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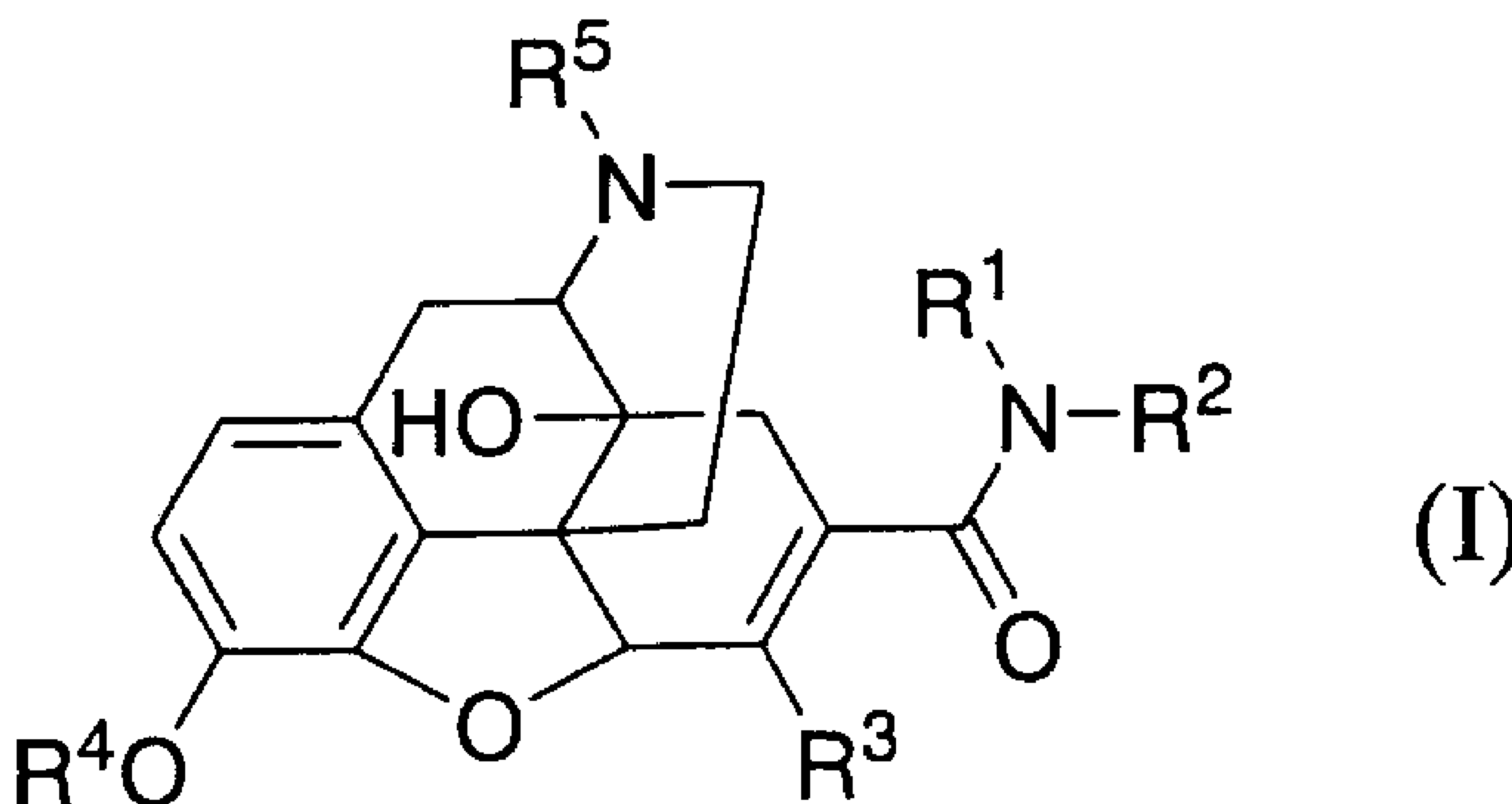
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(54) Titre : DERIVE DE LA MORPHINANE, INSATURE EN POSITION 6 ET 7 ET SUBSTITUE PAR UN CARBAMOYLE
EN POSITION 7

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



(57) Abrégé/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 I] (see formula I) wherein R¹ and R² are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted cycloalkyl, optionally substituted aryl etc., R³ is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkoxy etc., R⁴ is hydrogen or lower alkyl, R⁵ is hydrogen, lower alkyl, cycloalkyl lower alkyl or lower alkenyl, or a pharmaceutically acceptable salt, or a solvate thereof is provided.

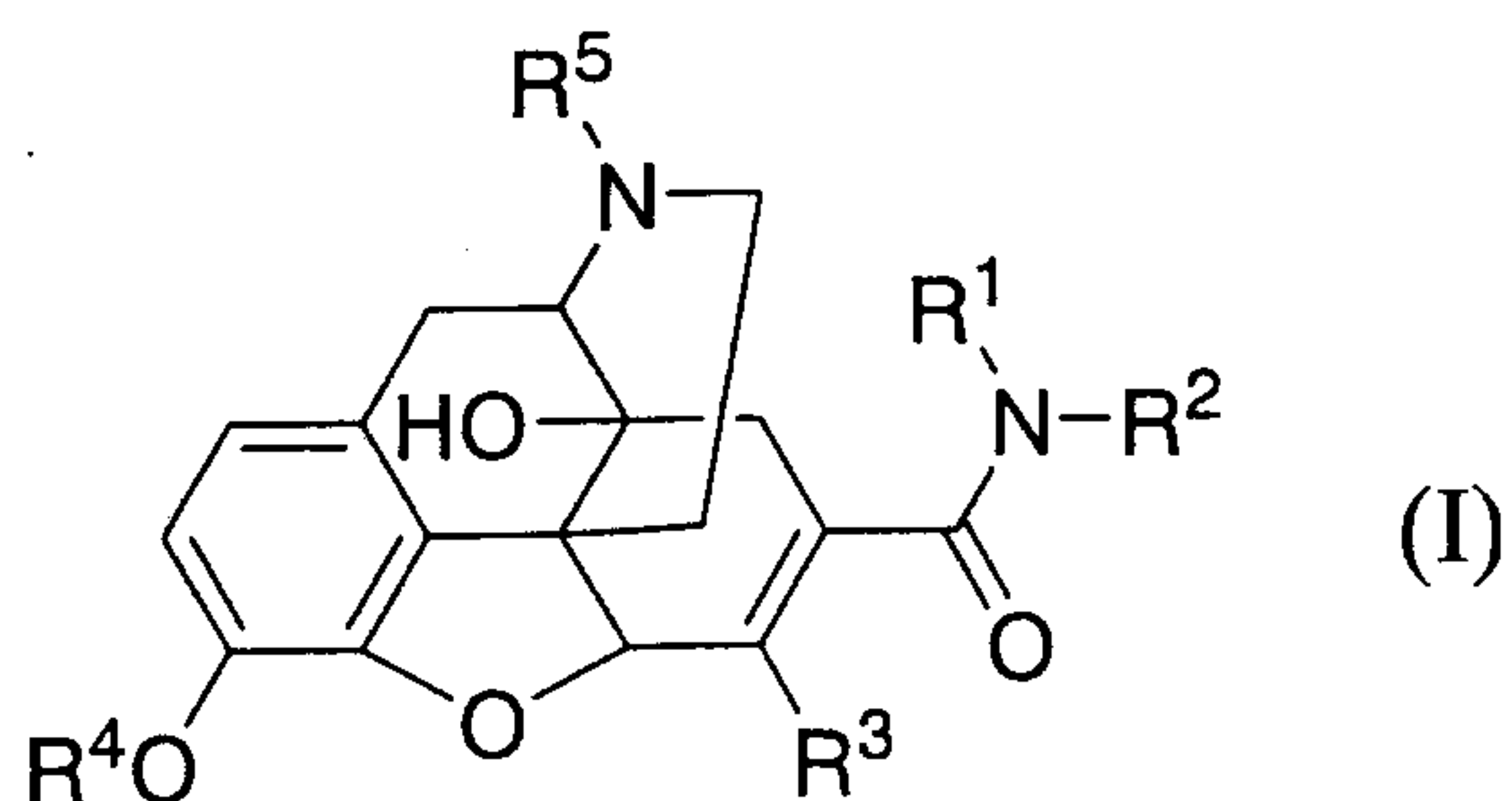


ABSTRACT

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]



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.

DESCRIPTION

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

[Technical field]

[0001]

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]

[0002]

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

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]

[0003]

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

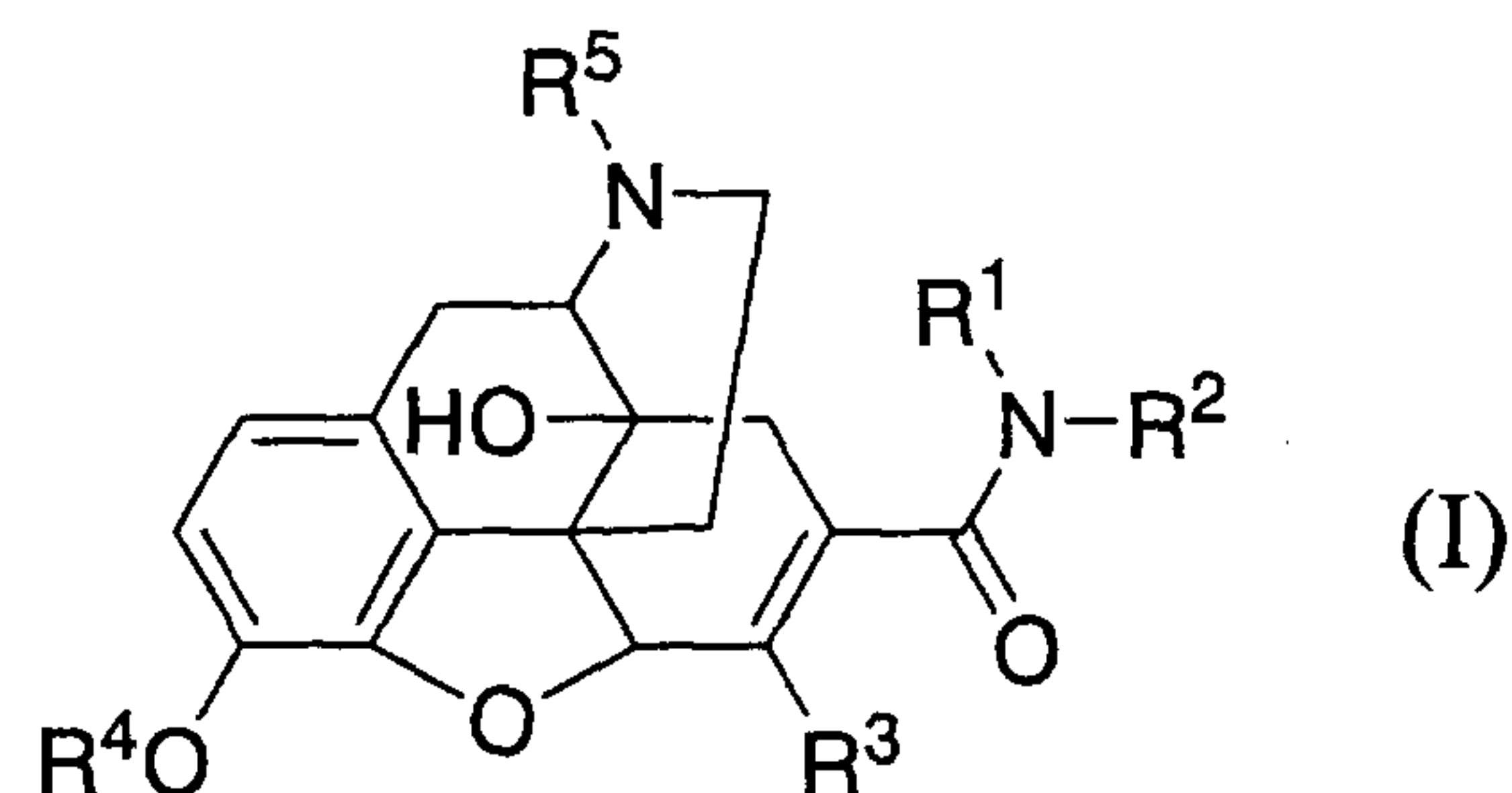
[Means to Solve the Problems]

[0004]

The present invention provides:

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

[Chemical formula 1]



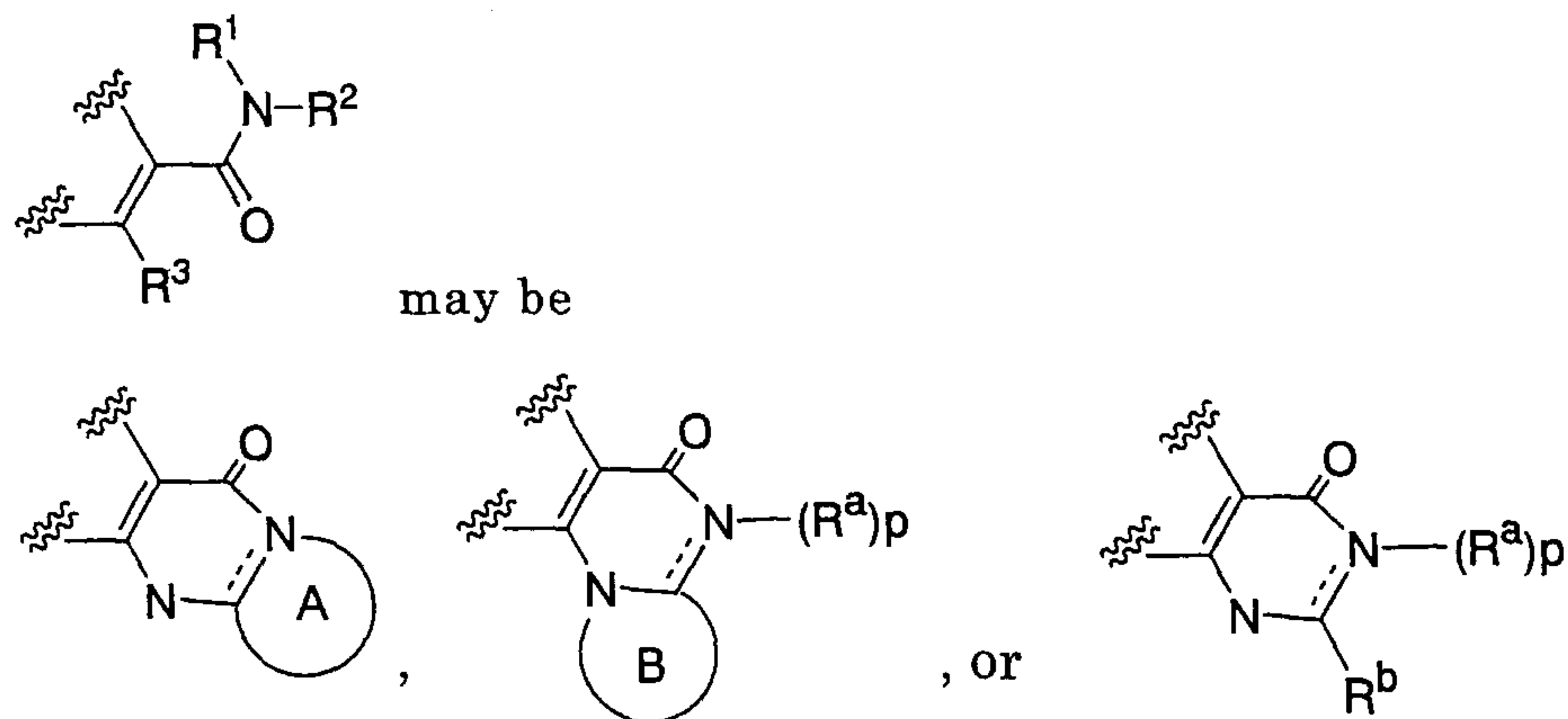
wherein R¹ and R² are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkylsulfonyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, an optionally substituted heterocyclic group, or optionally substituted arylsulfonyl, or R¹ and R² are taken together with the nitrogen atom to which they are attached to form optionally substituted heterocycle;

R³ is hydrogen, hydroxy, optionally substituted lower alkyl, lower optionally substituted lower alkenyl, optionally substituted lower alkynyl optionally substituted lower alkoxy, mercapto, optionally substituted lower alkylthio,

optionally substituted amino, optionally substituted carbamoyl, optionally substituted acyl, optionally substituted acyloxy, optionally substituted aryl, or an optionally substituted heterocyclic group,

a group represented by the formula:

[Chemical formula 2]



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;

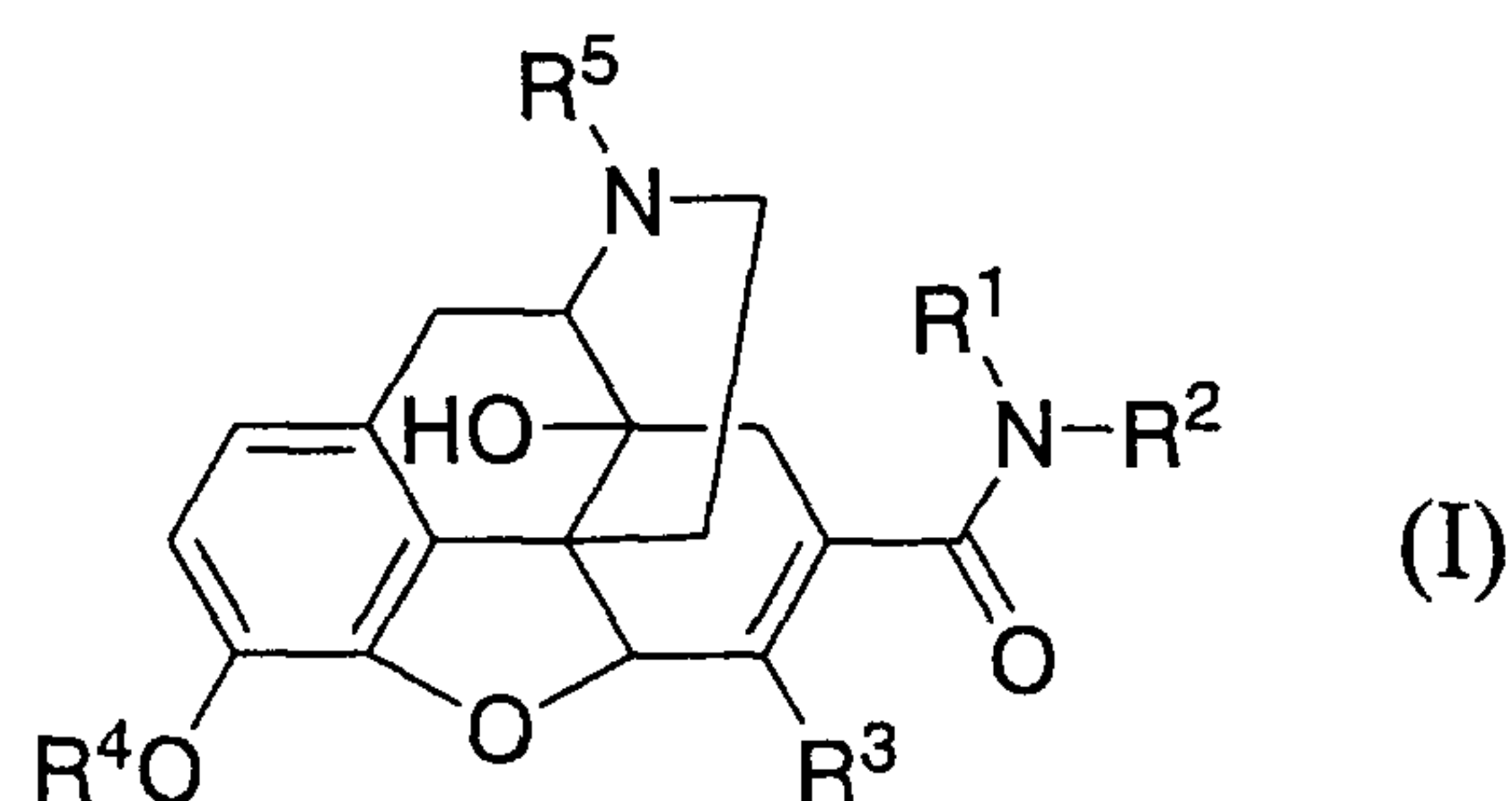
and R^b is hydrogen or oxo;

R⁴ is hydrogen or lower alkyl;

R⁵ 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]



wherein R¹ and R² are each independently hydrogen, optionally substituted

lower alkyl, optionally substituted lower alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, or an optionally substituted heterocyclic group, or R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form optionally substituted heterocycle;

R^3 is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkoxy, mercapto, optionally substituted lower alkylthio, optionally substituted aryl, or an optionally substituted heterocyclic group;

R^4 is hydrogen or lower alkyl;

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

or a pharmaceutically acceptable salt, or a solvate thereof,

(2) the compound according to (1) or (1'), wherein R^3 is hydroxy,

or a pharmaceutically acceptable salt, or a solvate thereof,

(3) the compound according to (1) or (1'), wherein R^3 is optionally substituted amino,

or a pharmaceutically acceptable salt, or a solvate thereof,

(4) the compound according to (1) or (1'), wherein R^3 is amino substituted with optionally substituted arylsulfonyl,

or a pharmaceutically acceptable salt, or a solvate thereof,,

(5) the compound according to any one of (1) to (4), and (1'), wherein R^1 is hydrogen or lower alkyl, R^2 is optionally substituted lower alkyl, optionally substituted phenyl, optionally substituted cycloalkyl, or an optionally substituted heterocyclic group, and R^5 is cyclopropylmethyl;

or a pharmaceutically acceptable salt, or a solvate thereof,

(6) the compound according to any one of (1) to (5), and (1'), wherein R^1 is hydrogen, R^2 is lower alkyl optionally substituted with a heterocyclic group optionally substituted with aryl or lower alkoxy; phenyl optionally substituted with lower alkyl or lower alkoxy, cycloalkyl substituted with lower alkylcarbonyl, or a heterocyclic group substituted with lower alkoxy or aryl, R^4 is hydrogen, and R^5 is cyclopropylmethyl,

or a pharmaceutically acceptable salt, or a solvate thereof,

(7) a pharmaceutical composition containing the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate

thereof,

(8) a composition having opioid receptor antagonistic activity containing the compound according to (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,

(9) a composition for treating and/or preventing emesis, vomiting and/or constipation containing the compound according to any one of (1) to (6), and (1'), or a pharmaceutically acceptable salt, or a solvate thereof,

[0005]

(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.

The composition of the invention can further comprise a
 pharmaceutically acceptable carrier.

[Effect of the invention]

[0006]

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

[Best mode for carrying out the invention]

[0007]

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 alkyl diarylsilyl", 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 alkylsulfonylethyl", the "lower alkylcarbamoyl", 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".

[0008]

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 R⁵ 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”.

[0009]

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 one or more substituents selected from the aforementioned Substituent group α . The substituent can replace at an arbitrary position, and may

replace at a carbon atom having a bond of cycloalkyl.

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 R¹ or R², 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, azetidiny, 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.

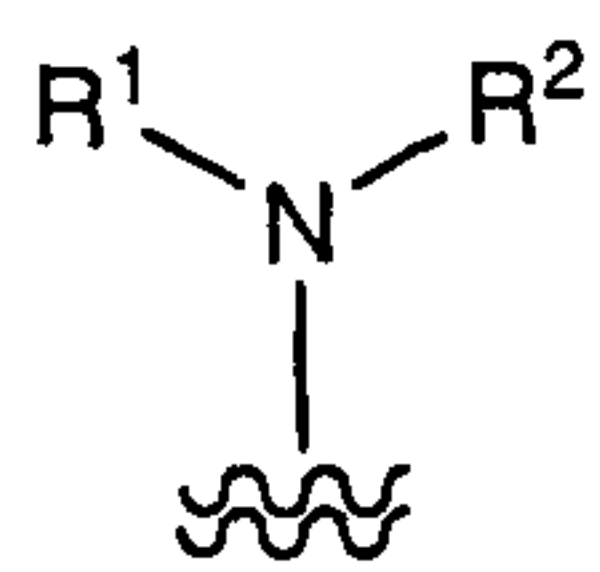
Herein, the "chain-like aliphatic" includes the aforementioned "lower alkyl", the aforementioned "lower alkenyl", and the aforementioned "lower alkynyl". The "cyclic aliphatic" includes the aforementioned "cycloalkyl" and the aforementioned "cycloalkenyl". A heterocyclic part of the heterocyclic carbonyl 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, pyridinecarbonyl, piperidinecarbonyl, piperazinecarbonyl, morpholinocarbonyl, and the like.

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

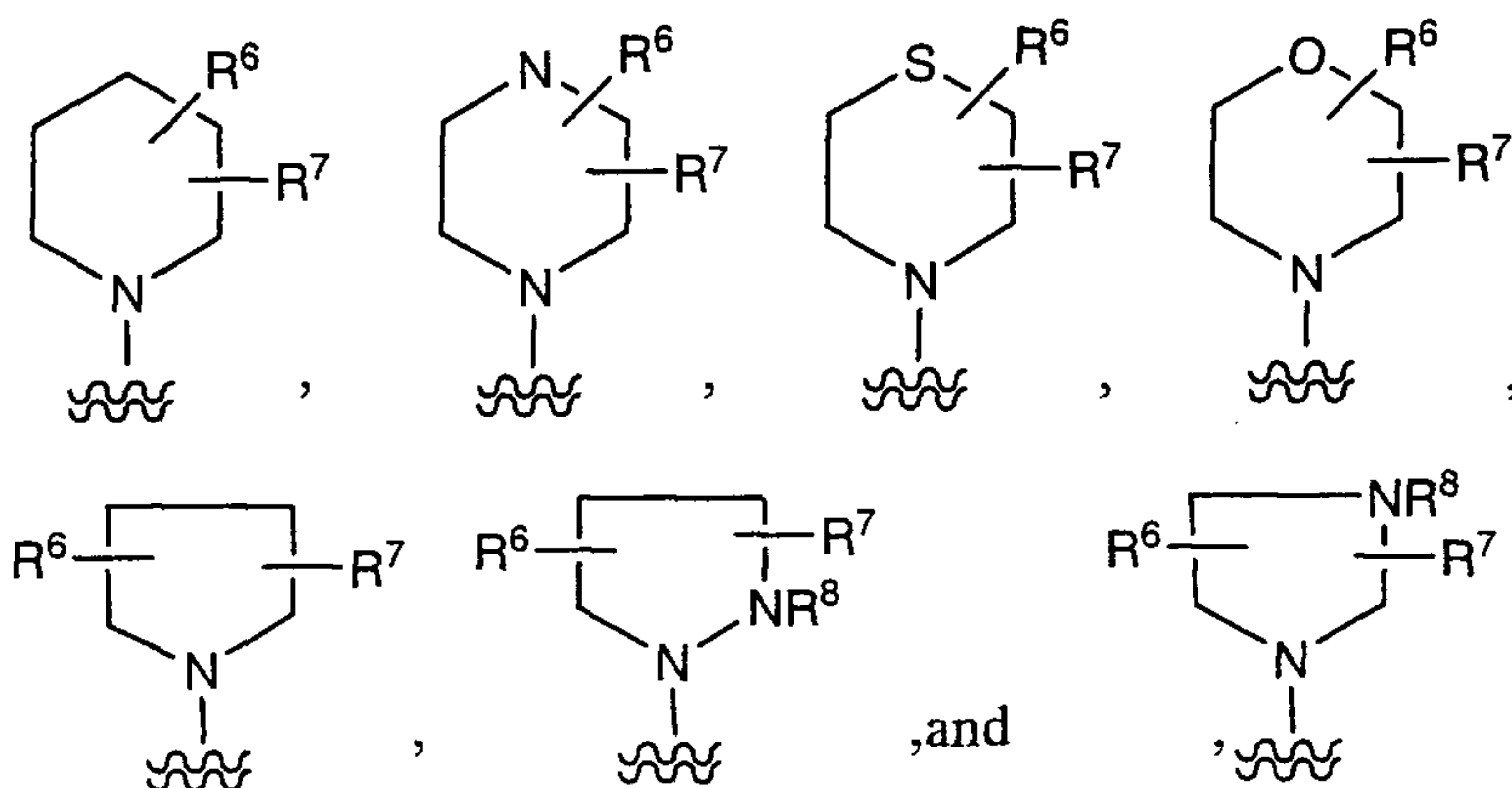
The substituent of the "optionally substituted acyl" or the "optionally substituted" is the same as the substituent of the aforementioned "optionally substituted lower alkyl" when the "acyl" is chain-like aliphatic acyl, and includes one or more groups selected from the Substituent group α when the "acyl"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

[0010]

