound of the formula:

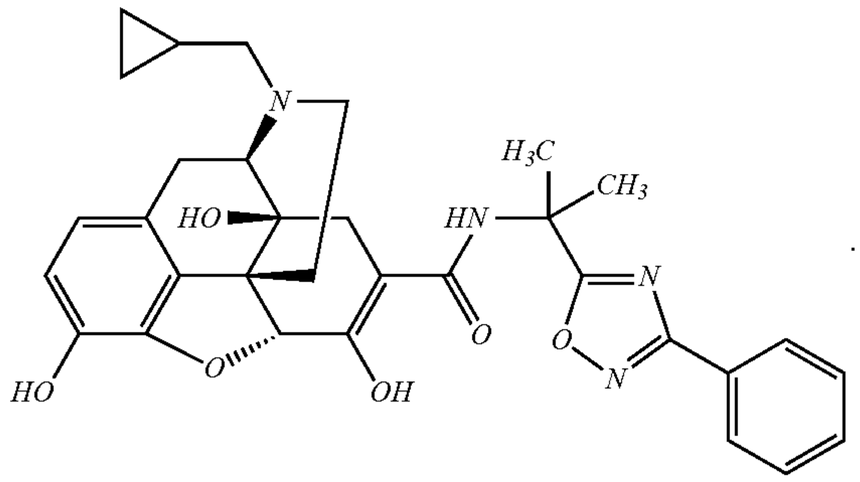


or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20 wherein the compound is



22. The compound of claim 20 wherein the compound is a pharmaceutically acceptable salt of



23. The compound of claim 22 wherein the pharmaceutically acceptable salt is the p-toluene sulfonic acid salt.

24. A pharmaceutical composition comprising the compound of claim 20 or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising the compound of claim 23.

26. A composition comprising a compound having an opioid receptor agonistic activity and an effective amount of the compound of claim 20 or a pharmaceutically acceptable

salt thereof, for alleviating and/or preventing a side effect induced by administering of the compound having an opioid receptor agonistic activity.

27. A composition comprising a compound having an opioid receptor agonistic activity and an effective amount of the compound of claim 23, for alleviating and/or preventing a side effect induced by administering of the compound having an opioid receptor agonistic activity.

28. The composition of claim 27 wherein the compound having the opioid receptor agonistic activity is morphine, oxycodone, or a pharmaceutically acceptable salt thereof.

29. The composition according to claim 25 in the form of a tablet.

30. The composition according to claim 27 in the form of a tablet.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

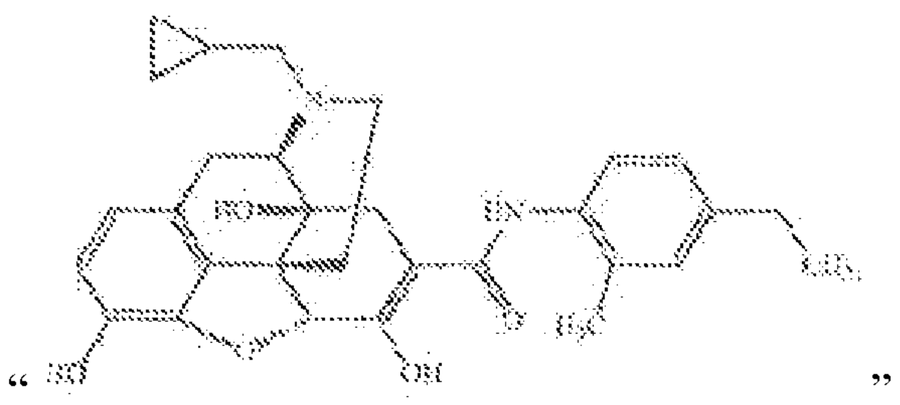
CERTIFICATE OF CORRECTION

PATENT NO. : RE46,365 E
APPLICATION NO. : 15/064511
DATED : April 11, 2017
INVENTOR(S) : Masanao Inagaki et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

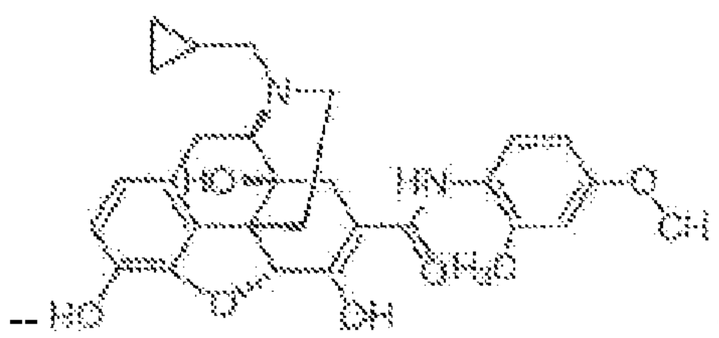
In the Claims

In Claim 14, Column 200, Lines 33-41, delete:



“ ”

And insert therefor:



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Signed and Sealed this
Fourth Day of July, 2017

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. 156

(68)	PATENT NO.	:	RE46,365
(45)	DATE OF REISSUED PATENT	:	April 11, 2017
(75)	INVENTOR	:	Masanao Inagaki et al.
(73)	PATENT OWNER	:	Shionogi & Co., Ltd.
(95)	PRODUCT	:	SYMPROIC® (naldemedine)

This is to certify that an application under 35 U.S.C. 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. RE46,365 based upon the regulatory review of the product SYMPROIC® (naldemedine) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is January 11, 2028. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,140 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 19th day of April 2022.

Kathi Vidal

Kathi Vidal
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office