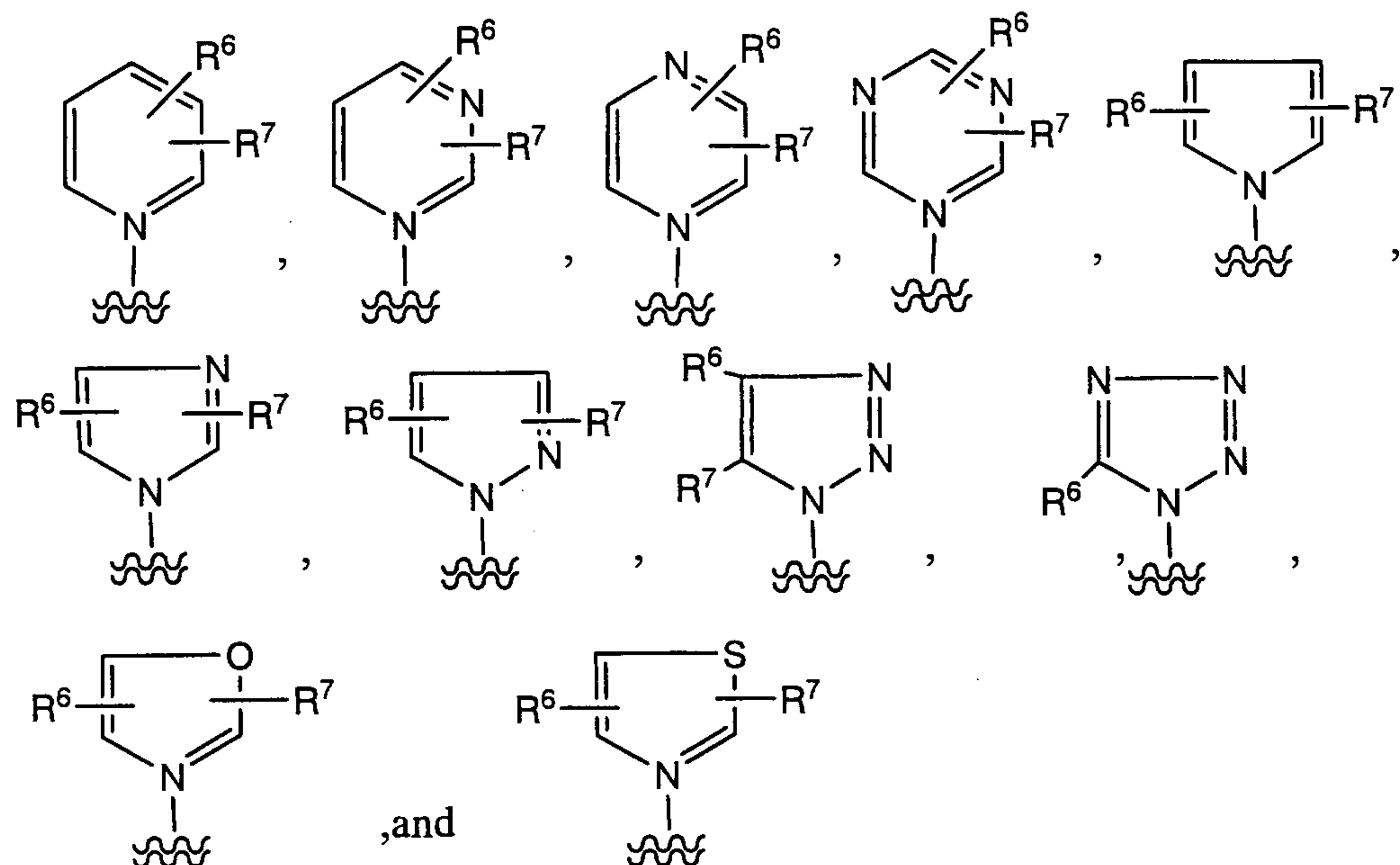
The "optionally substituted heterocycle" formed when R^1 and R^2 are taken together with the nitrogen atom to which they are attached, includes a 5-membered or 6-membered heterocycle containing the nitrogen atom to which R^1 and R^2 are attached and, further, optionally containing one or more heteroatoms 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



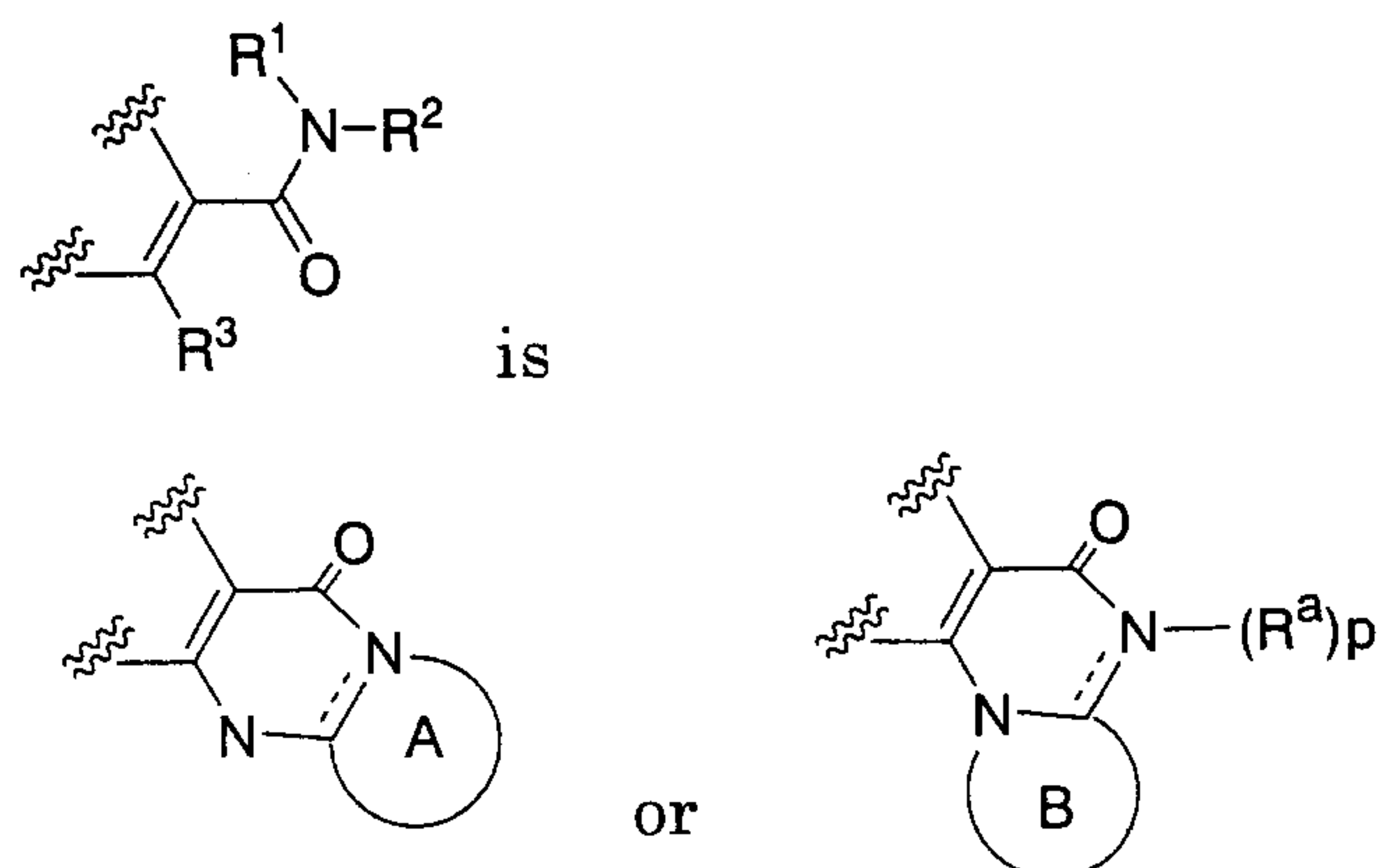
wherein R^6 , R^7 and R^8 are each independently hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, lower alkylthio, acyl, acyloxy, amino, lower alkylamino, acylamino, lower alkoxycarbonylamino, carboxy or lower alkoxycarbonyl,

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”.

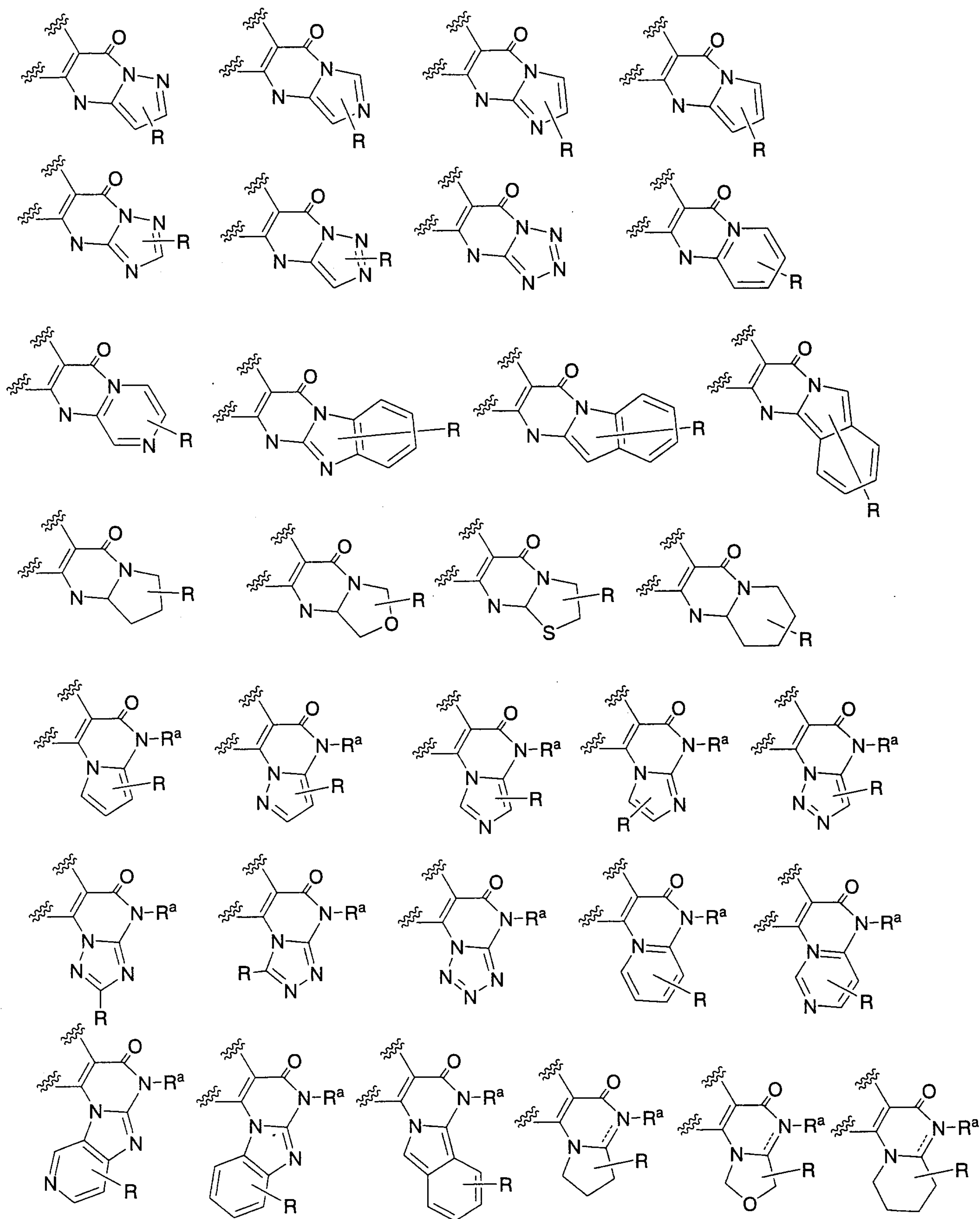
[0011]

[Chemical formula 5]



includes, for example, the following:

[Chemical formula 6]



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

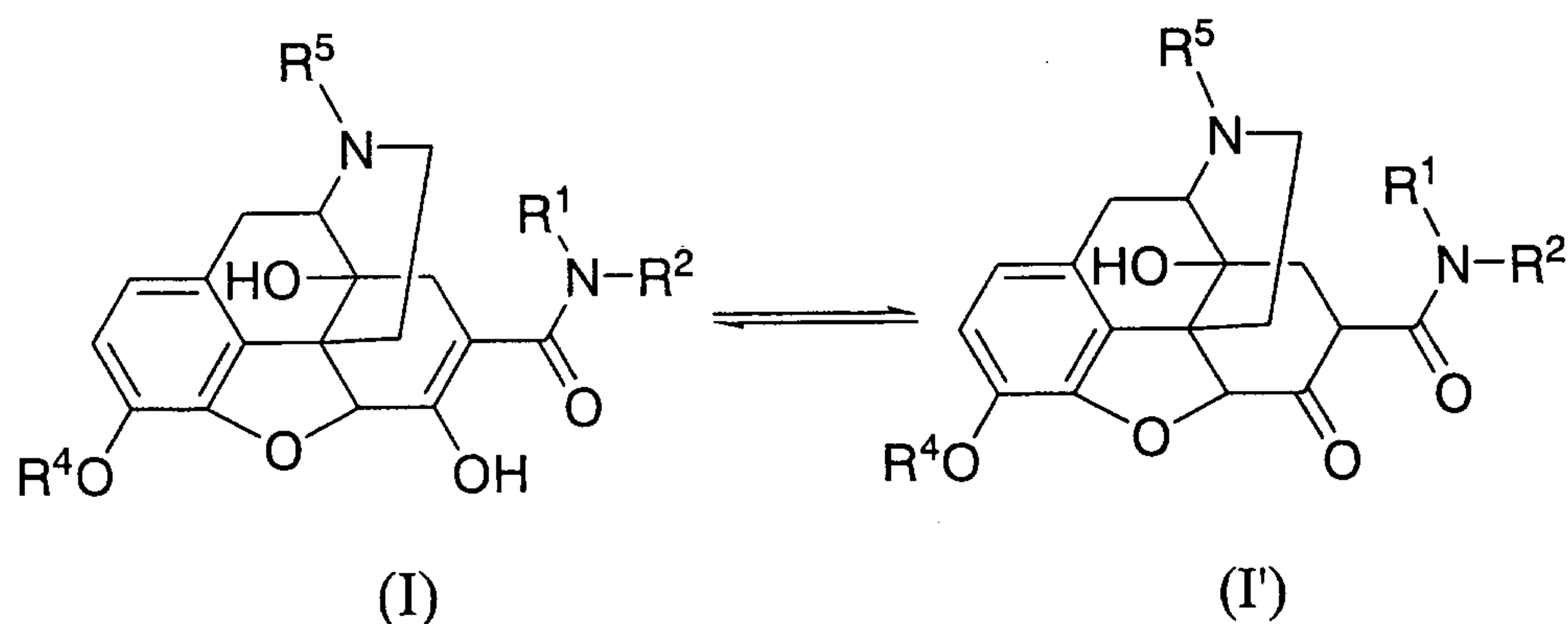
[0012]

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-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid). Particularly, hydrochloric acid, phosphoric acid, tartaric acid, or methanesulfonic acid is preferable. These salts can be formed by a conventional method.

In addition, the compound (I) is not limited to a specific isomer, but includes all possible isomers and racemates. For example, when R³ of the compound (I) is hydroxy, the compound (I) includes other tautomer, that is, the following compound (I').

[Chemical formula 7]

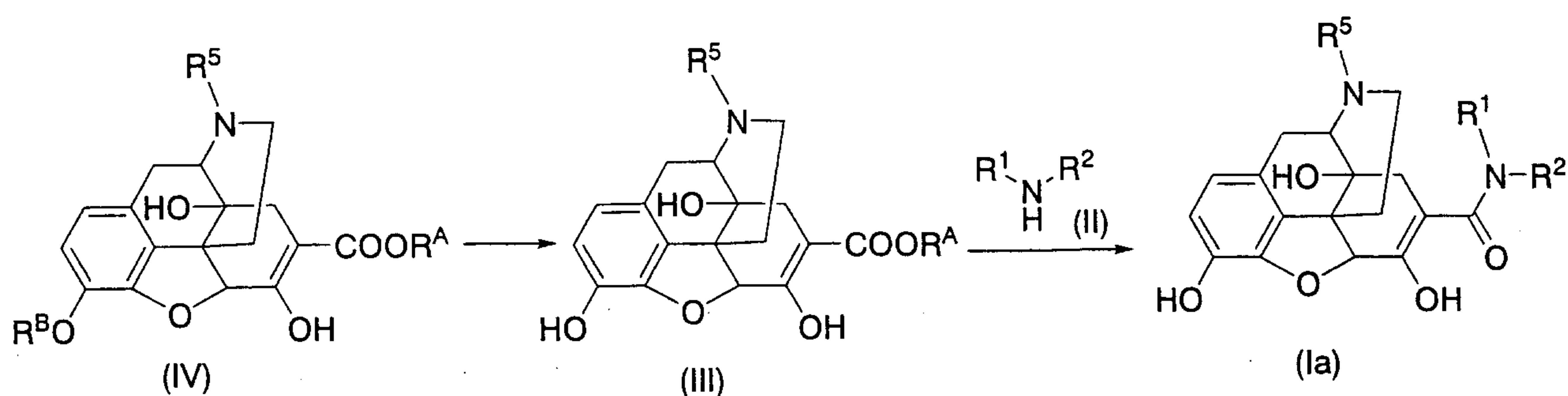


[0013]

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

(A process)

[Chemical formula 8]



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 alkyl diarylsilyl (tert-butyldiphenylsilyl etc.), triaryl lower alkylsilyl (tribenzylsilyl etc.), lower alkoxy lower alkyl (methoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl etc.), lower alkoxy lower alkoxy lower alkyl (methoxyethoxymethyl etc.), lower alkylthio lower alkyl (methylthiomethyl etc.), optionally substituted tetrahydropyranyl (tetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl etc.), tetrahydrothiopyranyl (tetrahydrothiopyran-2-yl etc.), tetrahydrofuranyl (tetrahydrofuran-2-yl etc.), tetrahydrothiofuranyl (tetrahydrothiofuran-2-yl etc.), aryl lower alkyloxy lower alkyl (benzyloxymethyl etc.), lower alkylsulfonyl (methanesulfonyl, ethanesulfonyl etc.), acyl (acetyl etc.) and arylsulfonyl (p-toluenesulfonyl etc.).

(First step)

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.

[0014]

(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.).

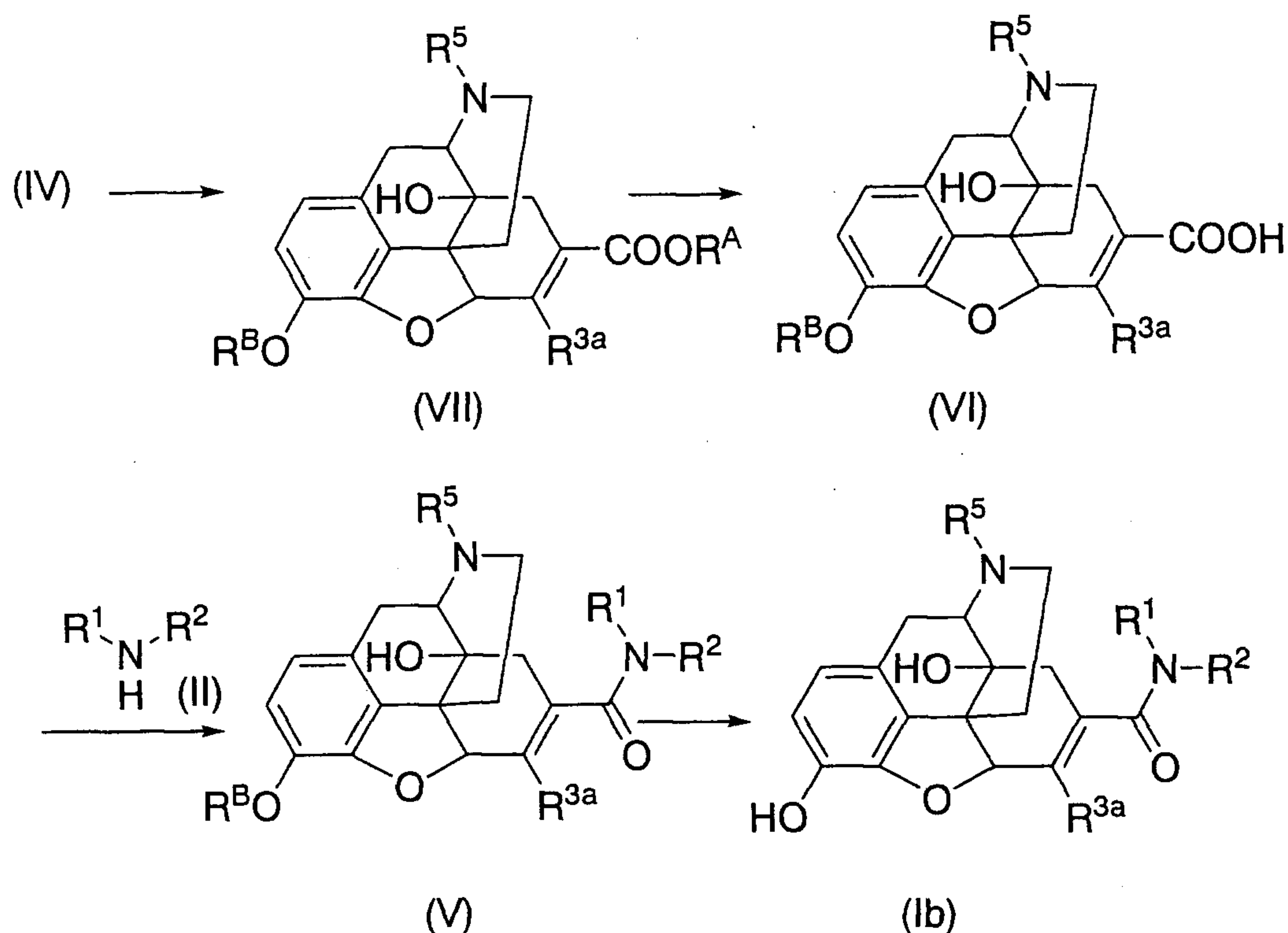
In order to effectively carry a reaction forward, the reaction may be performed by microwave irradiation. A reaction temperature, and an irradiation time are not particularly limited, but are about 100°C to about 200°C and about 5 minutes to about 5 hours, preferably about 10 minutes to about 1 hour. 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 R⁴ of objective compound (I) is lower alkyl, an objective compound can be obtained by the conventional etherization reaction at an arbitrary stage.

[0015]

(B process)

[Chemical formula 9]



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

(First step)

When R³ 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)

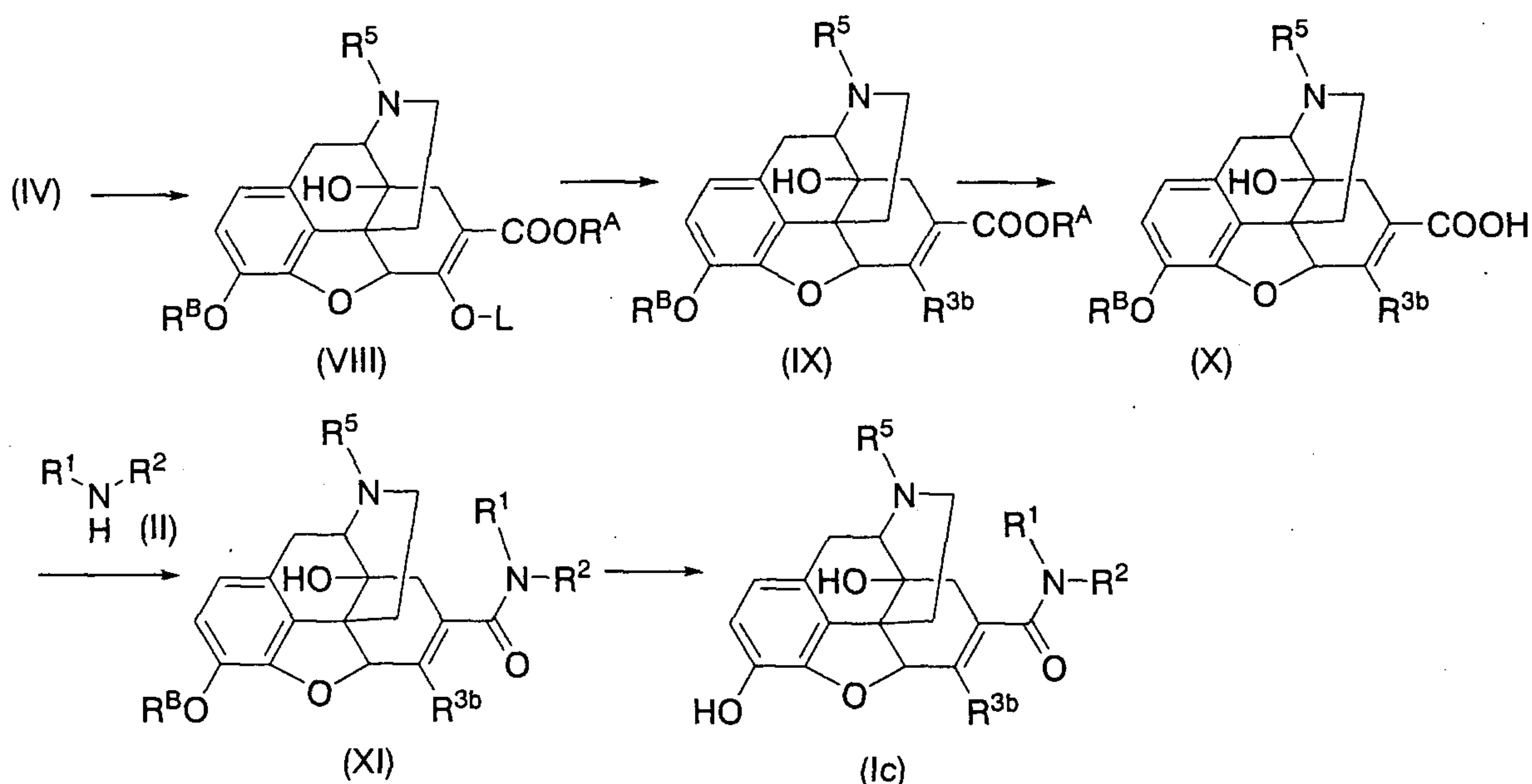
Then, compound (VI) is amidated, and the resulting compound (V) is deprotected to obtain objective compound (Ib). These reactions may be performed by the same methods as those of the second step and the first step in A process, respectively. In an amidation step, the reaction may be performed, if necessary,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

In addition, when R⁴ of objective compound (I) is lower alkyl, an etherization reaction may be performed at an arbitrary stage as described above.

[0016]

(C process)

[Chemical formula 10]



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

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

(First step)

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.

[0017]

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

- a) a compound in which R^1 is hydrogen or lower alkyl,
- b) a compound in which R^1 is hydrogen or C1-C3 alkyl,
- c) a compound in which R^2 is:
 - (c-i) lower alkyl optionally substituted with one or more groups selected from Substituent group β (herein, Substituent group β is cycloalkyl optionally substituted with hydroxy, halogen, hydroxy, lower alkoxy, halogeno lower alkoxy, lower alkylthio, amino, lower alkylamino, carboxy, lower alkoxycarbonyl, cyano, lower alkylsulfonyl, aryl, aryloxy and lower alkylenedioxy),
 - (c-ii) phenyl optionally substituted with one or more groups selected from group consisting of Substituent group β , lower alkyl and halogeno lower alkyl,
 - (c-iii) aryl lower alkyl optionally substituted with one or more groups selected from Substituent group β ,
 - (c-iv) cycloalkyl optionally substituted with one or more groups selected from Substituent group β ,
 - (c-v) heterocyclic group optionally substituted with one or more groups selected from Substituent group β , or
 - (c-vi) heterocyclic lower alkyl optionally substituted with one or more groups selected from Substituent group β ,
- [0018]
- 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,

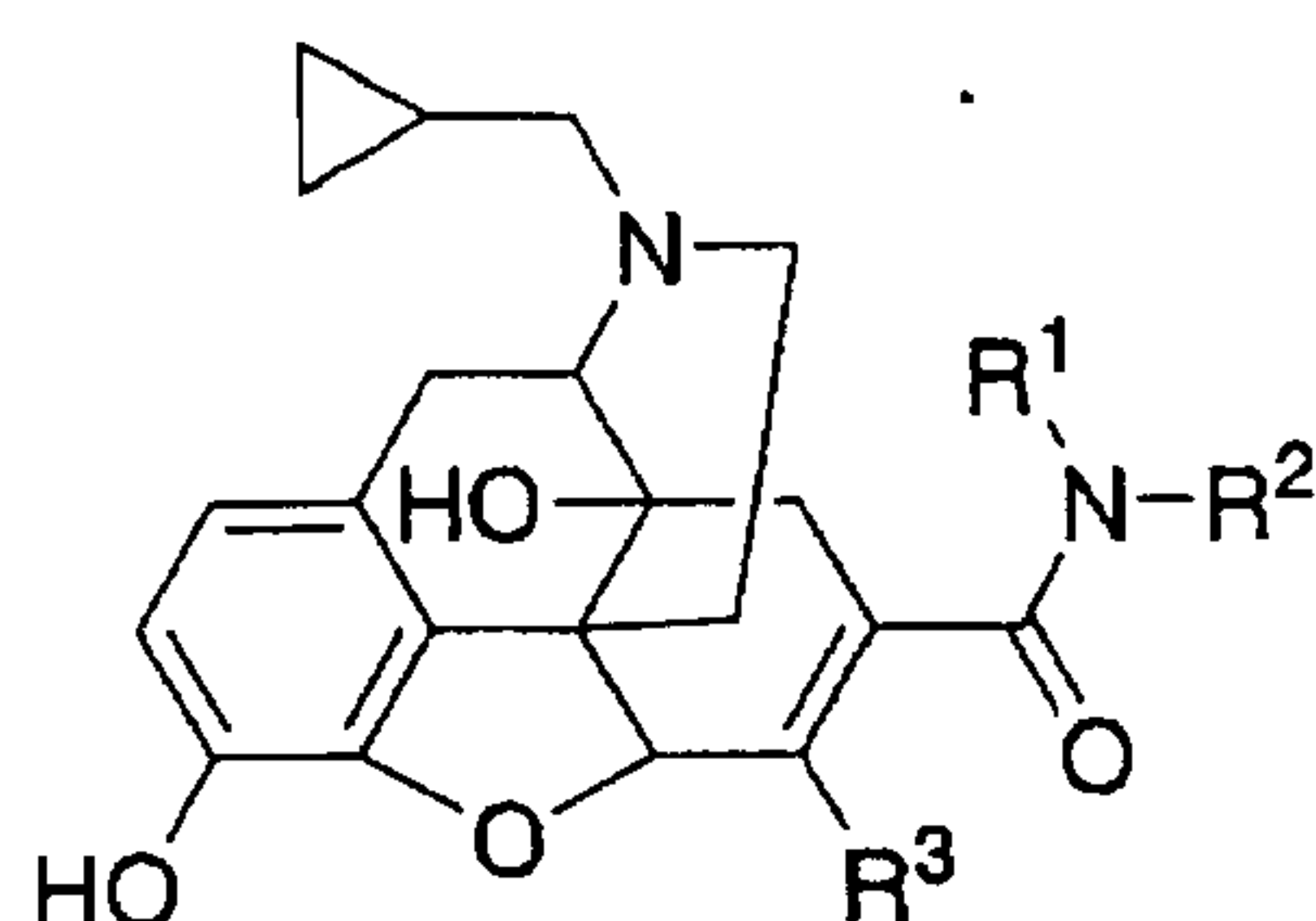
- (d-iv) cycloalkyl optionally substituted with lower alkyl, carboxy or lower alkoxy carbonyl,
- (d-v) a heterocyclic group optionally substituted with lower alkyl, lower alkoxy or phenyl, or
- (d-vi) heterocyclic lower alkyl optionally substituted with lower alkyl or aryl,
- e) a compound in which R¹ and R² 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 R³ is hydroxy or lower alkoxy,
- g) a compound in which R³ is hydroxy,
- h) a compound in which R³ is amino optionally substituted with one or more groups selected from Substituent group α ,
- i) a compound in which R³ is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy,
- j) a compound in which R⁴ is hydrogen or methoxy,
- k) a compound in which R⁵ is cycloalkyl lower alkyl or lower alkenyl,
- l) a compound in which R⁵ is cyclopropylmethyl or allyl,
- m) a compound in which R⁵ is cyclopropylmethyl,
- n) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-i), R³ is hydroxy or lower alkoxy, R⁴ is hydrogen, and R⁵ is cycloalkyl lower alkyl or lower alkenyl,
- o) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-i), R³ is hydroxy or lower alkoxy, R⁴ is hydrogen, and R⁵ is cyclopropylmethyl,
- p) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-i), R³ is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy, R⁴ is hydrogen, and R⁵ is cycloalkyl lower alkyl or lower alkenyl,
- q) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-i), R³ is halogen, lower alkyl, or amino substituted with arylsulfonyl optionally substituted with lower alkoxy, R⁴ is hydrogen, and R⁵ is cyclopropylmethyl,
- r) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-ii), R³ is hydroxy or lower alkoxy, R⁴ is hydrogen, and R⁵ is cycloalkyl lower alkyl or lower alkenyl,
- s) a compound in which R¹ is hydrogen or lower alkyl, R² is the (d-ii), R³ is

- hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- t) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
- u) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iii), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- v) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iv), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
- w) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-iv), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- x) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-v), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
- y) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-v), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- z) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-vi), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl or lower alkenyl,
- aa) a compound in which R^1 is hydrogen or lower alkyl, R^2 is the (d-vi), R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- ab) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle, R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cycloalkyl lower alkyl group or lower alkenyl,
- ac) a compound in which R^1 and R^2 are taken together with a N atom to which they bind to form a 5-membered or 6-membered saturated heterocycle, R^3 is hydroxy or lower alkoxy, R^4 is hydrogen, and R^5 is cyclopropylmethyl,
- or a pharmaceutically acceptable salt or a solvate thereof.

[0019]

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	-NHPr	—
AB		—
AC		—
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	RI
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

	NR1R2	CR9R10
BJ	-NHCR9R10CONMe2	Rj
BK	-NHCR9R10CONMe2	Rk
BL	-NHCR9R10CONMe2	RI
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
BZ	-NHCR9R10COOH	Rf
CA	-NHCR9R10COOH	Rg
CB	-NHCR9R10COOH	Rh
CC	-NHCR9R10COOH	Ri
CD	-NHCR9R10COOH	Rj
CE	-NHCR9R10COOH	Rk
CF	-NHCR9R10COOH	RI
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

[0020]

[Table 2]

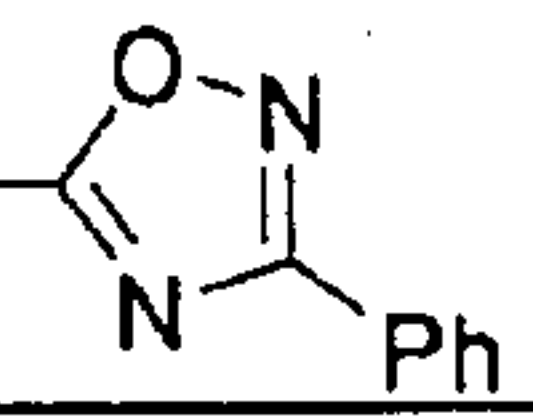
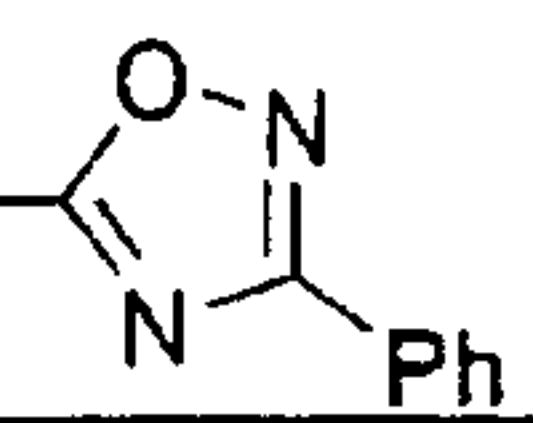
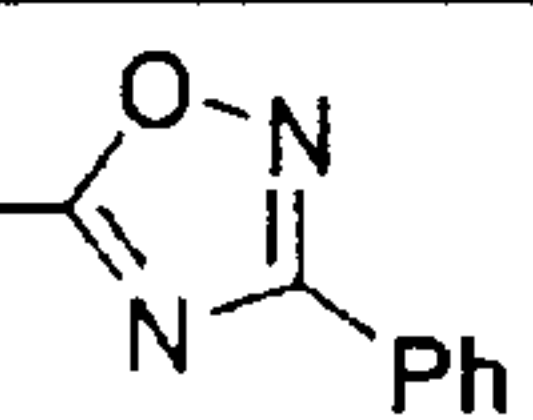
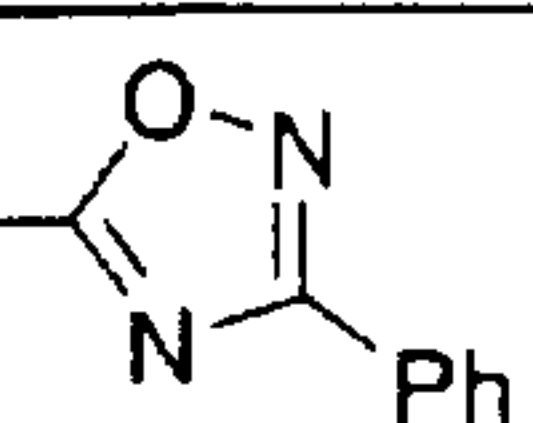
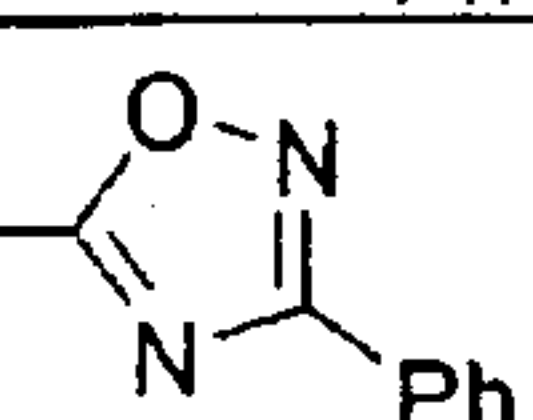
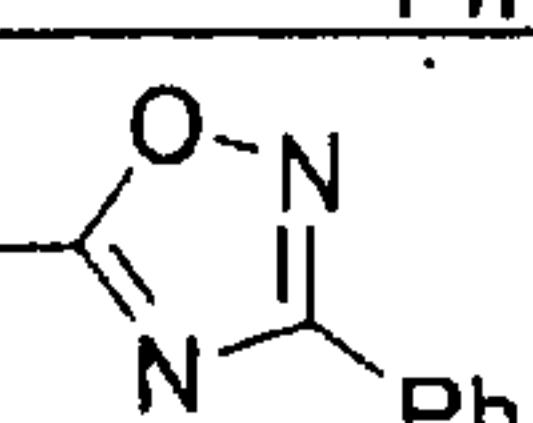
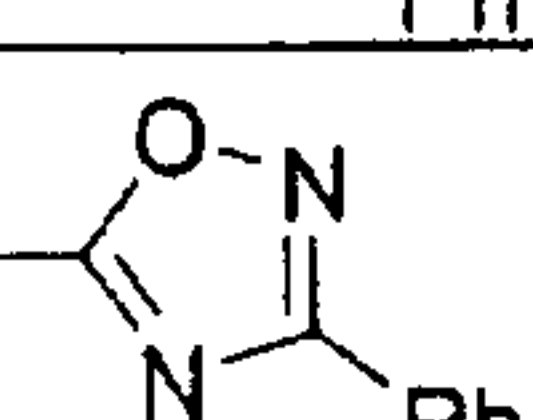
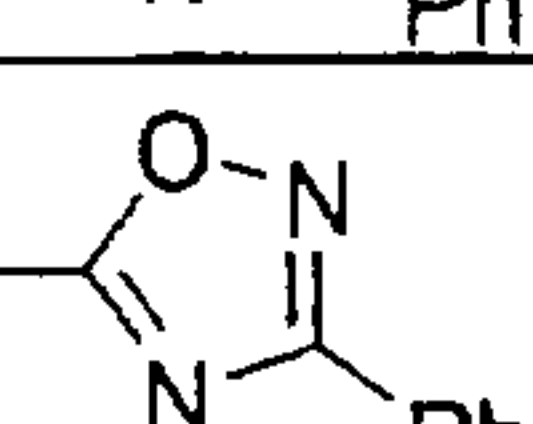
	NR1R2	CR9R10
CS	-NHCR9R10COOMe	Re
CT	-NHCR9R10COOMe	Rf
CU	-NHCR9R10COOMe	Rg
CV	-NHCR9R10COOMe	Rh
CW	-NHCR9R10COOMe	Ri
CX	-NHCR9R10COOMe	Rj
CY	-NHCR9R10COOMe	Rk
CZ	-NHCR9R10COOMe	RI
DA	-NHCR9R10COOMe	Rm
DB	-NHCR9R10COOMe	Rn
DC	-NHCR9R10COOMe	Ro
DD	-NHCR9R10COOMe	Rp
DE	-NHCR9R10COOMe	Rq
DF	-NHCR9R10COOMe	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	RI
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
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	RI
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

	NR1R2	CR9R10
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	RI
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	RI
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	RI
GW	-NHCR9R10CONHPh	Rm
GX	-NHCR9R10CONHPh	Rn
GY	-NHCR9R10CONHPh	Ro
GZ	-NHCR9R10CONHPh	Rp
HA	-NHCR9R10CONHPh	Rq
HB	-NHCR9R10CONHPh	Rr
HC	-NHCR9R10CONHPh	Rs
HD	-NHCR9R10CONHPh	Rt

[0021]

[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	RI
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	RI
IK	-NHCR9R10CONHSO2Me	Rm
IL	-NHCR9R10CONHSO2Me	Rn

	NR1R2	CR9R10
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	RI
JE	-NHCR9R10CH2OMe	Rm
JF	-NHCR9R10CH2OMe	Rn
JG	-NHCR9R10CH2OMe	Ro
JH	-NHCR9R10CH2OMe	Rp
JI	-NHCR9R10CH2OMe	Rq
JJ	-NHCR9R10CH2OMe	Rr
JK	-NHCR9R10CH2OMe	Rs
JL	-NHCR9R10CH2OMe	Rt
JM	-NHCR9R10- 	Ra
JN	-NHCR9R10- 	Rb
JO	-NHCR9R10- 	Rc
JP	-NHCR9R10- 	Rd
JQ	-NHCR9R10- 	Re
JR	-NHCR9R10- 	Rf
JS	-NHCR9R10- 	Rg
JT	-NHCR9R10- 	Rh

[0022]

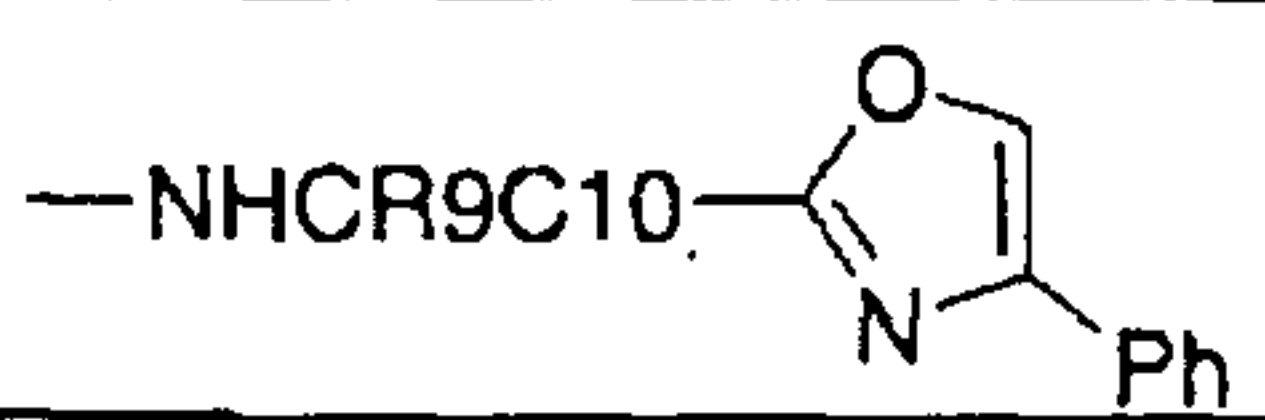
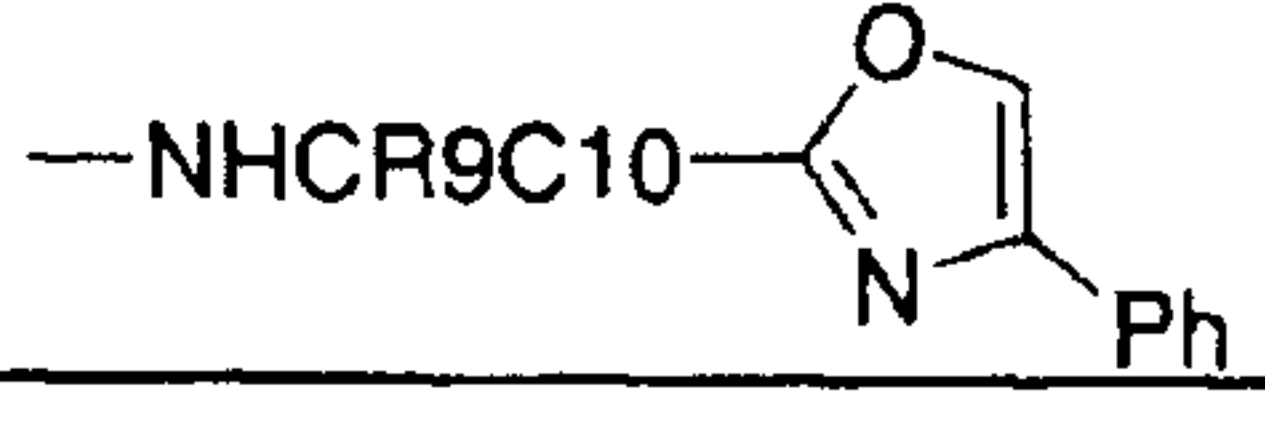
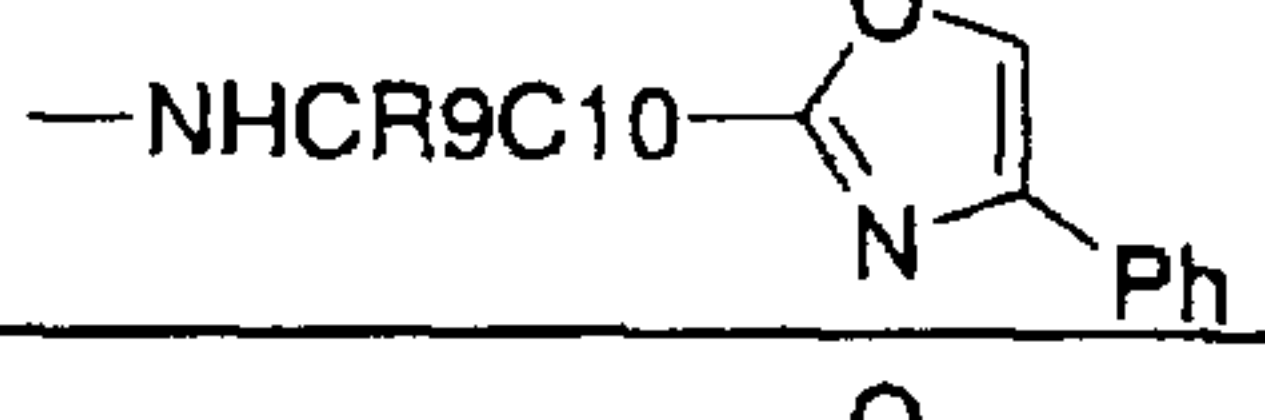
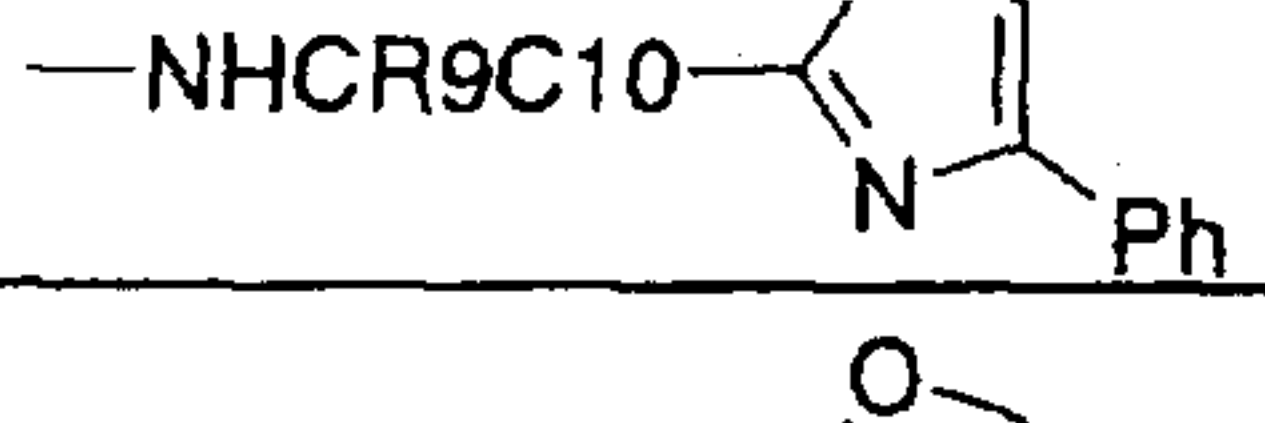
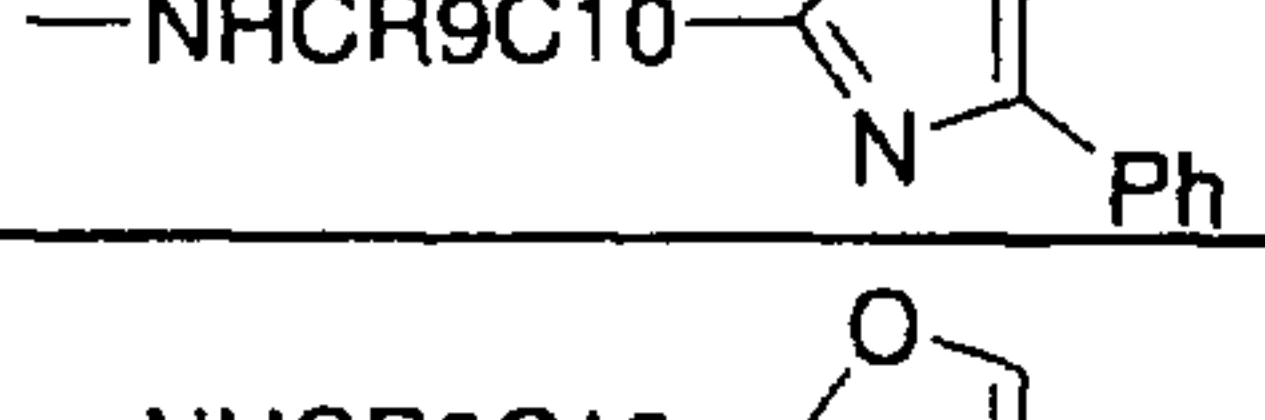
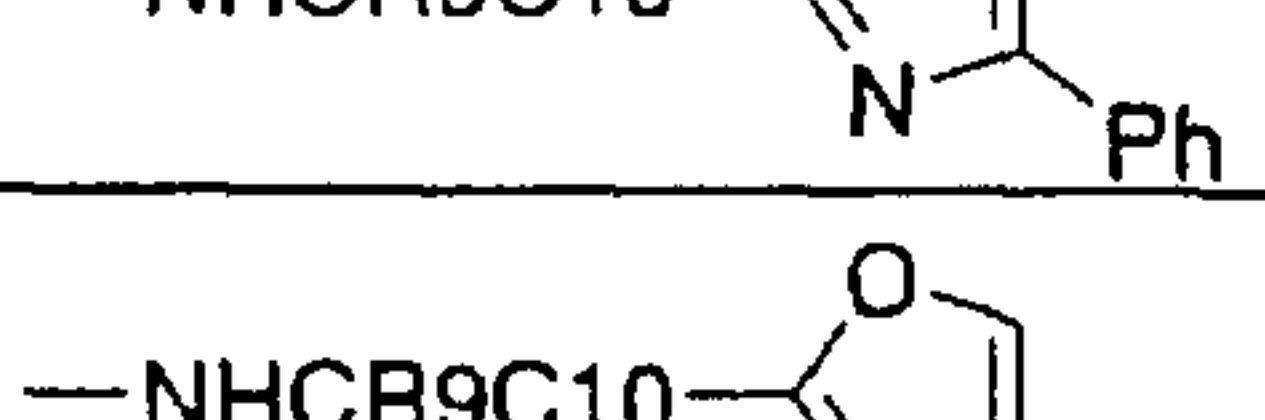
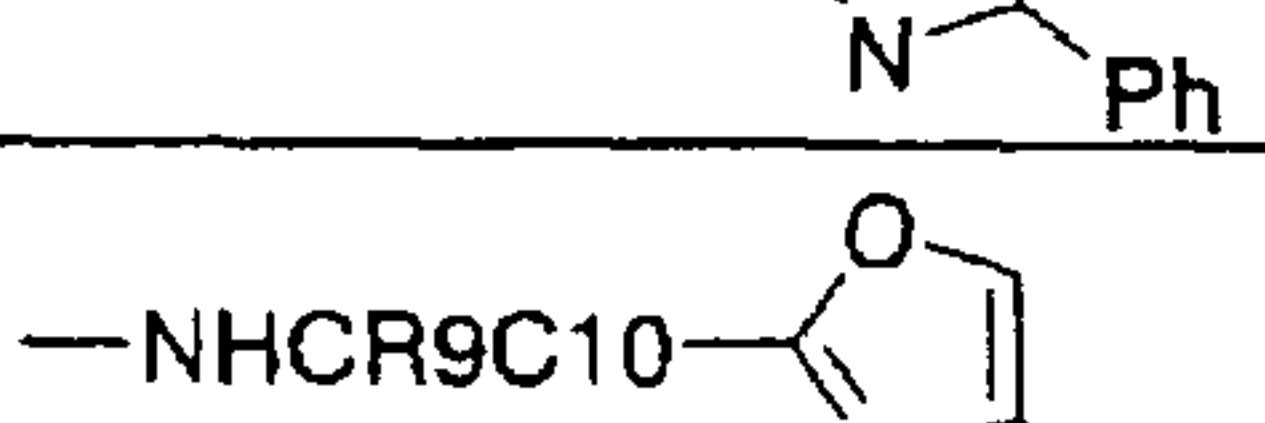
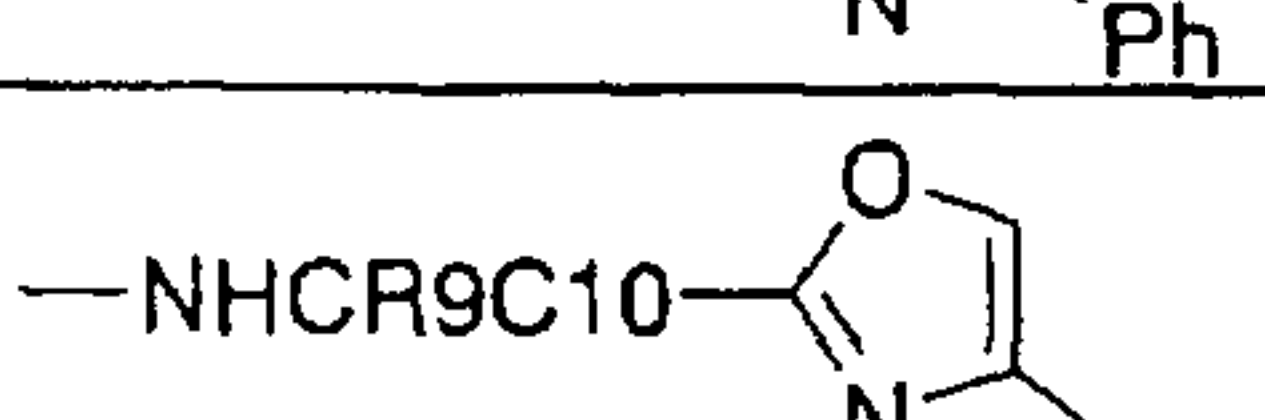
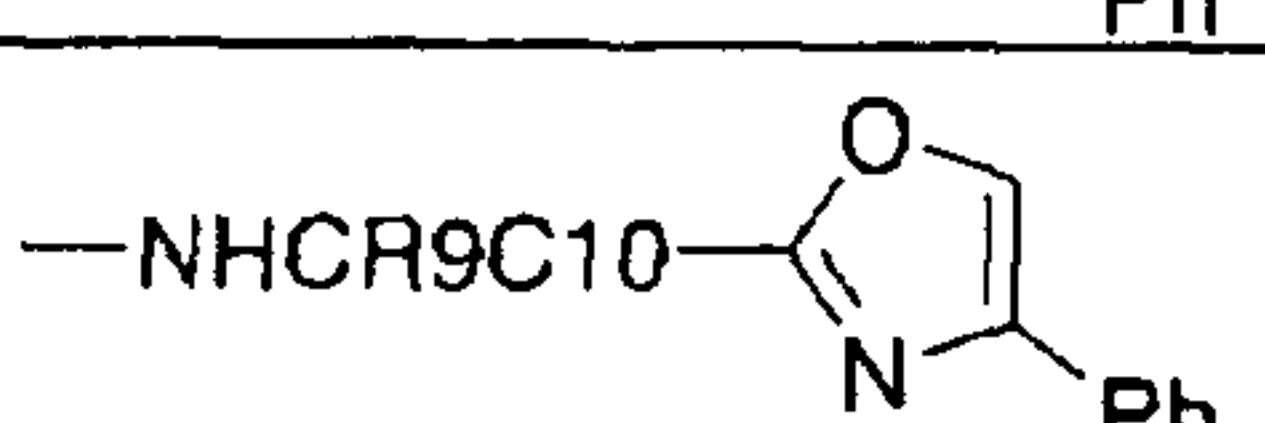
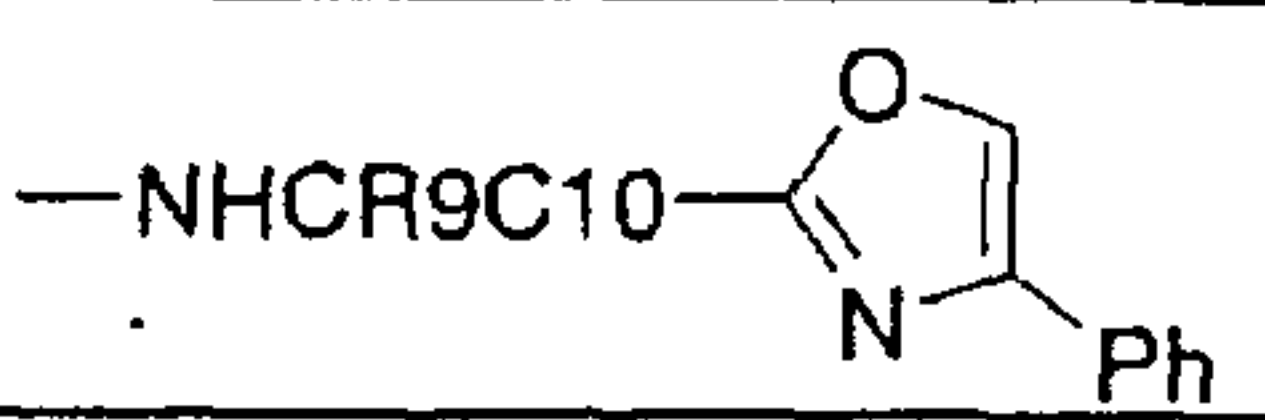
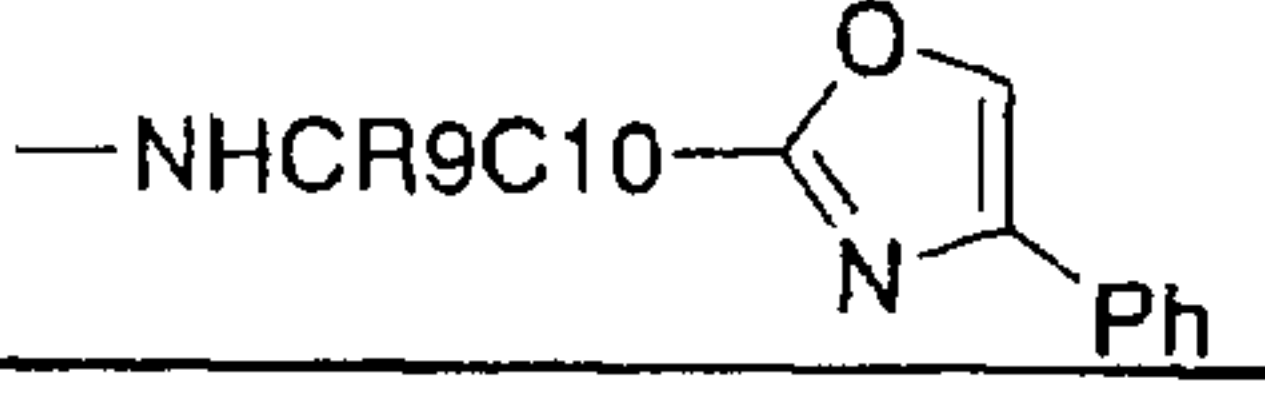
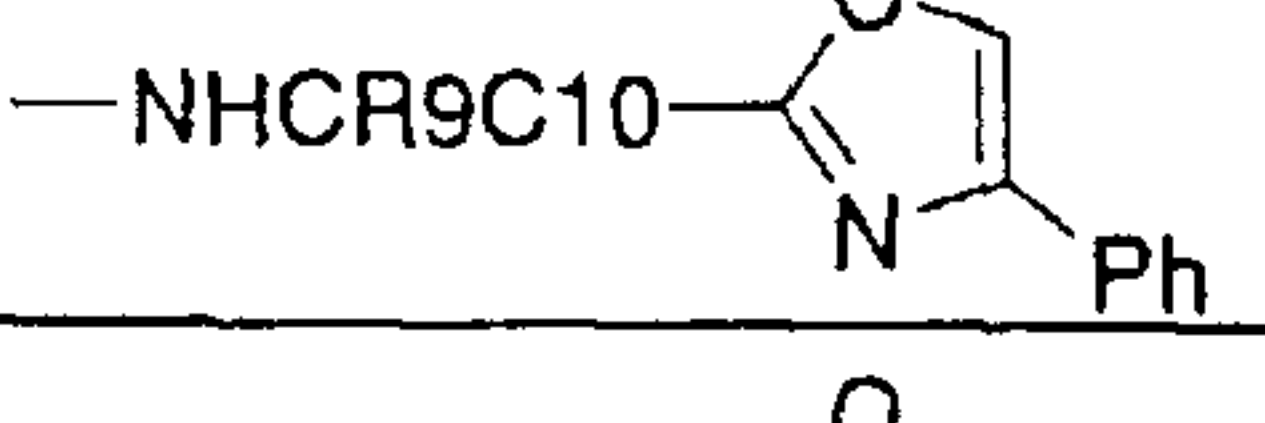
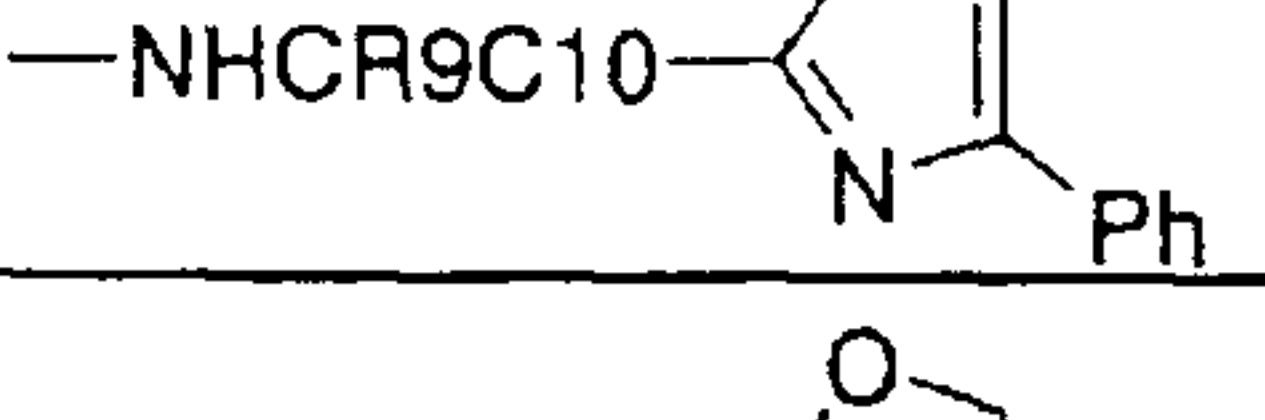
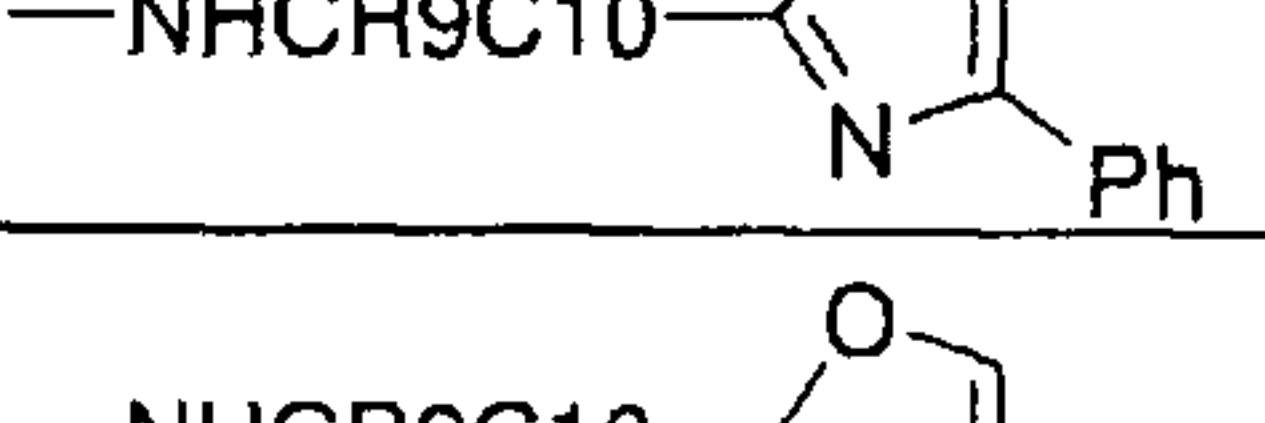
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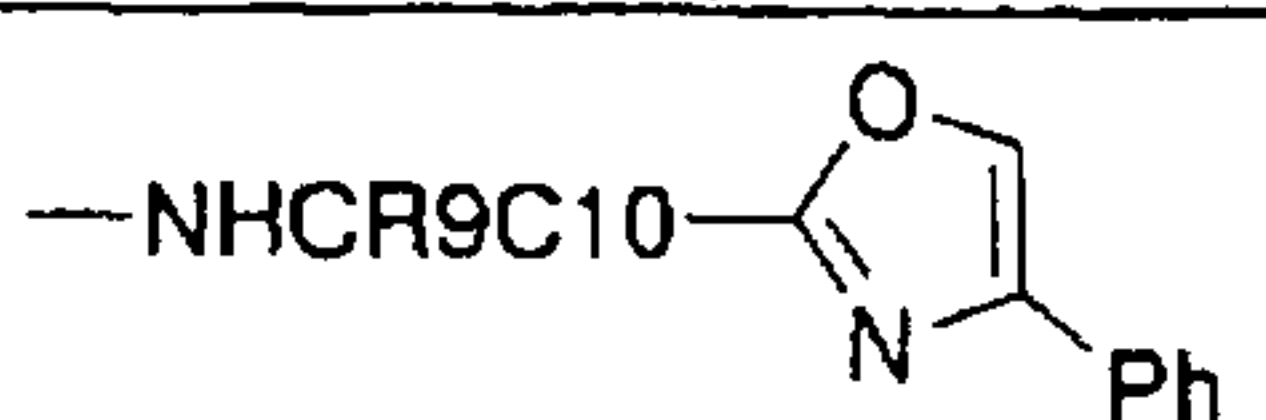
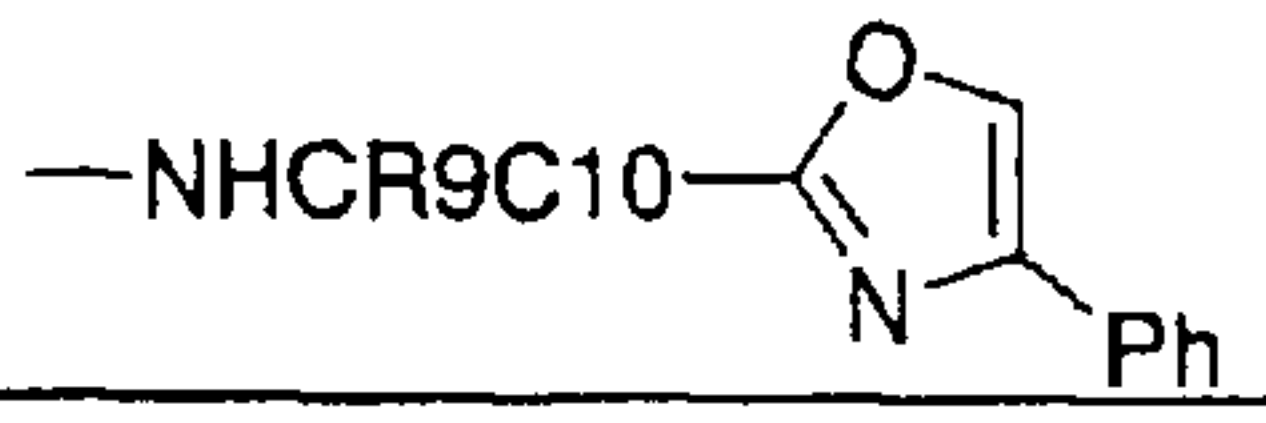
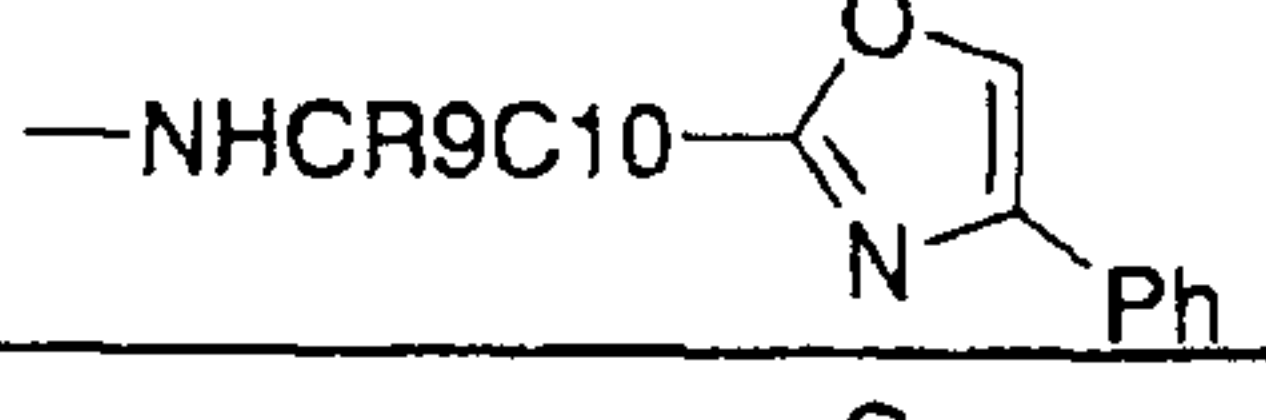
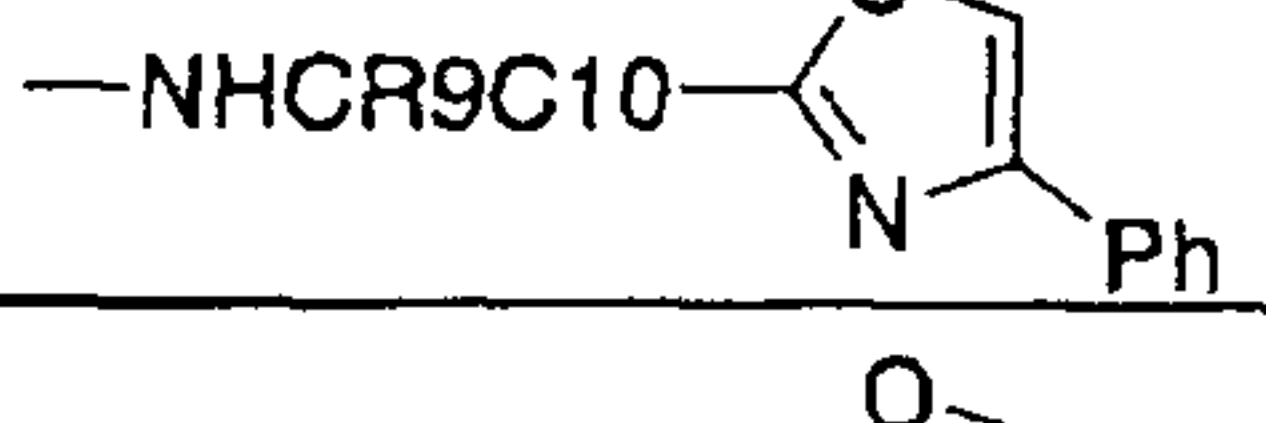
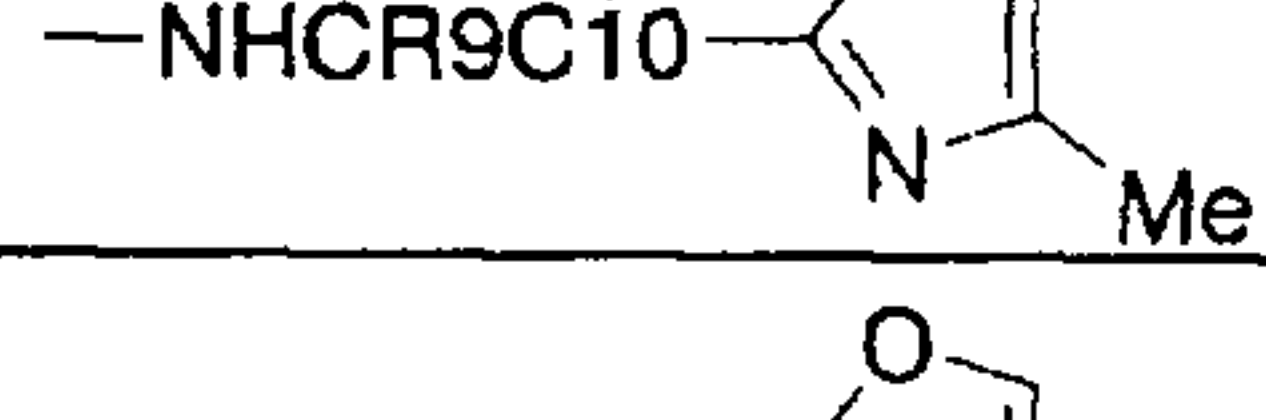
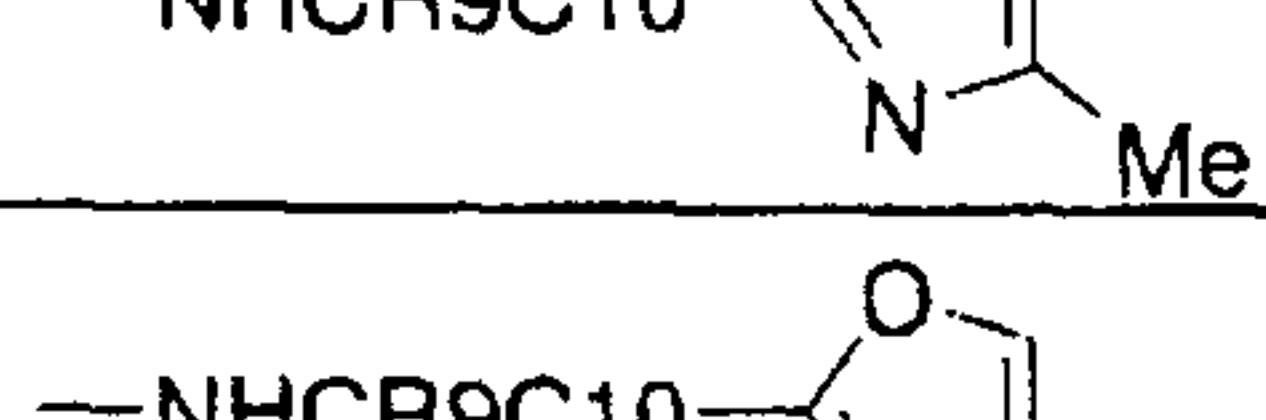
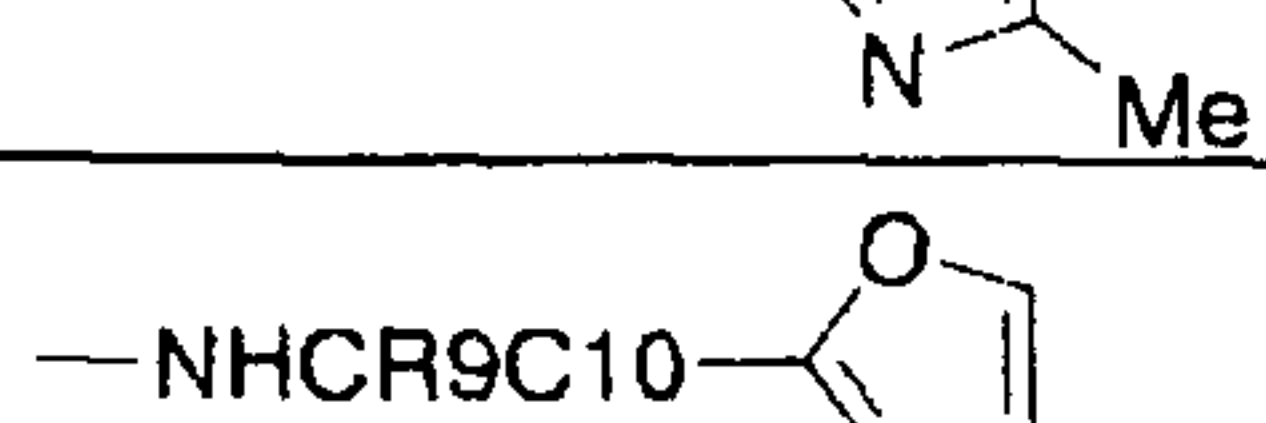
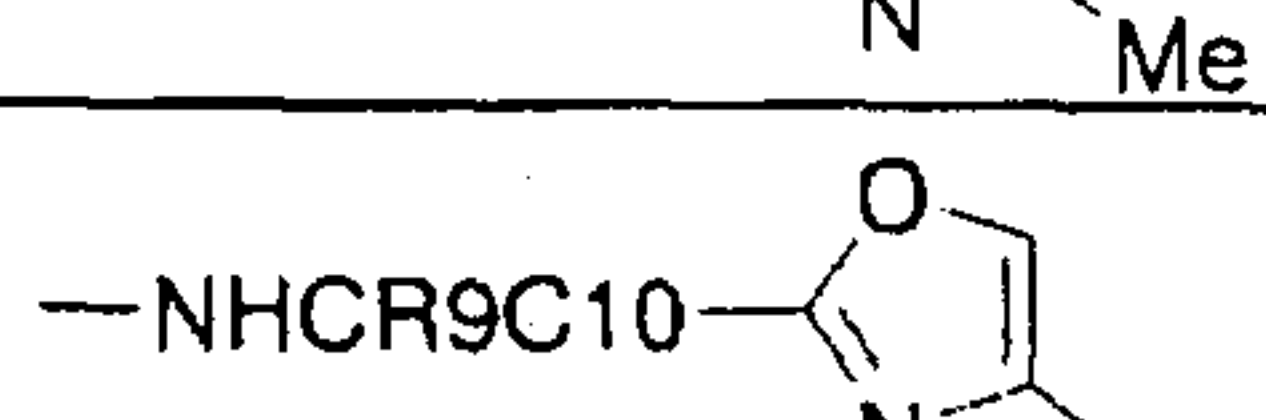
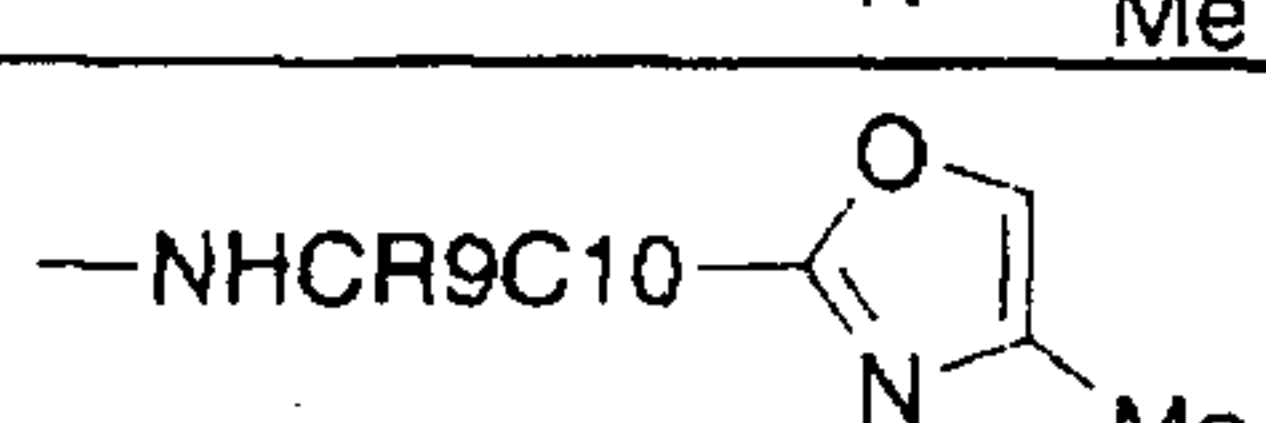
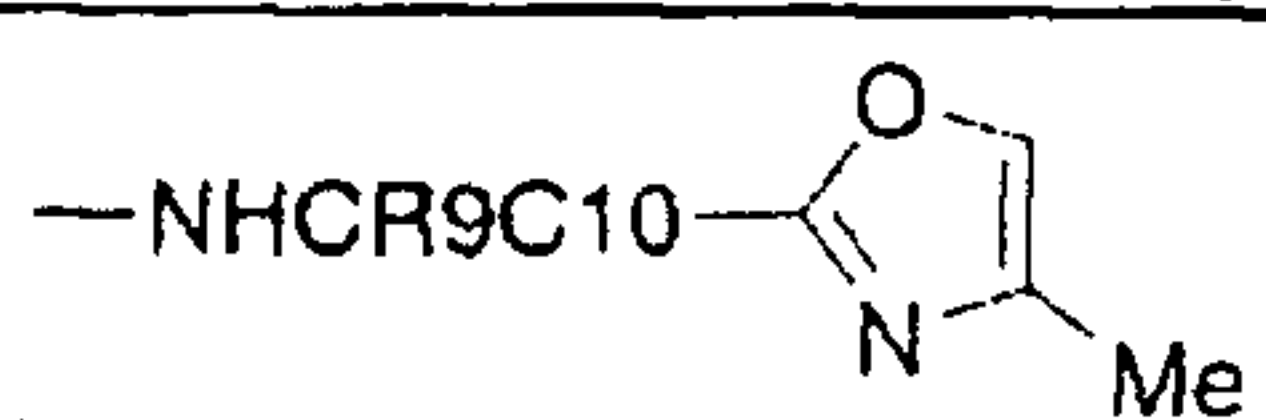
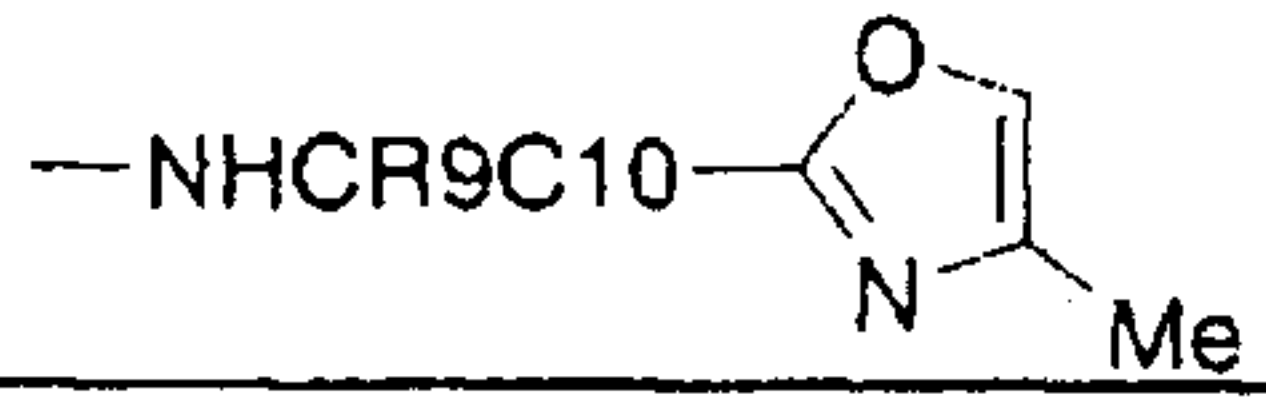
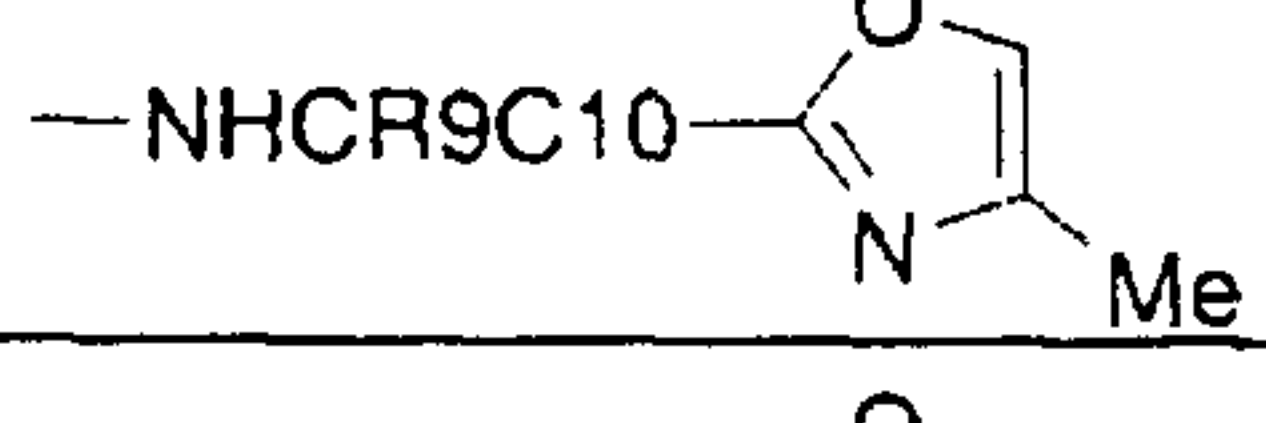
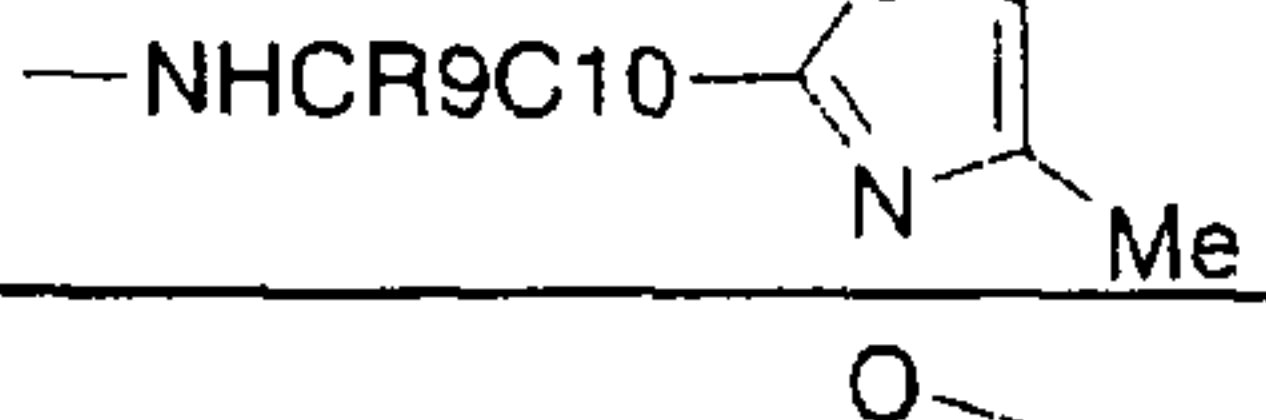
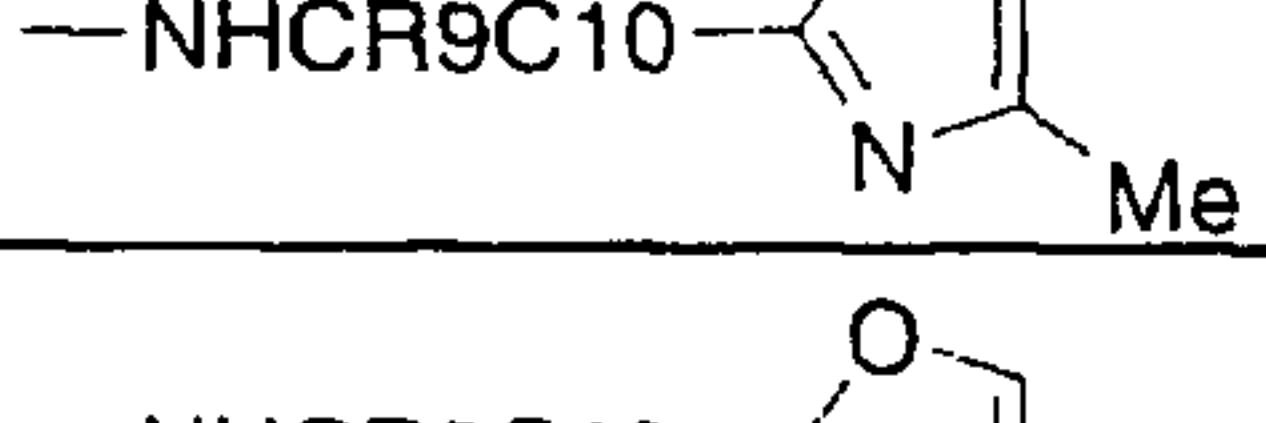
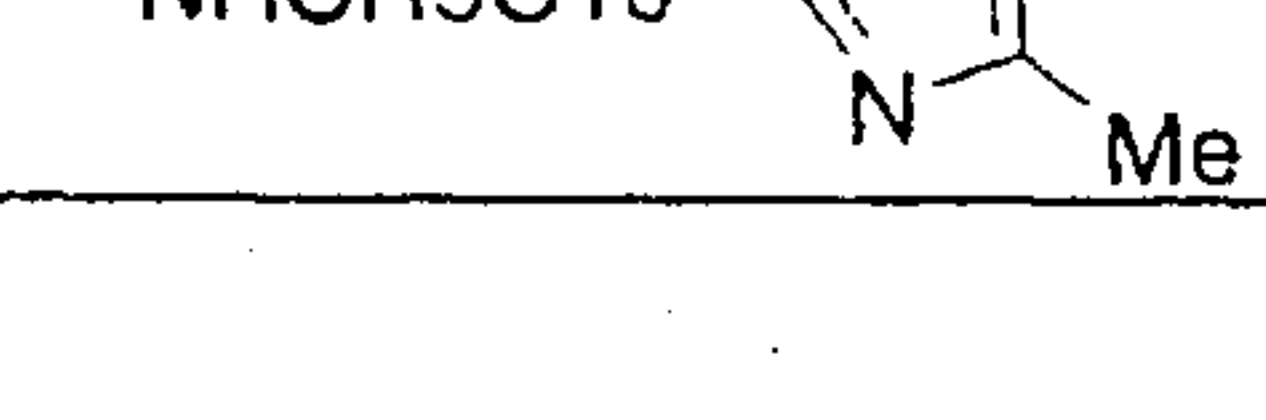
	NR1R2	CR9R10
JU		Ri
JV		Rj
JW		Rk
JX		RI
JY		Rm
JZ		Rn
KA		Ro
KB		Rp
KC		Rq
KD		Rr
KE		Rs
KF		Rt
KG		Ra
KH		Rb
KI		Rc
KJ		Rd

	NR1R2	CR9R10
KK		Re
KL		Rf
KM		Rg
KN		Rh
KO		Ri
KP		Rj
KQ		Rk
KR		RI
KS		Rm
KT		Rn
KU		Ro
KV		Rp
KW		Rq
KX		Rr
KY		Rs
KZ		Rt

[0023]

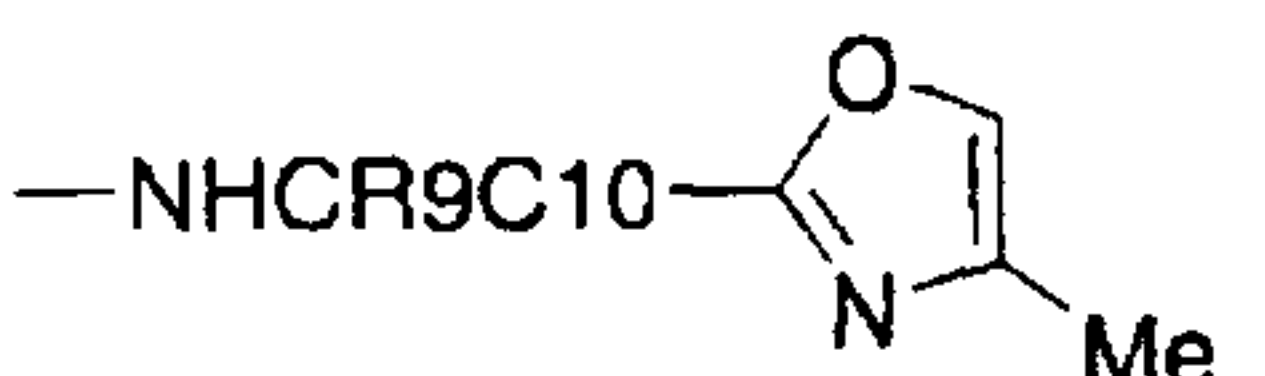
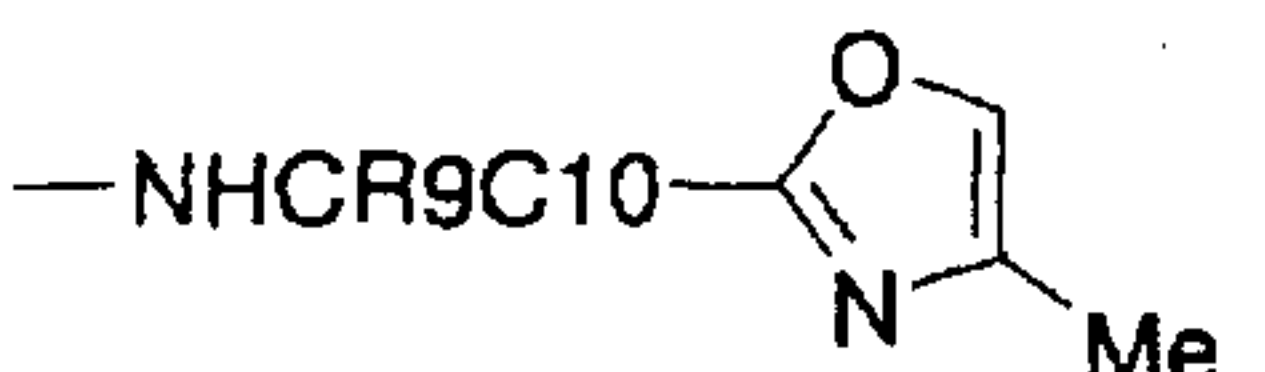
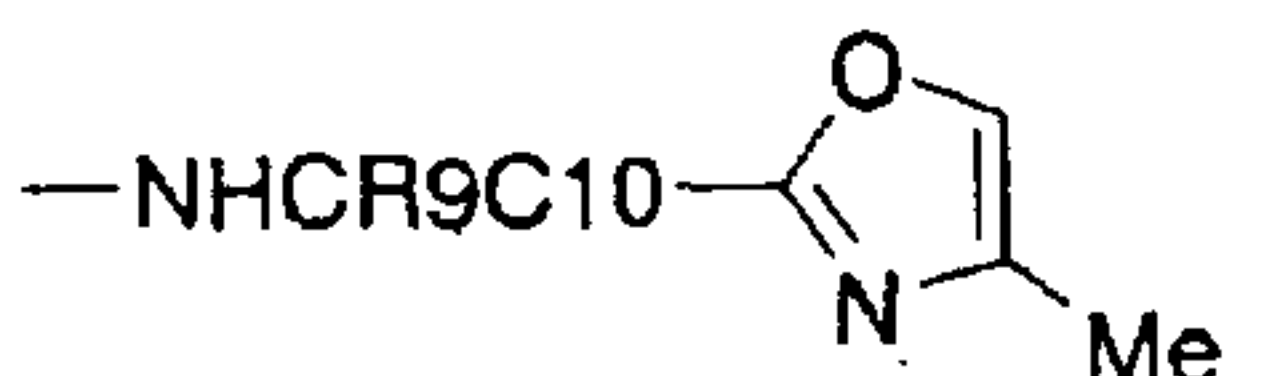
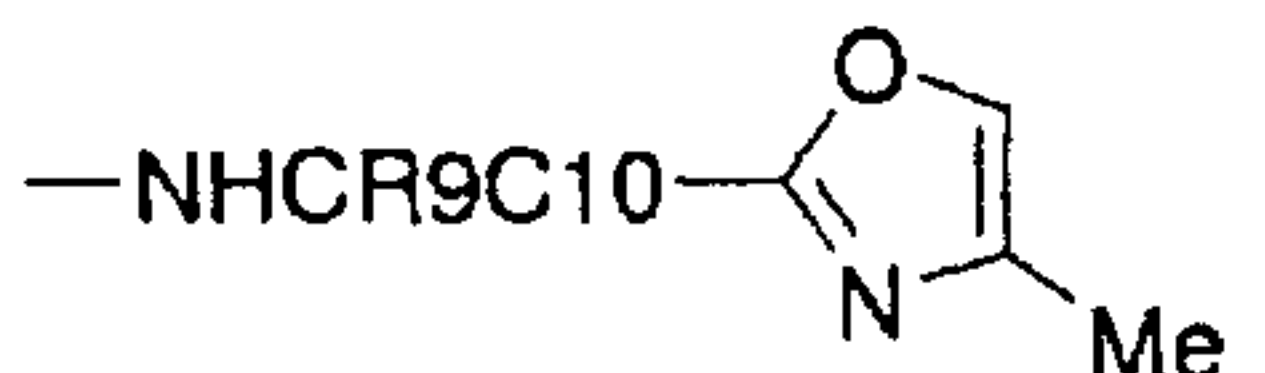
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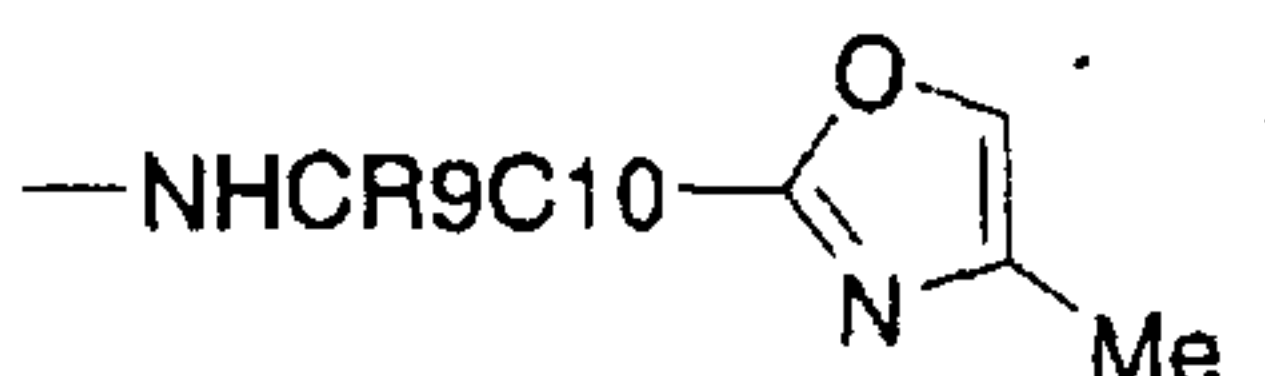
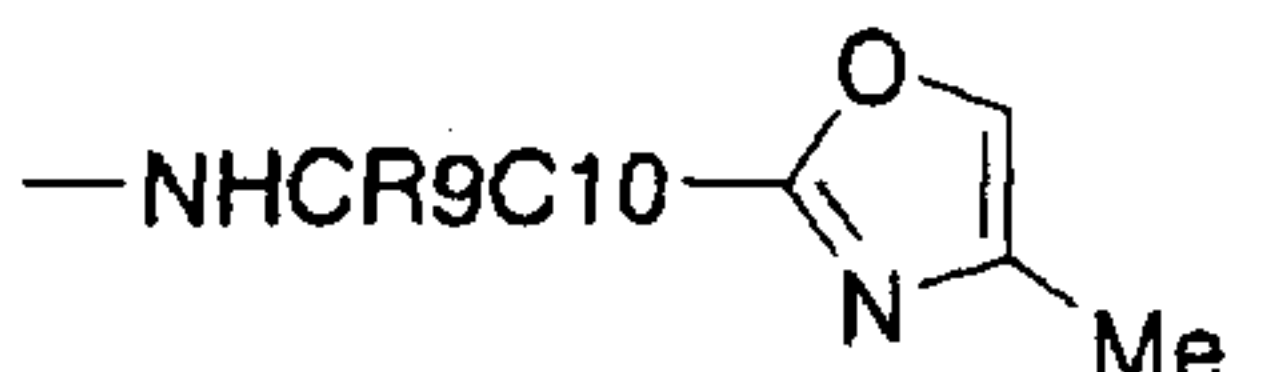
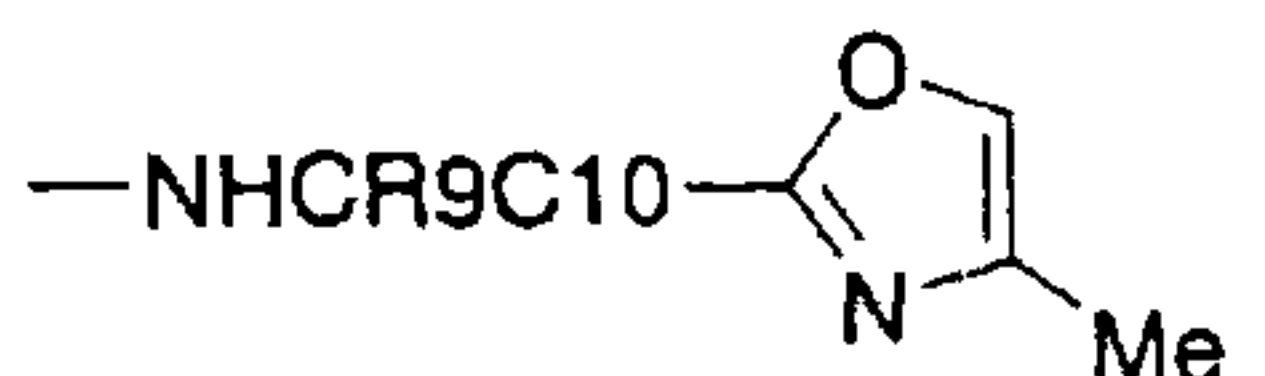
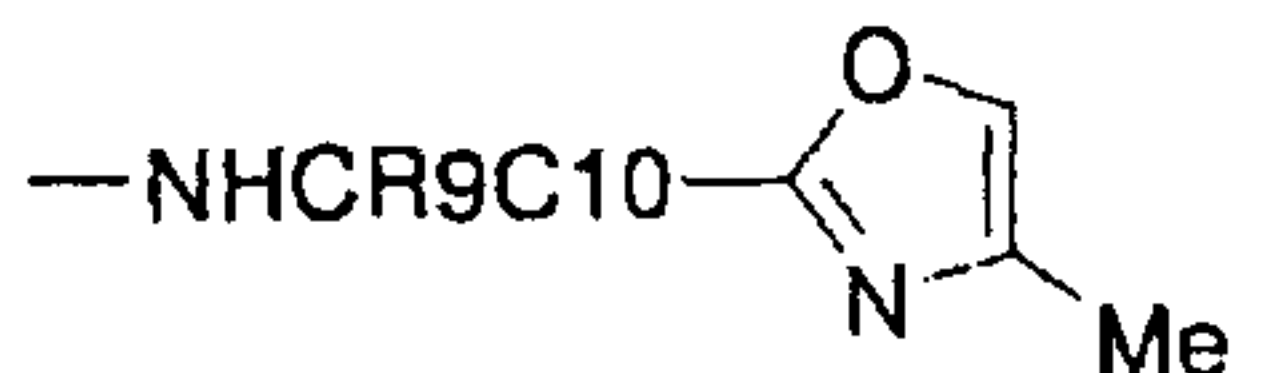
	NR1R2	CR9R10
LA		Ra
LB		Rb
LC		Rc
LD		Rd
LE		Re
LF		Rf
LG		Rg
LH		Rh
LI		Ri
LJ		Rj
LK		Rk
LL		RI
LM		Rm
LN		Rn
LO		Ro
LP		Rp

	NR1R2	CR9R10
LQ		Rq
LR		Rr
LS		Rs
LT		Rt
LU		Ra
LV		Rb
LW		Rc
LX		Rd
LY		Re
LZ		Rf
MA		Rg
MB		Rh
MC		Ri
MD		Rj
ME		Rk
MF		RI

[0024]

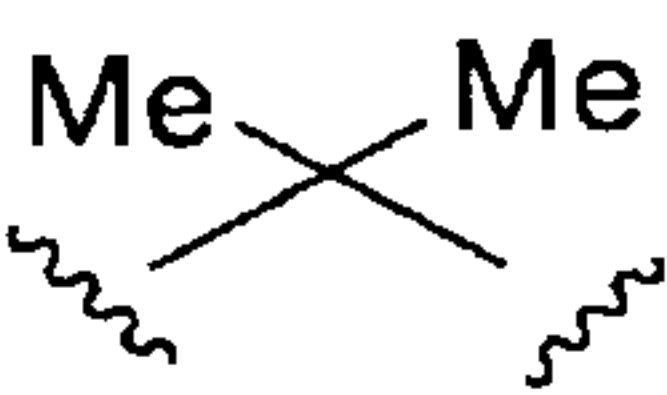
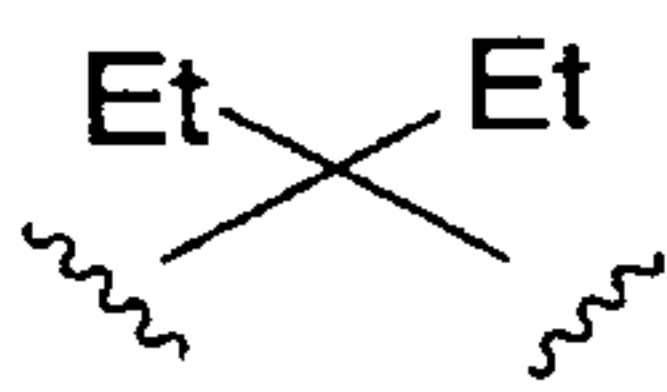
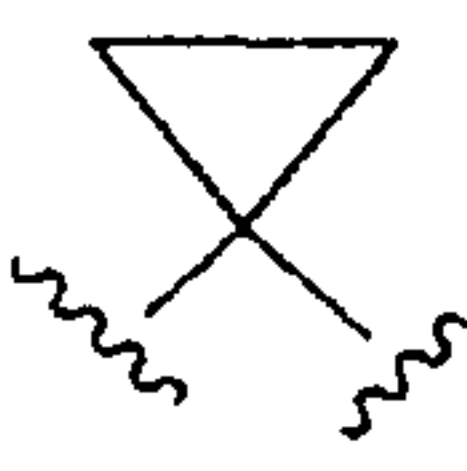
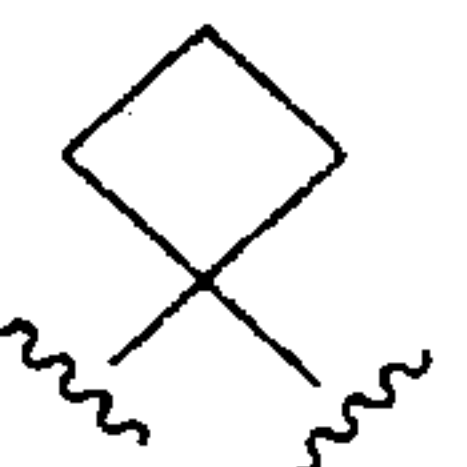
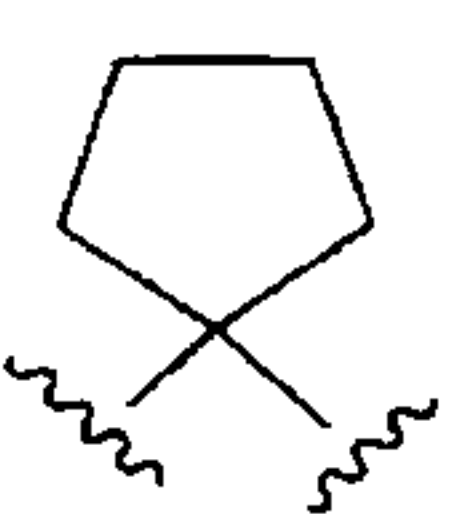
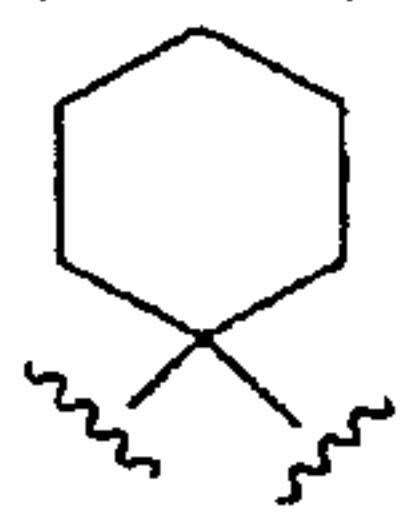
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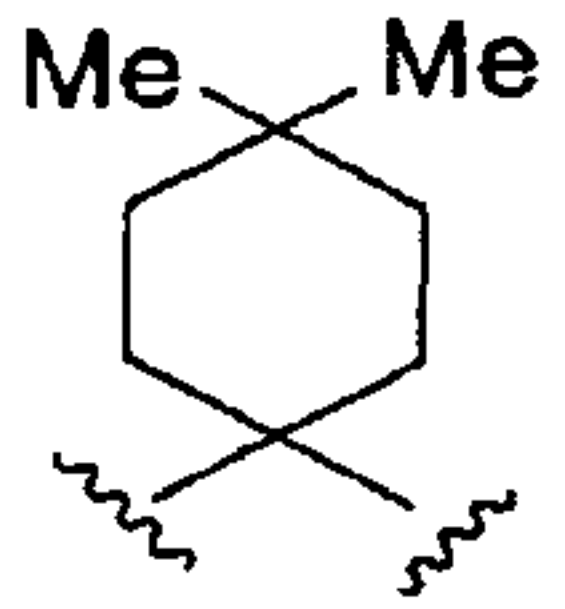
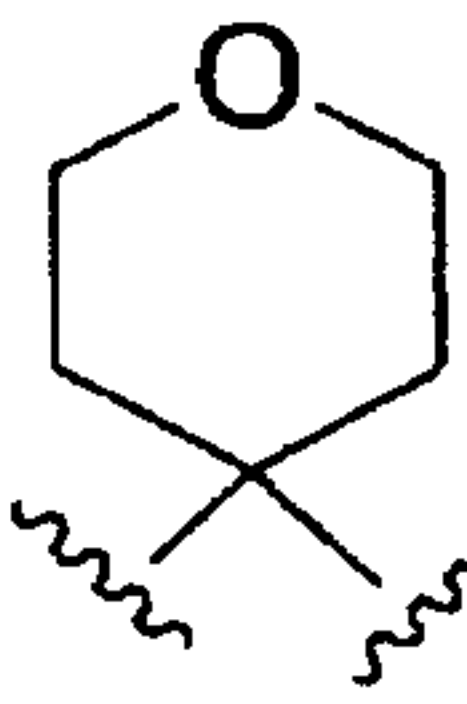
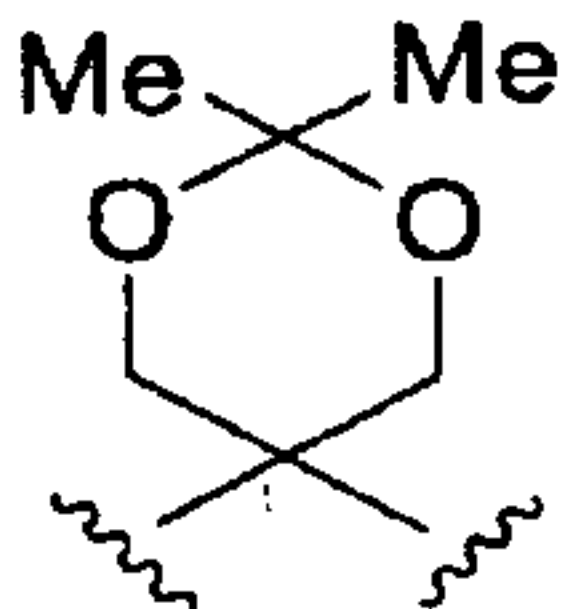
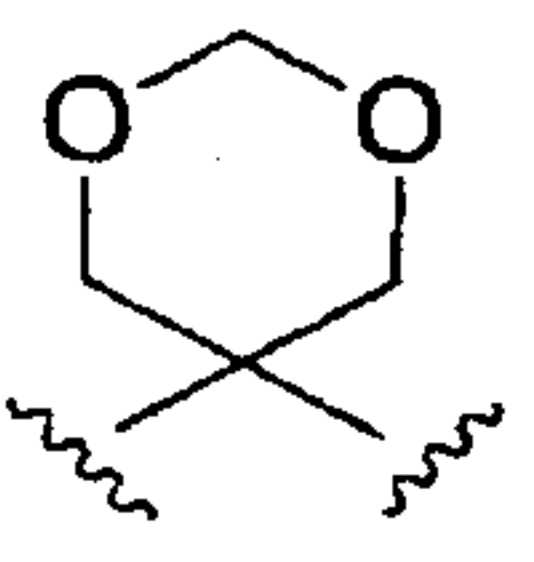
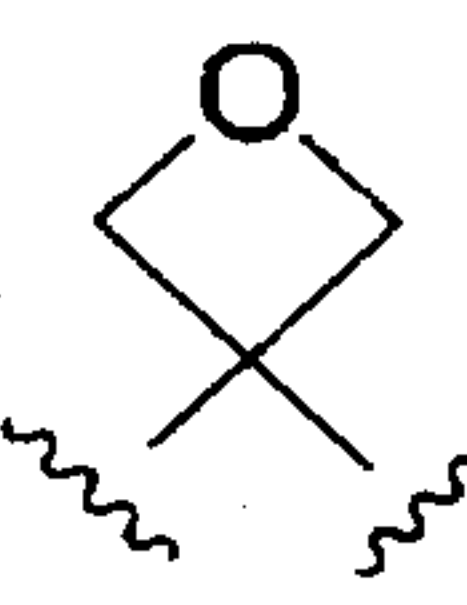
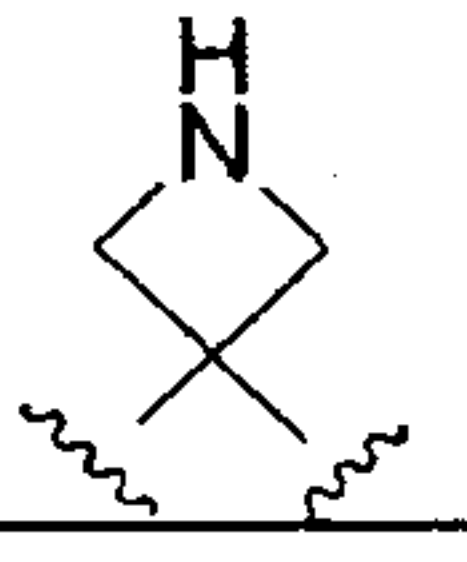
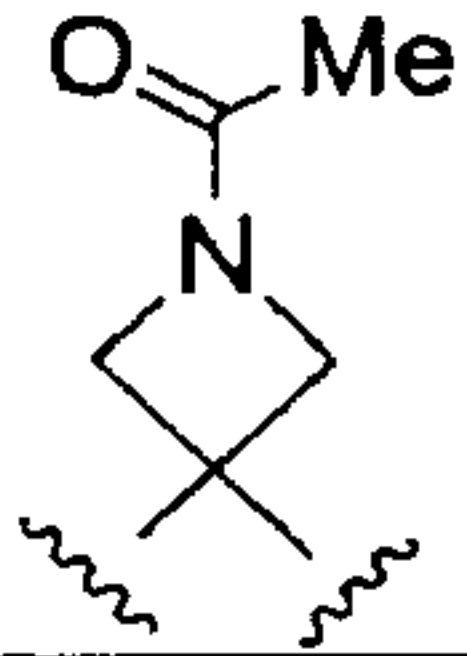
	NR1R2	CR9R10
MG		Rm
MH		Rn
MI		Ro
MJ		Rp

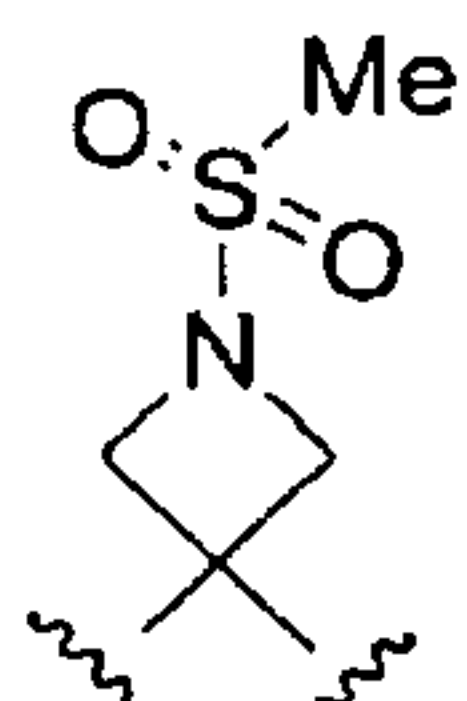
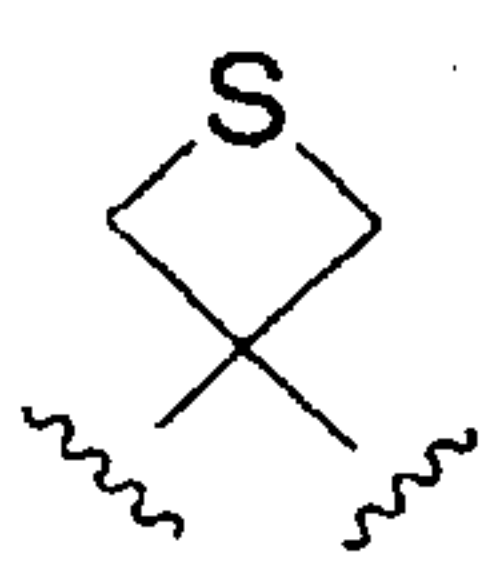
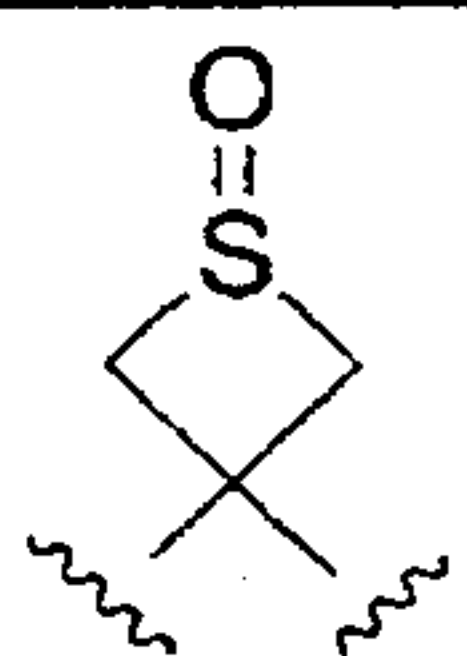
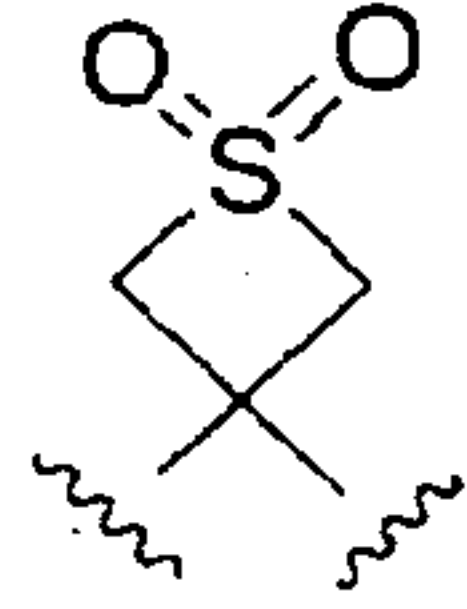
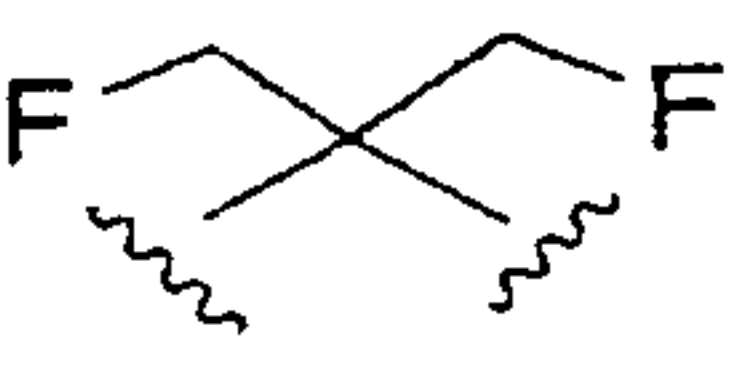
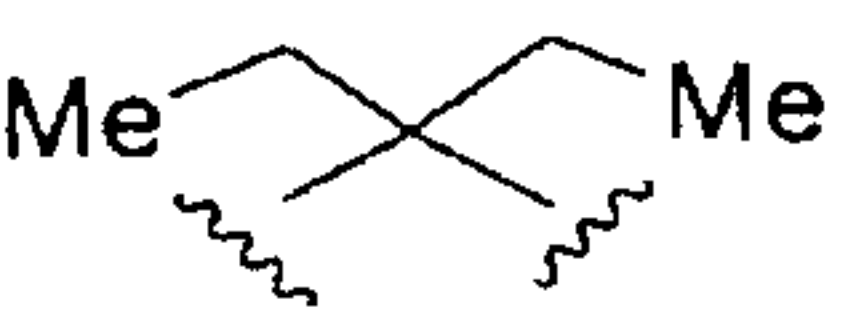
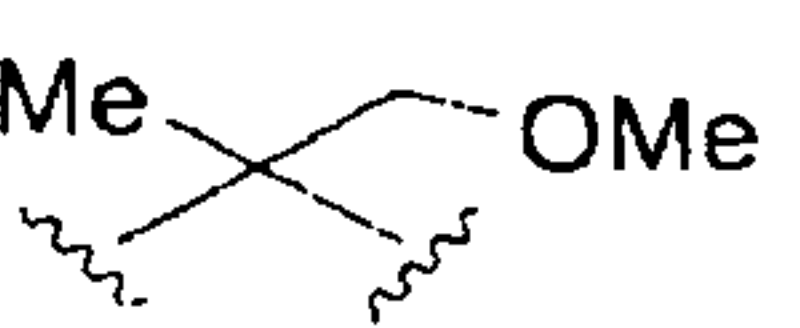
	NR1R2	CR9R10
MK		Rq
ML		Rr
MM		Rs
MN		Rt

In the above Tables, CR⁹CR¹⁰ is represented by the following symbol.

[Table 7]

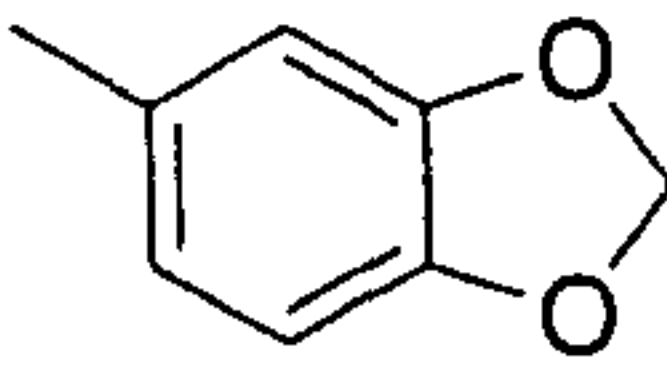
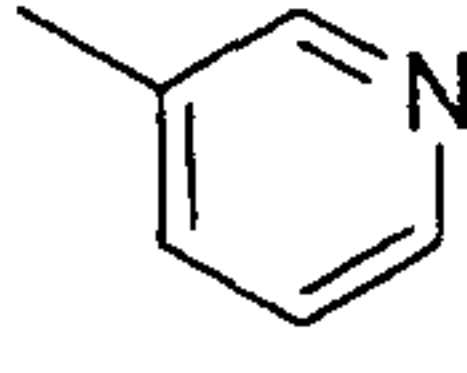
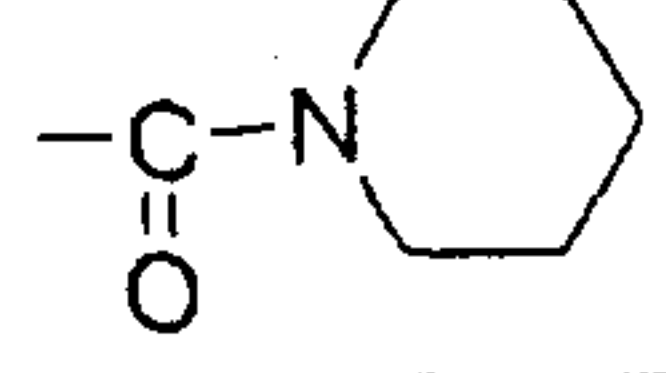
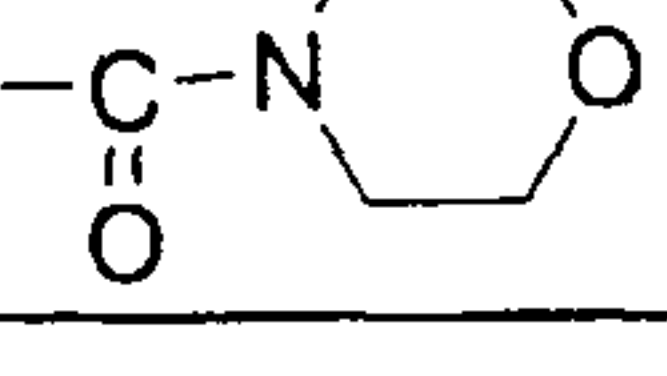
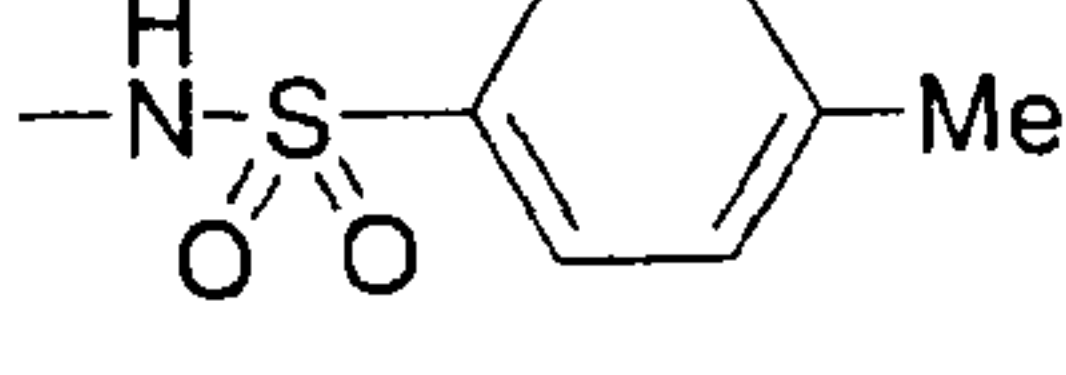
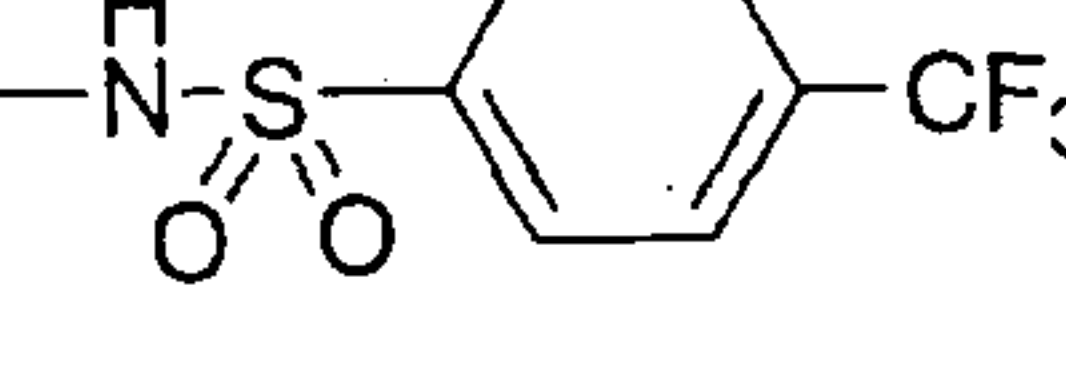
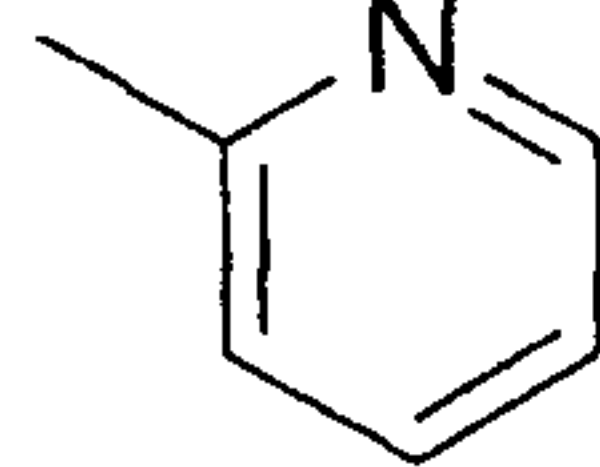
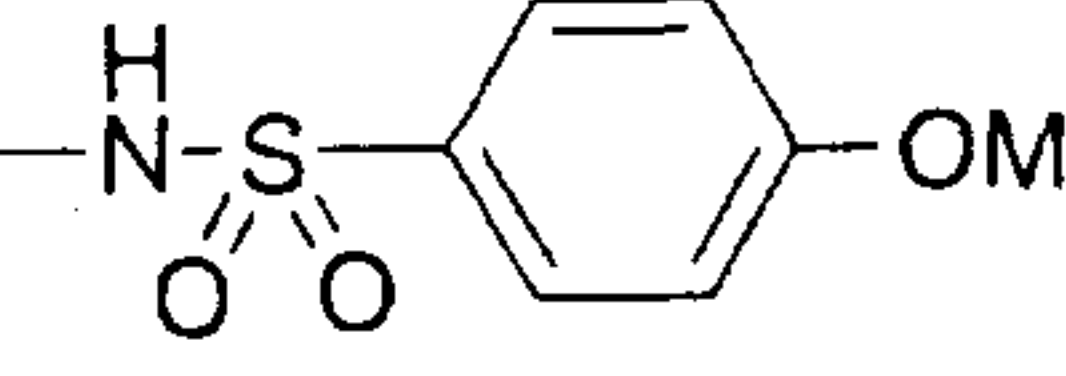
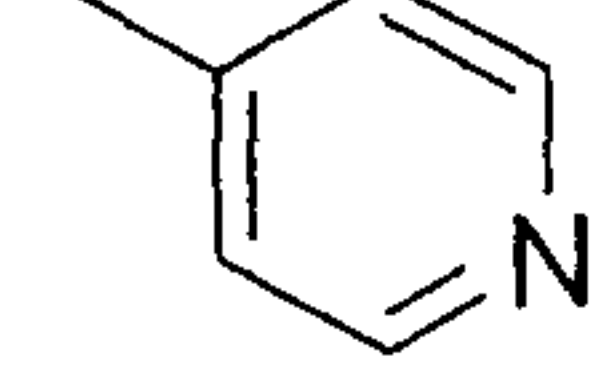
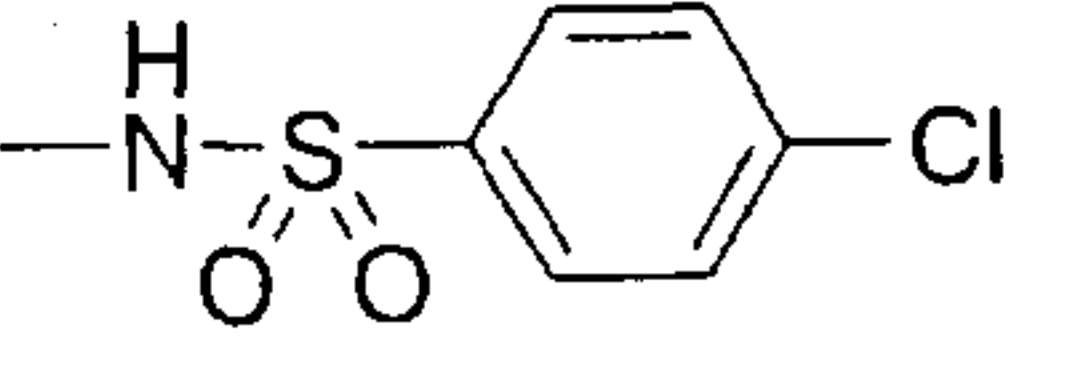
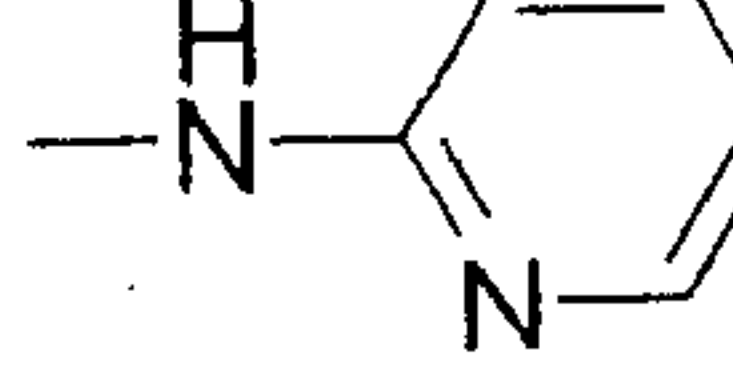
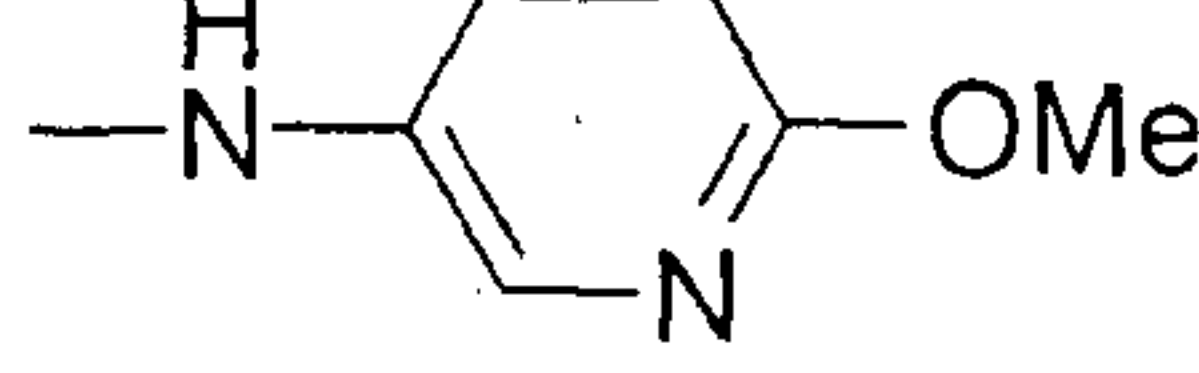
	CR9R10
Ra	
Rb	
Rc	
Rd	
Re	
Rf	

	CR9R10
Rg	
Rh	
Ri	
Rj	
Rk	
RI	
Rm	

	CR9R10
Rn	
Ro	
Rp	
Rq	
Rr	
Rs	
Rt	

[0025]

[Table 8]

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

[0026]

(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),
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[0028]

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[0029]

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[0031]

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[0032]

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[0033]

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[0034]

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[0035]

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[0038]

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[0039]

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.

[0040]

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.

[0041]

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 ED₅₀ value is calculated by reverse estimation of regression a SAS program using %MPE and letting a value of a control group to be 100%.

[0042]

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.

[0043]

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 disease 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.

[0044]

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 ondansetron 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 μ g to 1 g/day, preferably 0.01 to 200 mg/day when orally administered to an adult, and is usually 0.1 μ g to 10 g/day, preferably 0.1 to 2 g/day when parenterally administered.

Following Examples and Test Examples illustrate the present

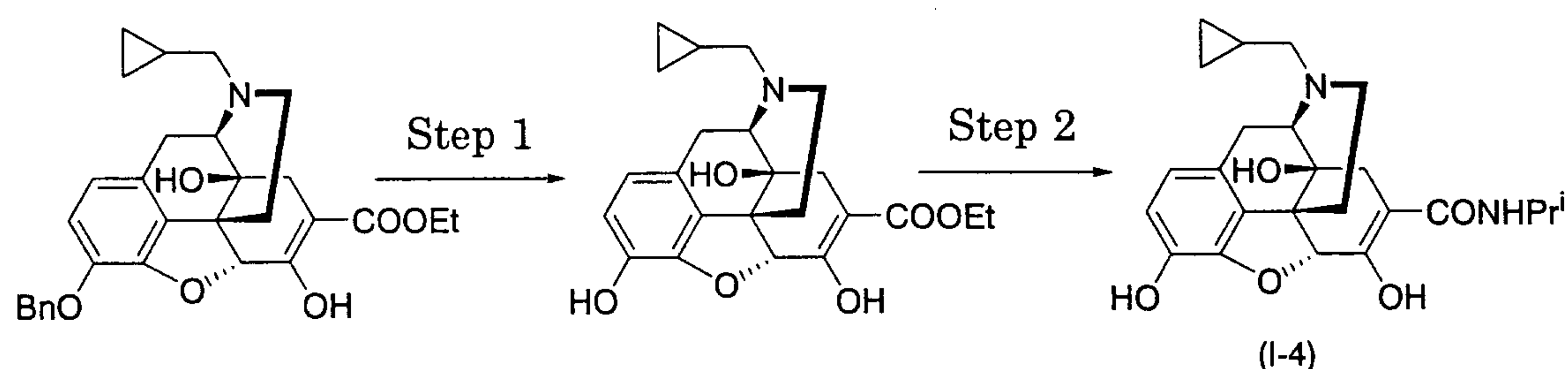
invention in more detail, but the present invention is not limited by these Examples.

[Example 1]

[0045]

Production of Compound (I-4)

[Chemical formula 11]



wherein Bn indicates benzyl, Et indicates ethyl, and Prⁱ indicates isopropyl.

[0046]

(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 (Perlmans catalyst) (1.2 g), and the mixture was vigorously stirred for 2 hours under a hydrogen atmosphere. After filtration of the catalyst, the filtrate was concentrated, and the residue was crystallized from ethyl acetate and hexane to obtain 8.96 g (92%) of the title compound as colorless crystals.

NMR (300MHz, CDCl₃)

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 ($C_{23}H_{27}NO_6 \cdot 0.2H_2O$)

(Calculated value) C, 66.24; H, 6.62; N, 3.36.

(Found value) C, 66.29; H, 6.50; N, 3.45.

[0047]

(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 5mol/L hydrochloric acid was added to the reaction mixture, and stirring was continued at 70°C for 20 minutes. After the reaction solution was cooled, pH value was adjusted to 8.5 with aqueous ammonia, followed by extraction with ethyl acetate. The organic layer was washed with water, and dried, and the solvent was evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol= 99:1 to 94:6) to obtain 140 mg of the title compound at a yield of 68%.

NMR (300MHz, d_6 -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 ($C_{24}H_{30}N_2O_5 \cdot 0.2H_2O$)

(Calculated value) C, 67.02; H, 7.12; N, 6.51.

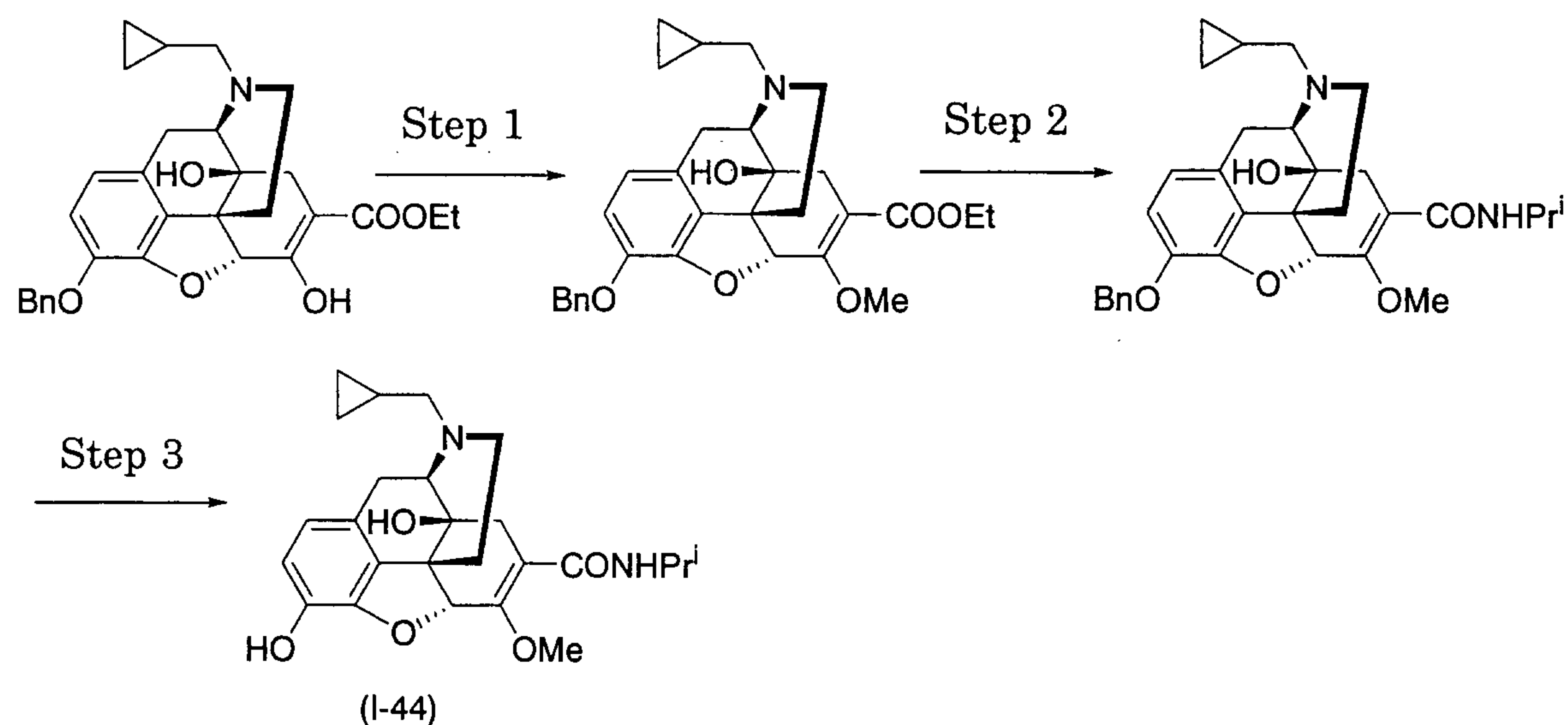
(Found value) C, 67.02; H, 7.20; N, 6.49.

[Example 2]

[0048]

Preparation of Compound (I-44)

[Chemical formula 12]



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

[0049]

(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 μ L, 1.5 mmol) and methanol (41 μ L, 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.

^1H 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)

[0050]

(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.

^1H 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)

[0051]

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

To a solution of

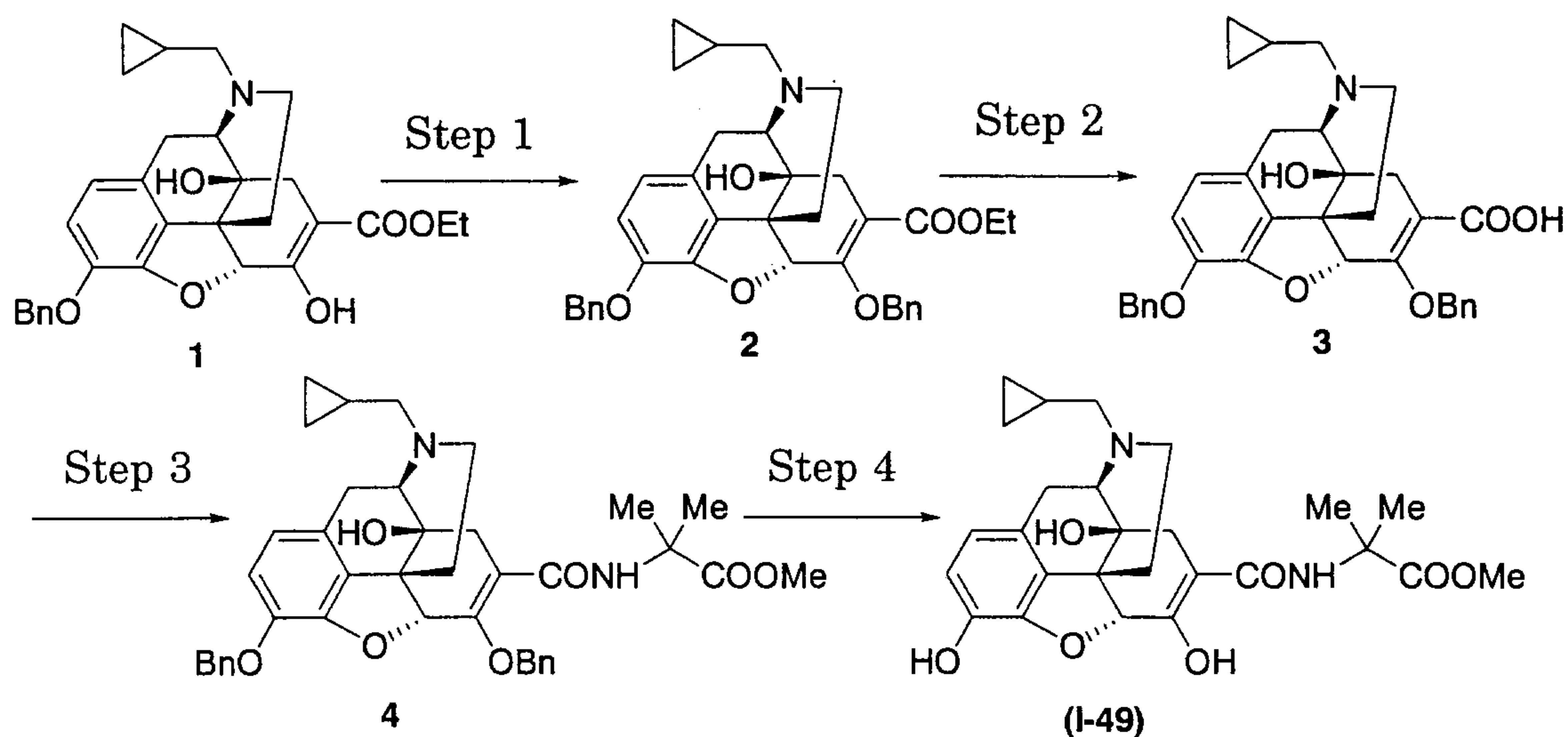
3-O-benzyl-7-isopropylaminocarbonyl-6-O-methylnaltrexone obtained in the second step (33 mg, 0.073 mmol) in tetrahydrofuran (5 mL) was added palladium hydroxide (33 mg), and the mixture was stirred for 1 hour under a hydrogen atmosphere. The reaction solution was filtered with CeliteTM, and the filtrate 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.

^1H 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]

[0052]

[Chemical formula 13]



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 $\rightarrow$ chloroform/methanol= 50/1) to obtain quantitatively the objective compound (2) (33.8 g) as a pale yellow oil.

^1H 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.

^1H 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-methylmorpholine (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.

¹H NMR (CDCl₃, 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.

¹H NMR (DMSO-d₆, 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)

[0053]

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, Prⁱ indicates isopropyl, and Ph indicates phenyl.

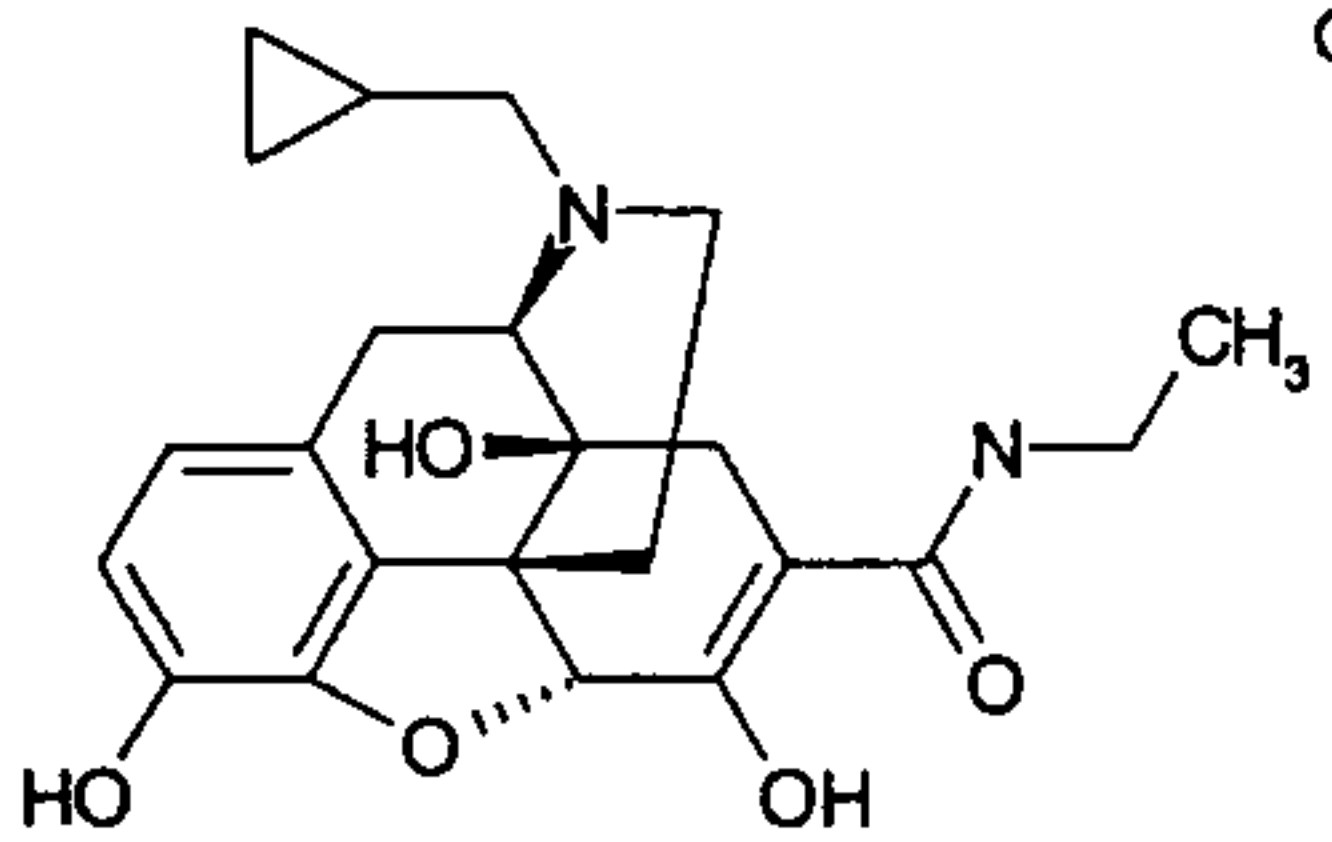
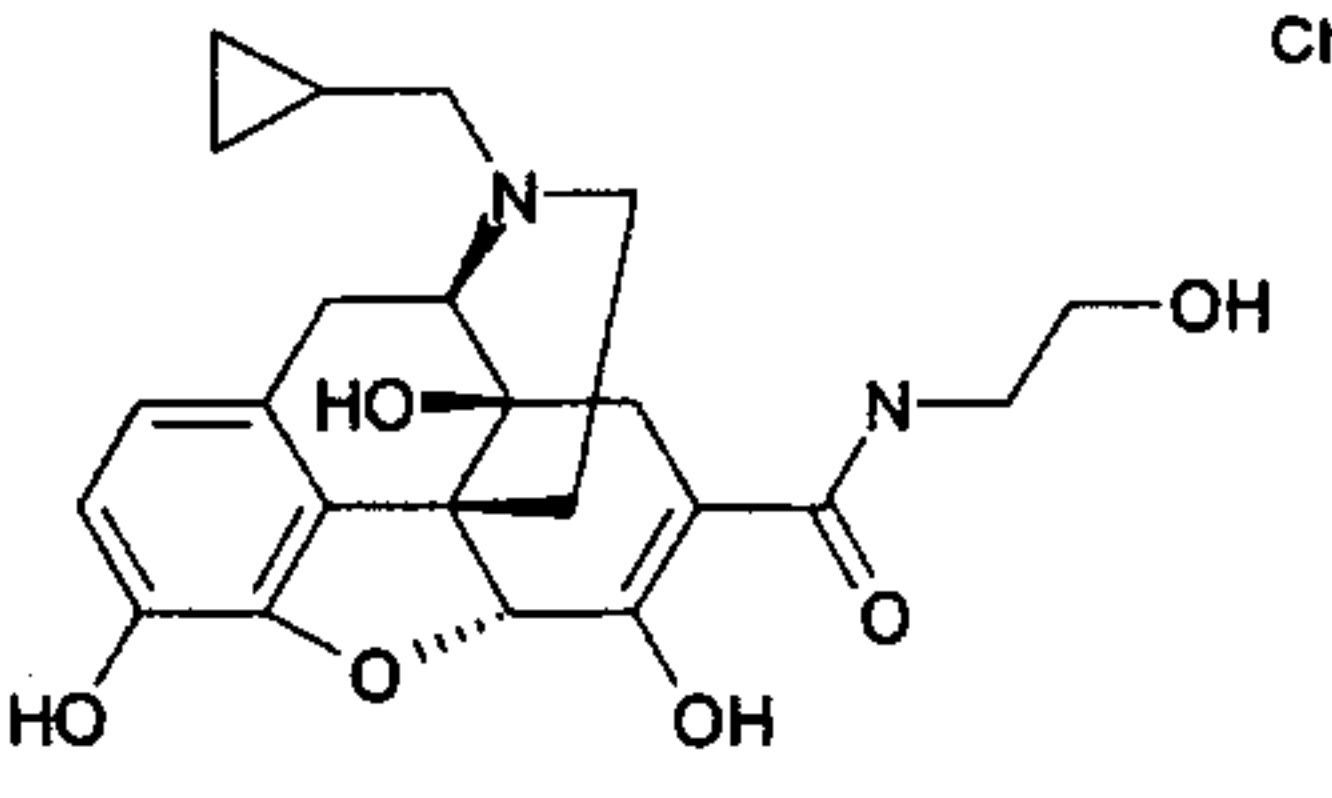
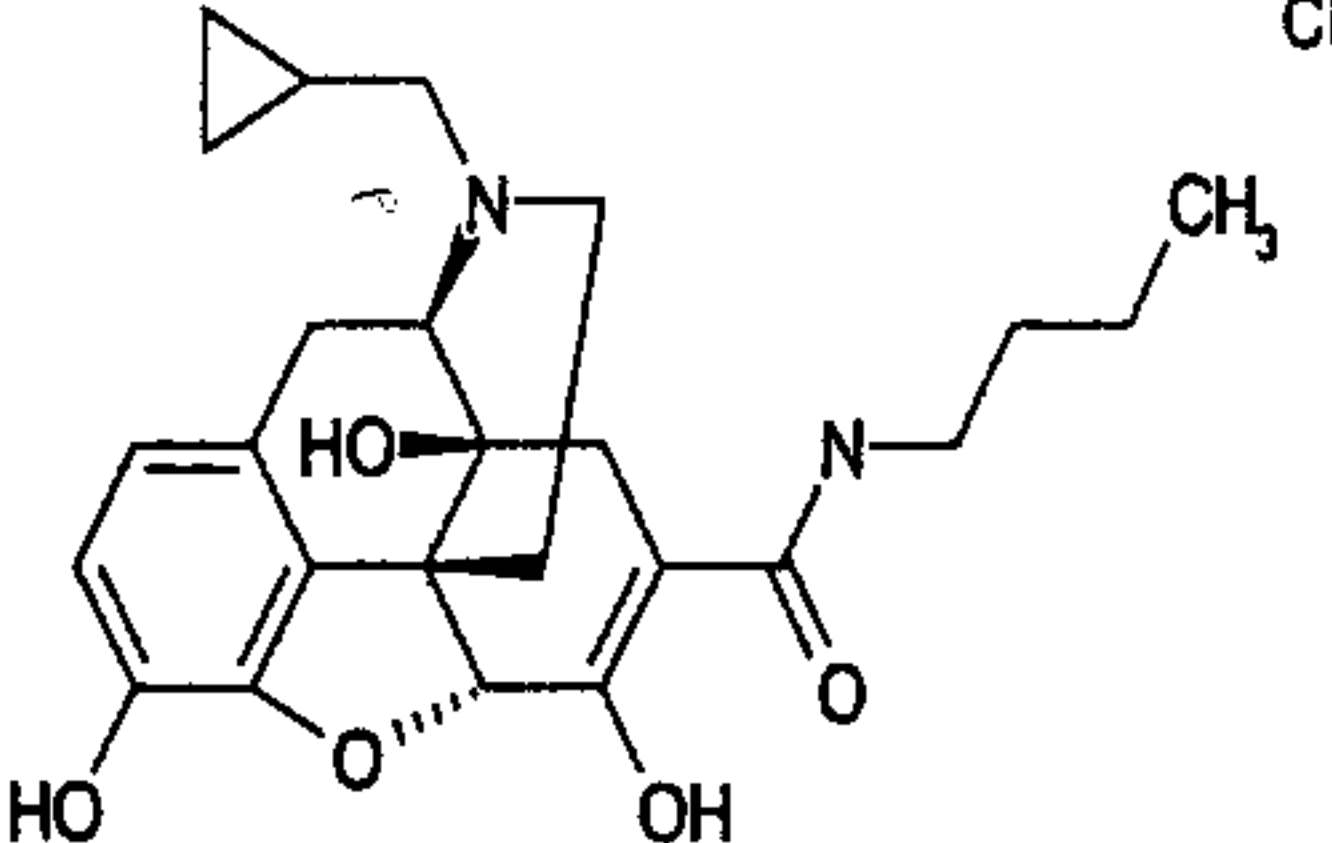
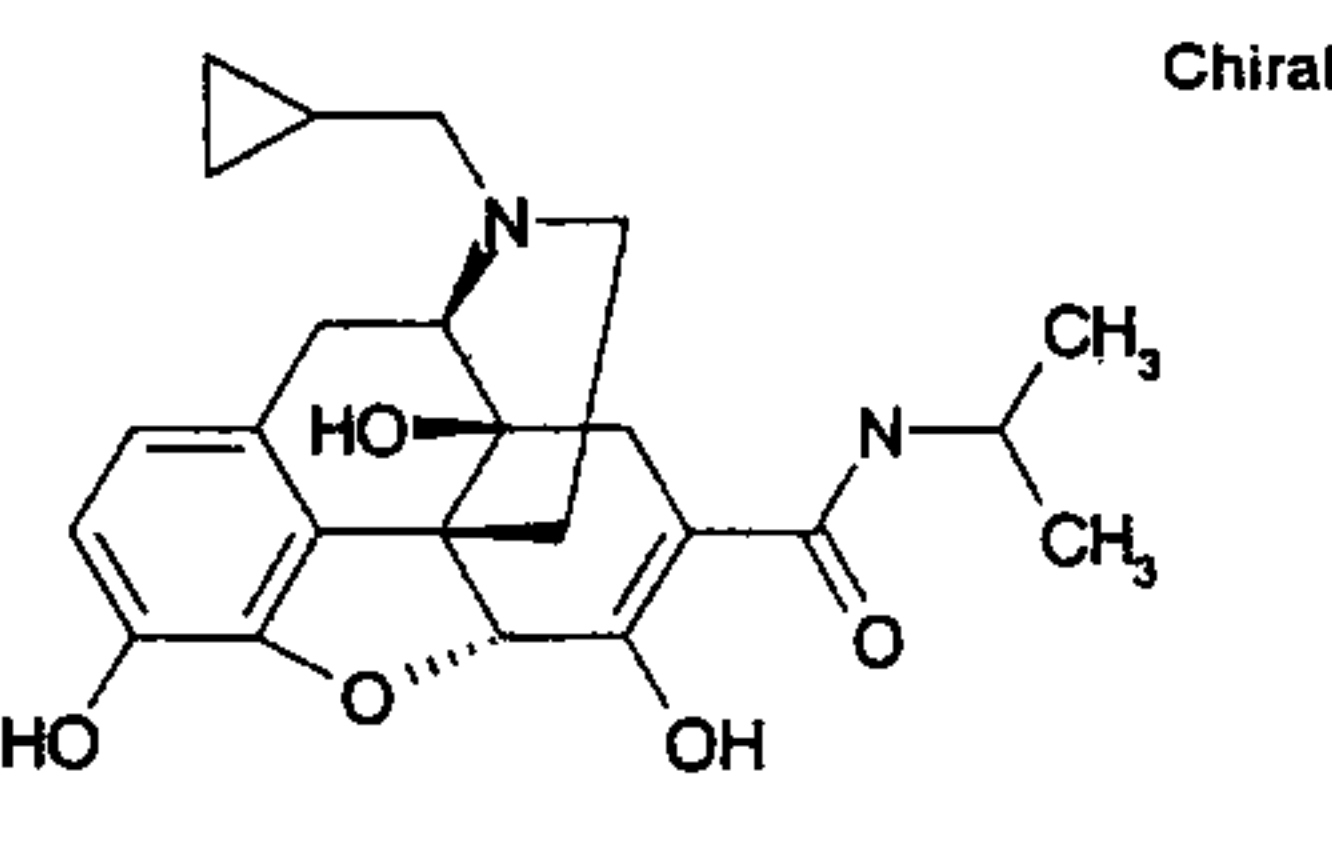
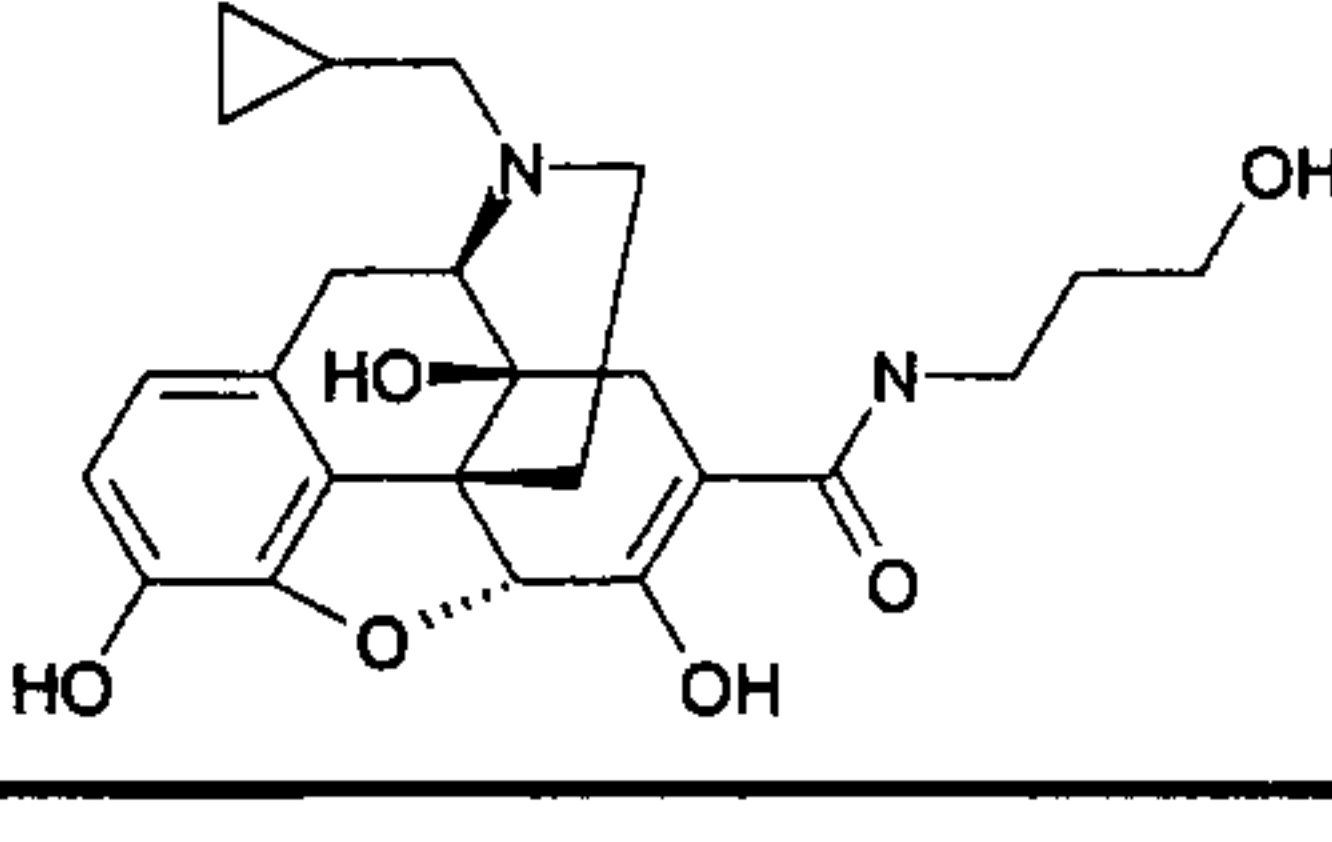
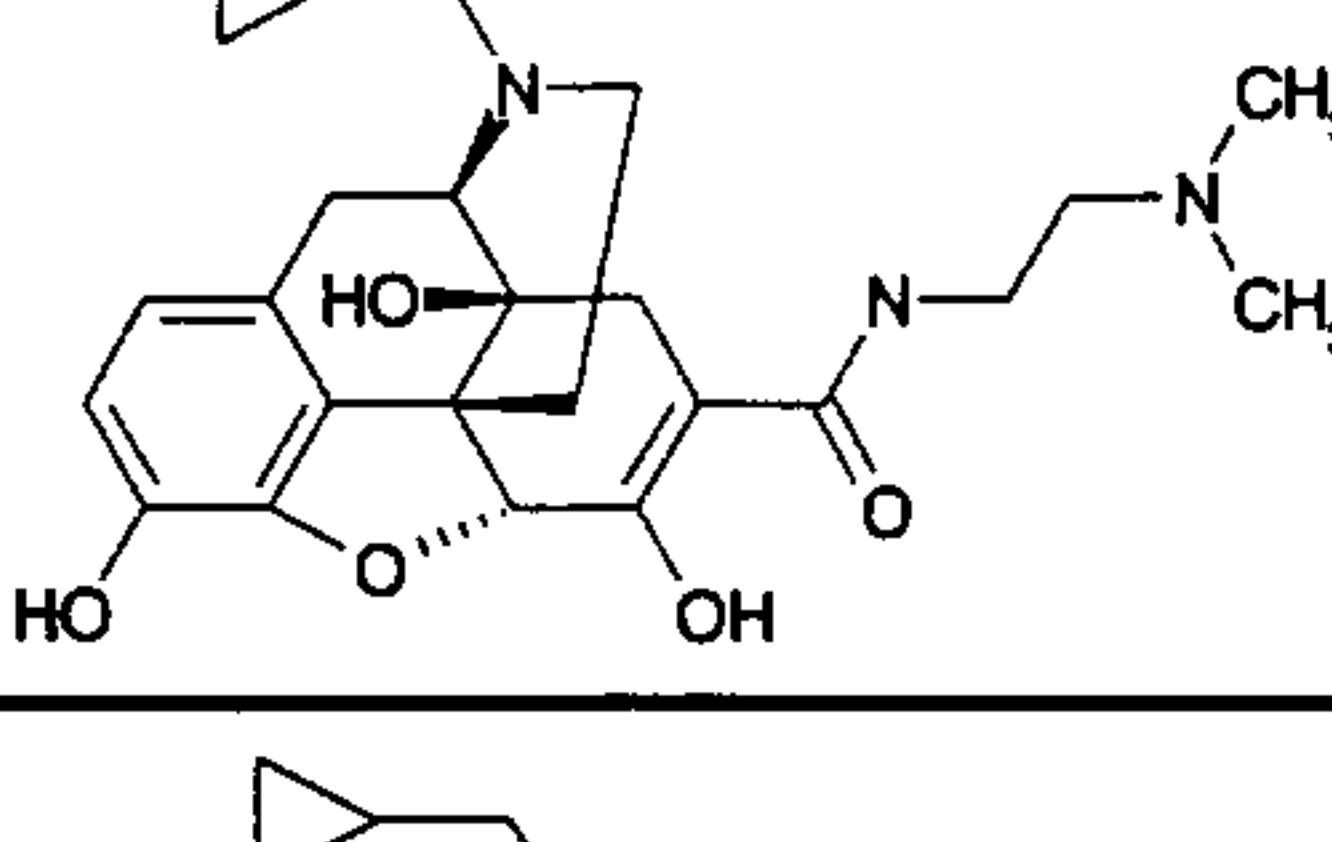
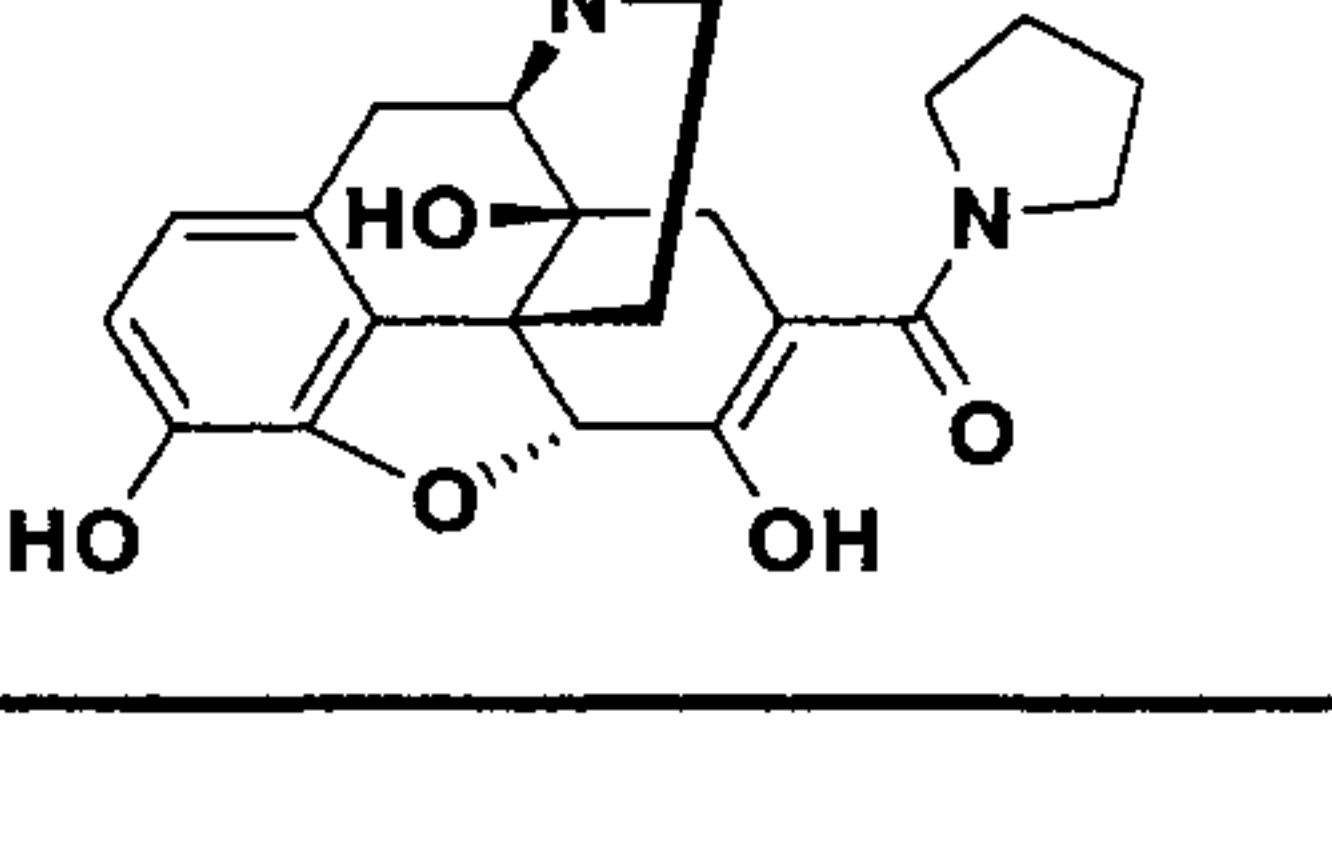
In addition, in Tables,

[Chemical formula 14]



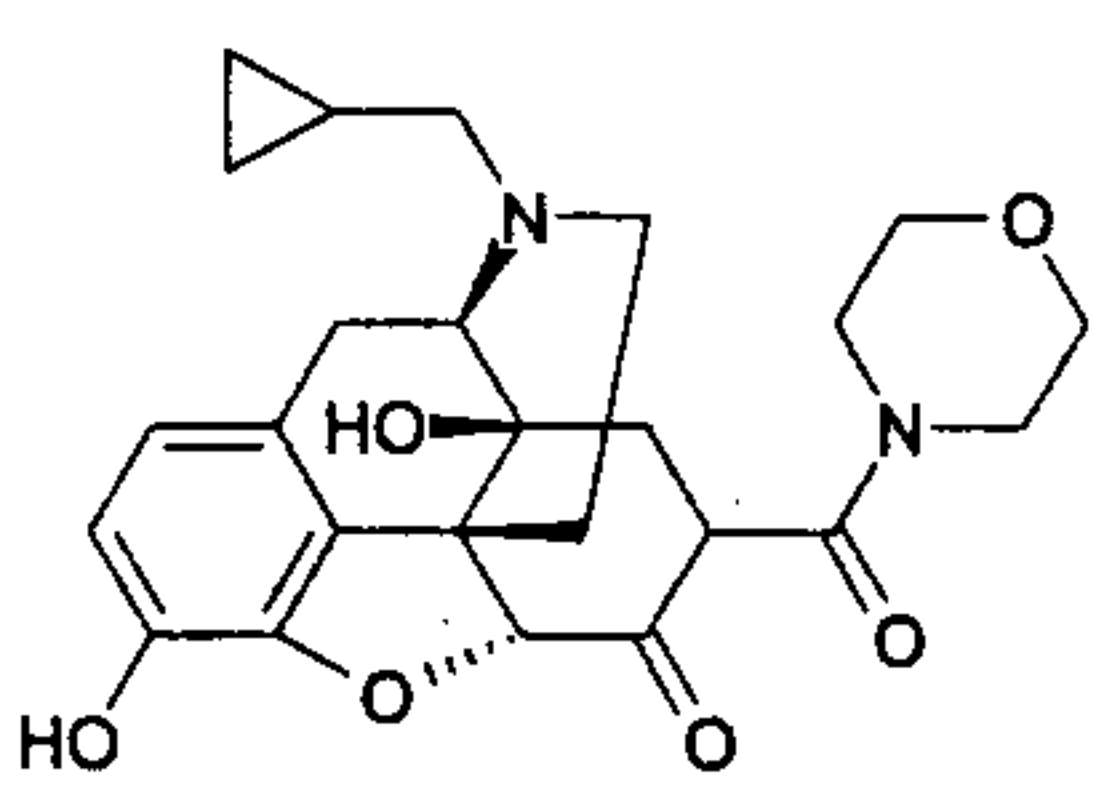
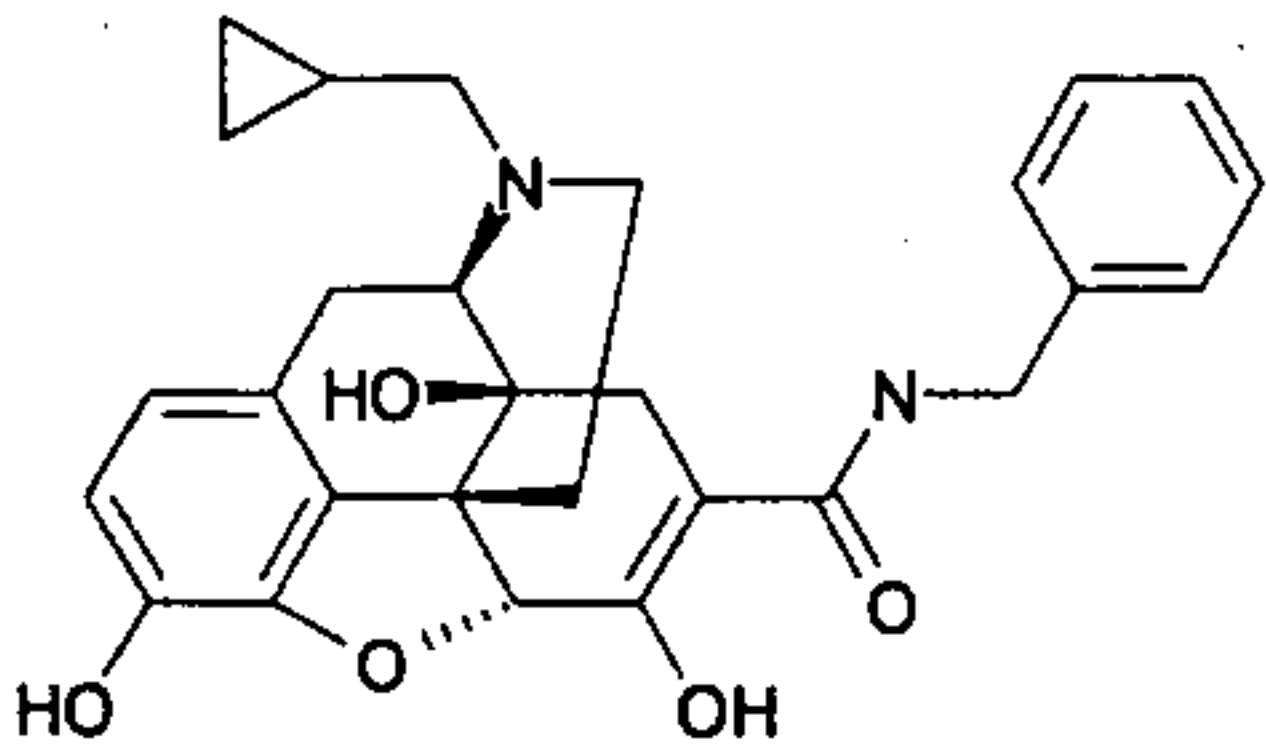
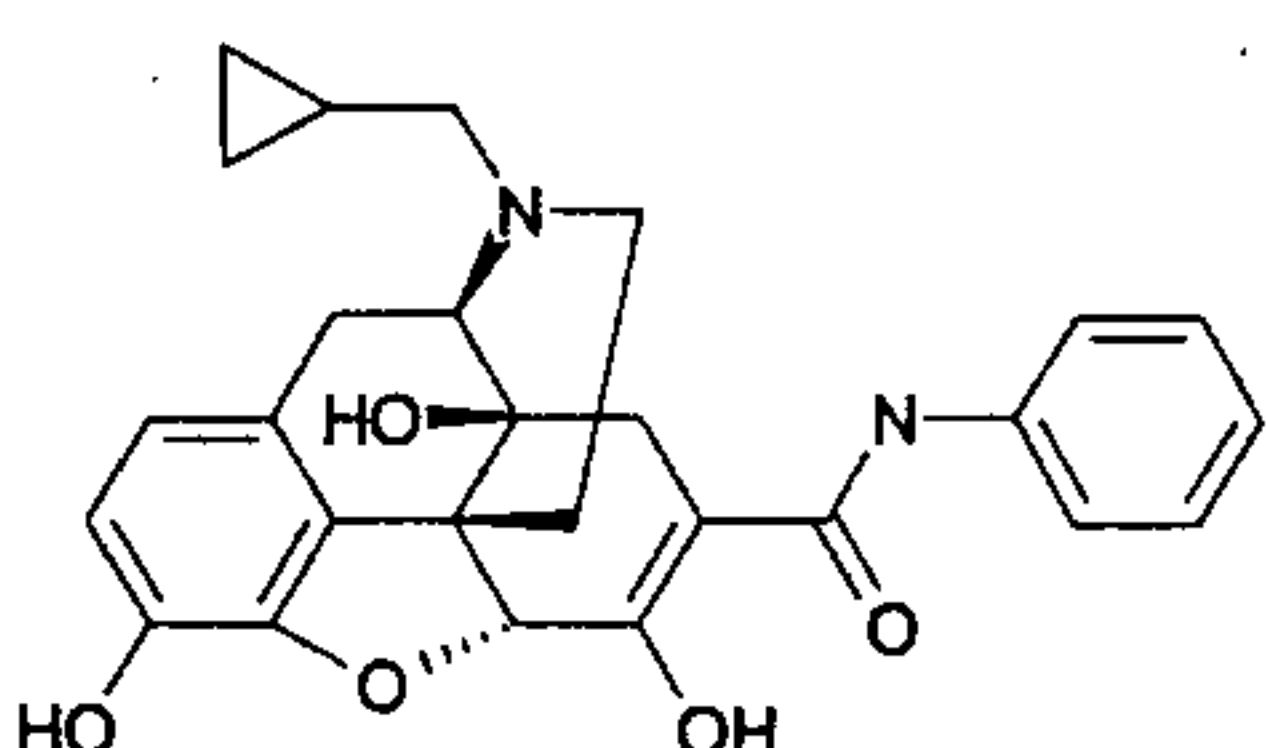
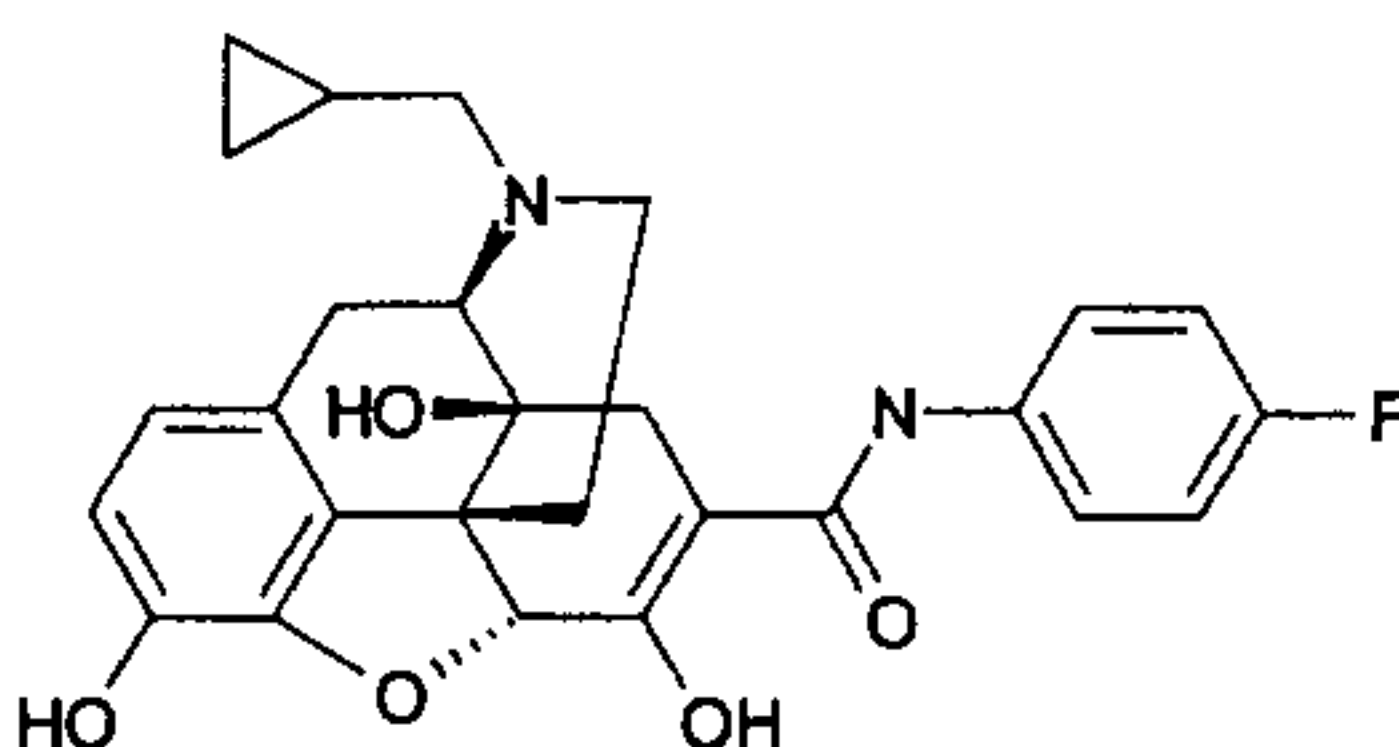
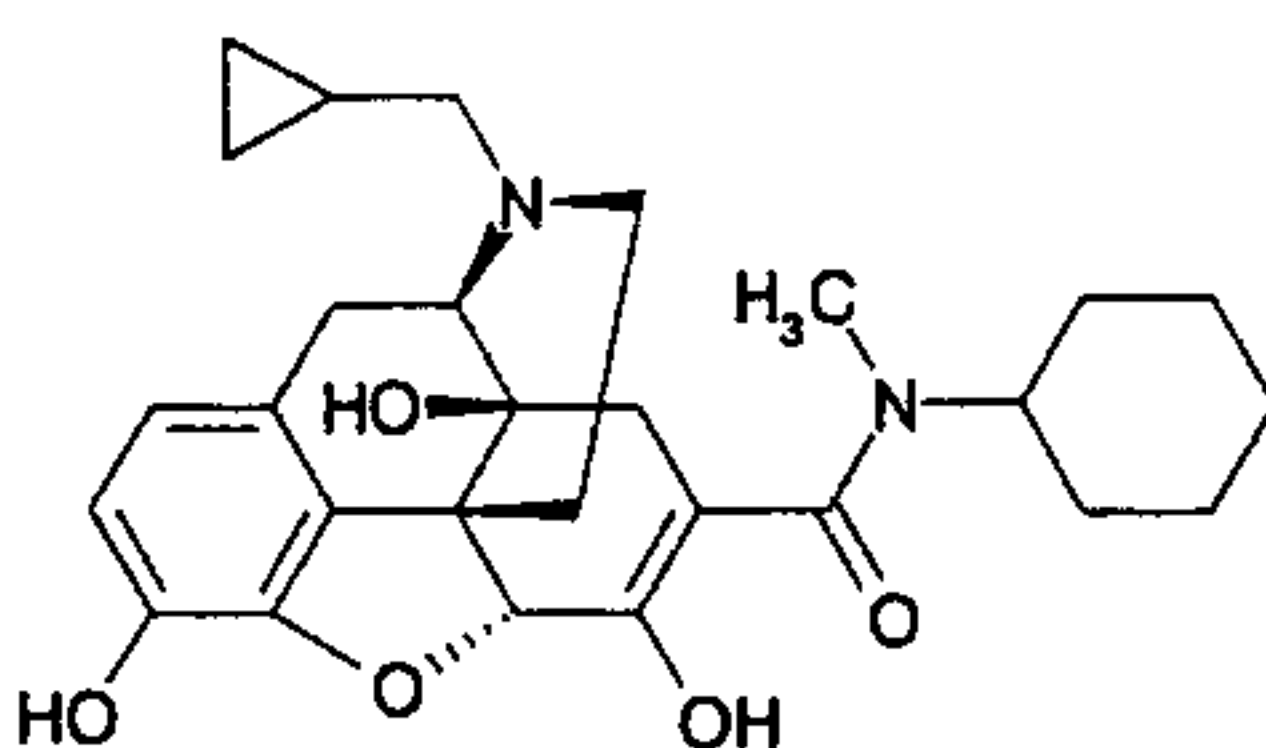
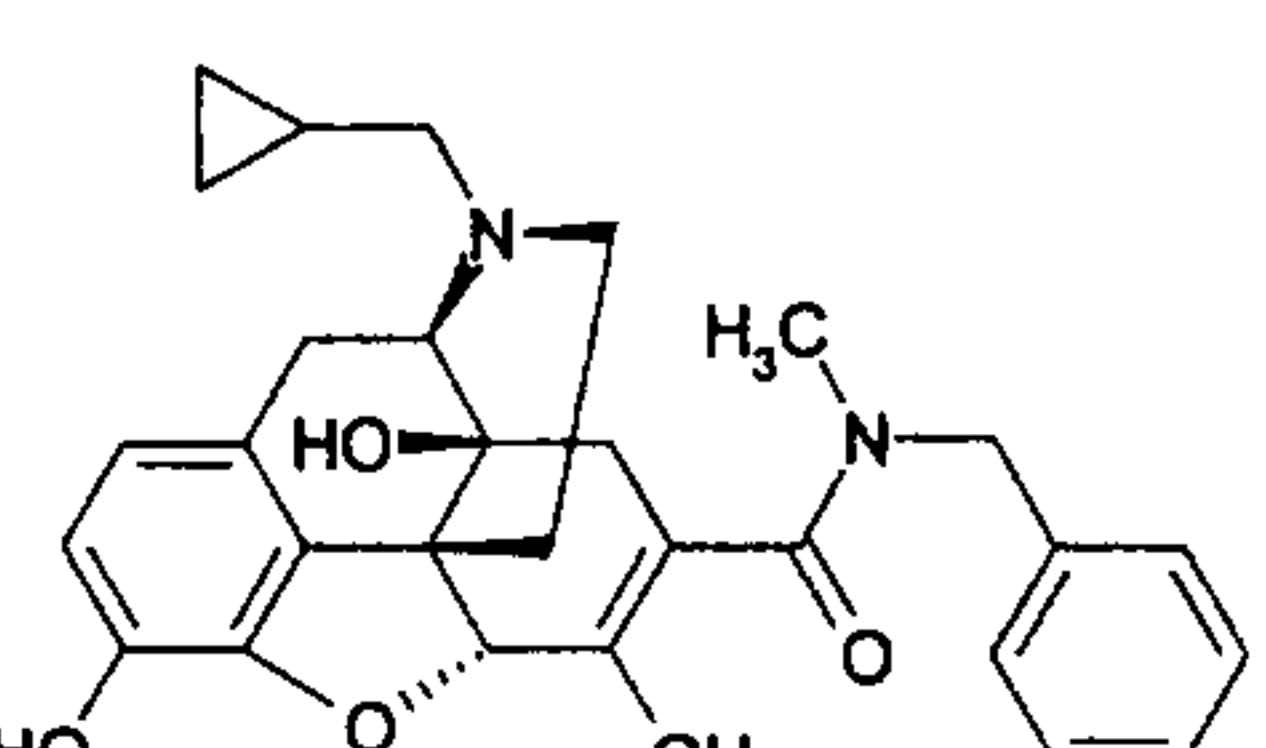
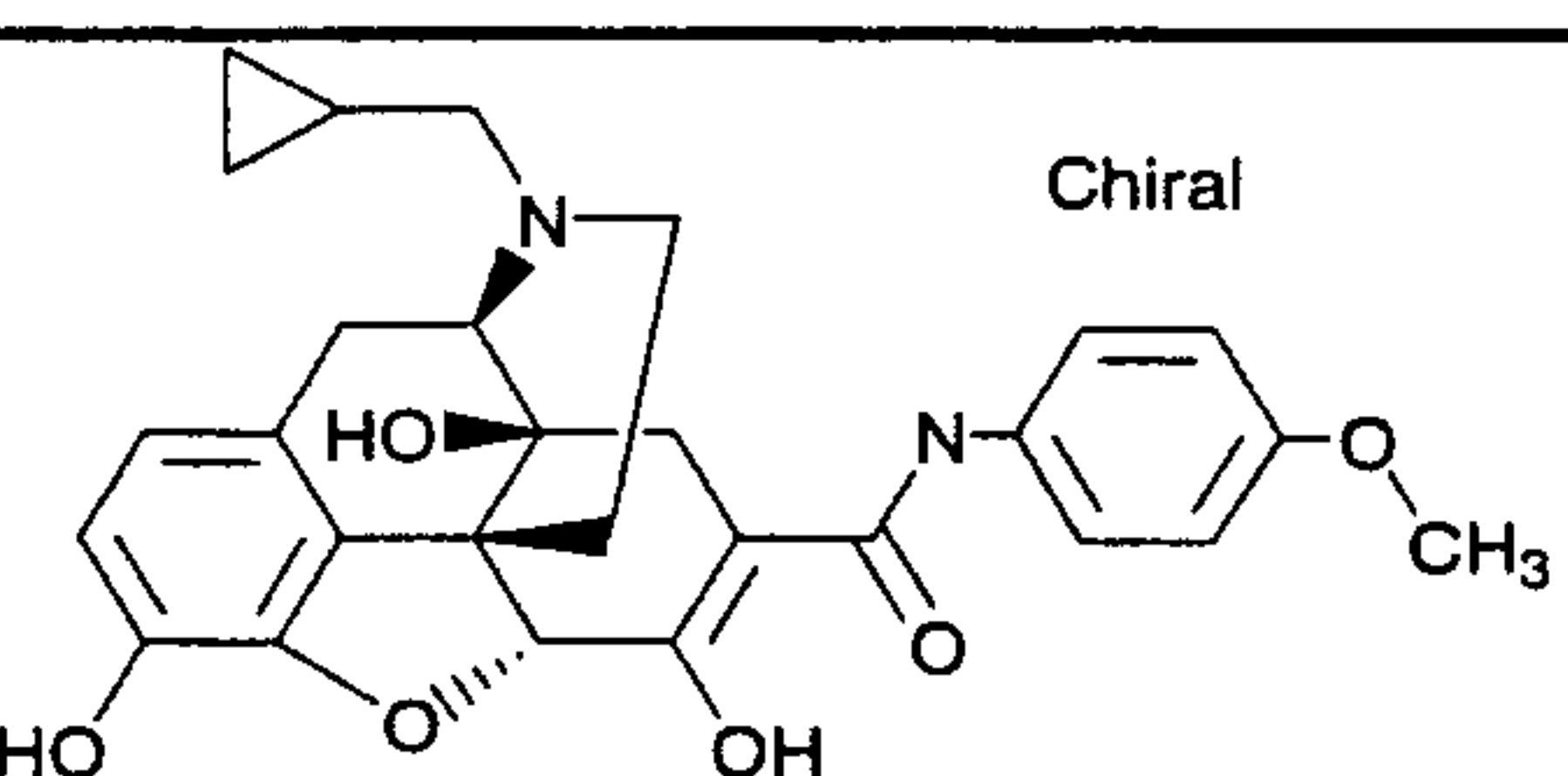
[0054]

[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 (br 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	(CDCl ₃) 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)
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)

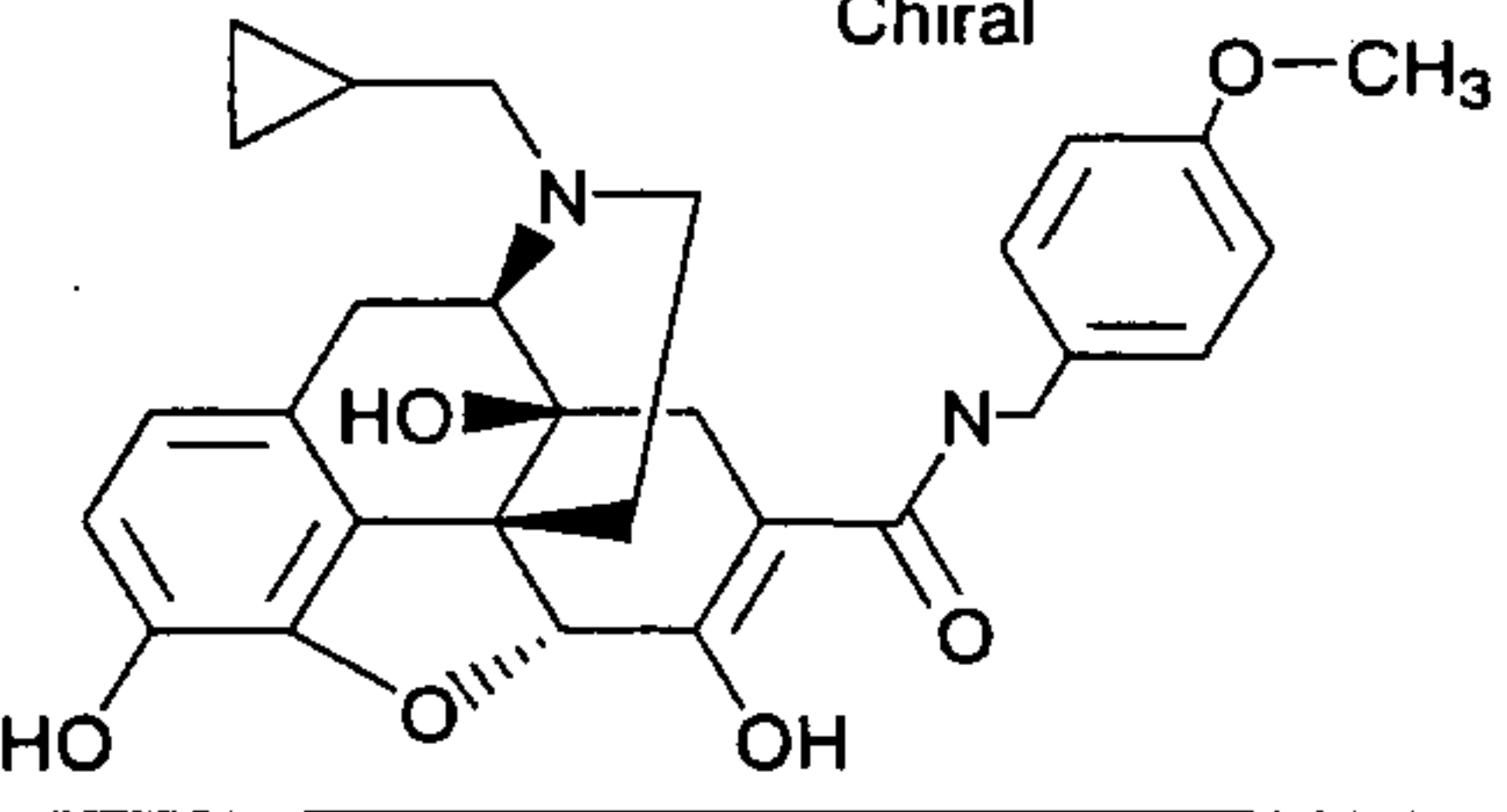
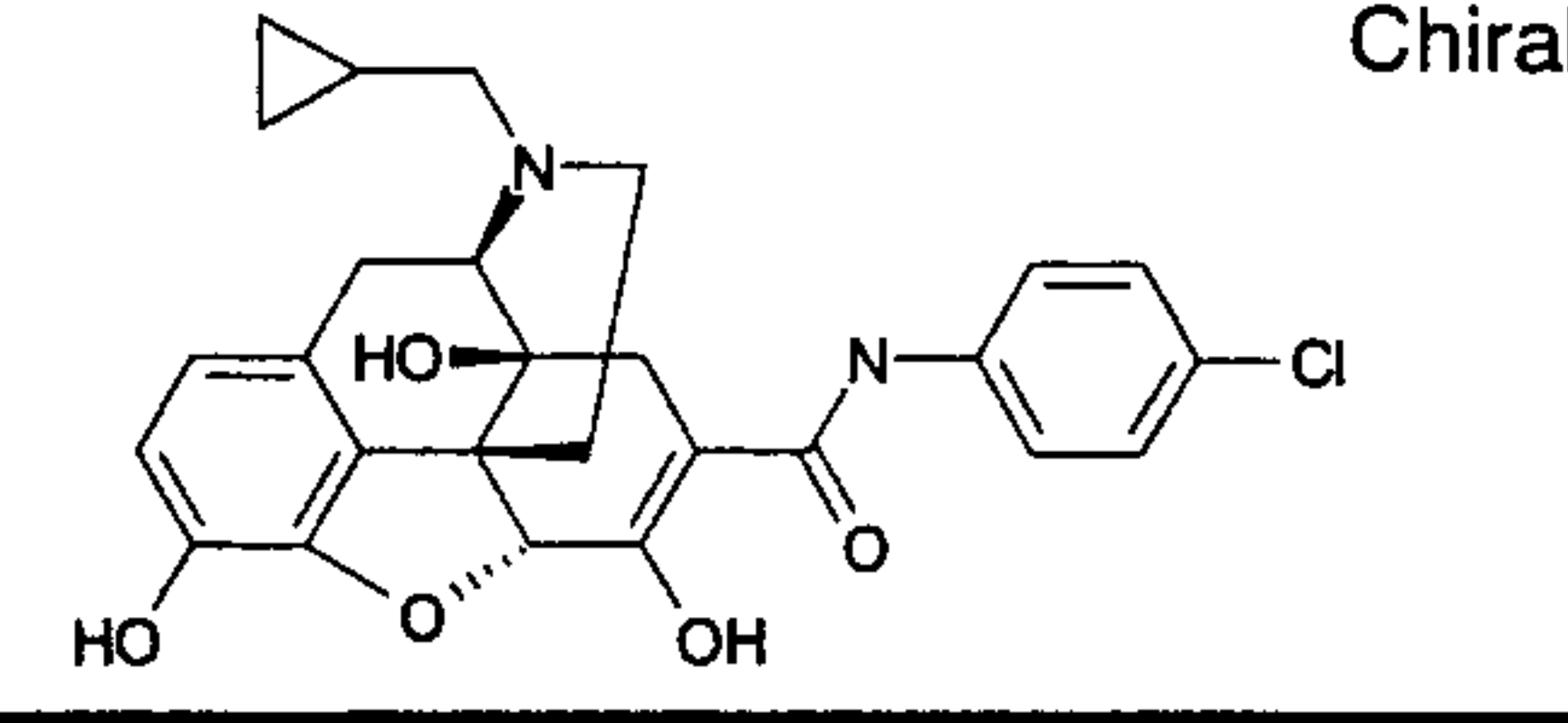
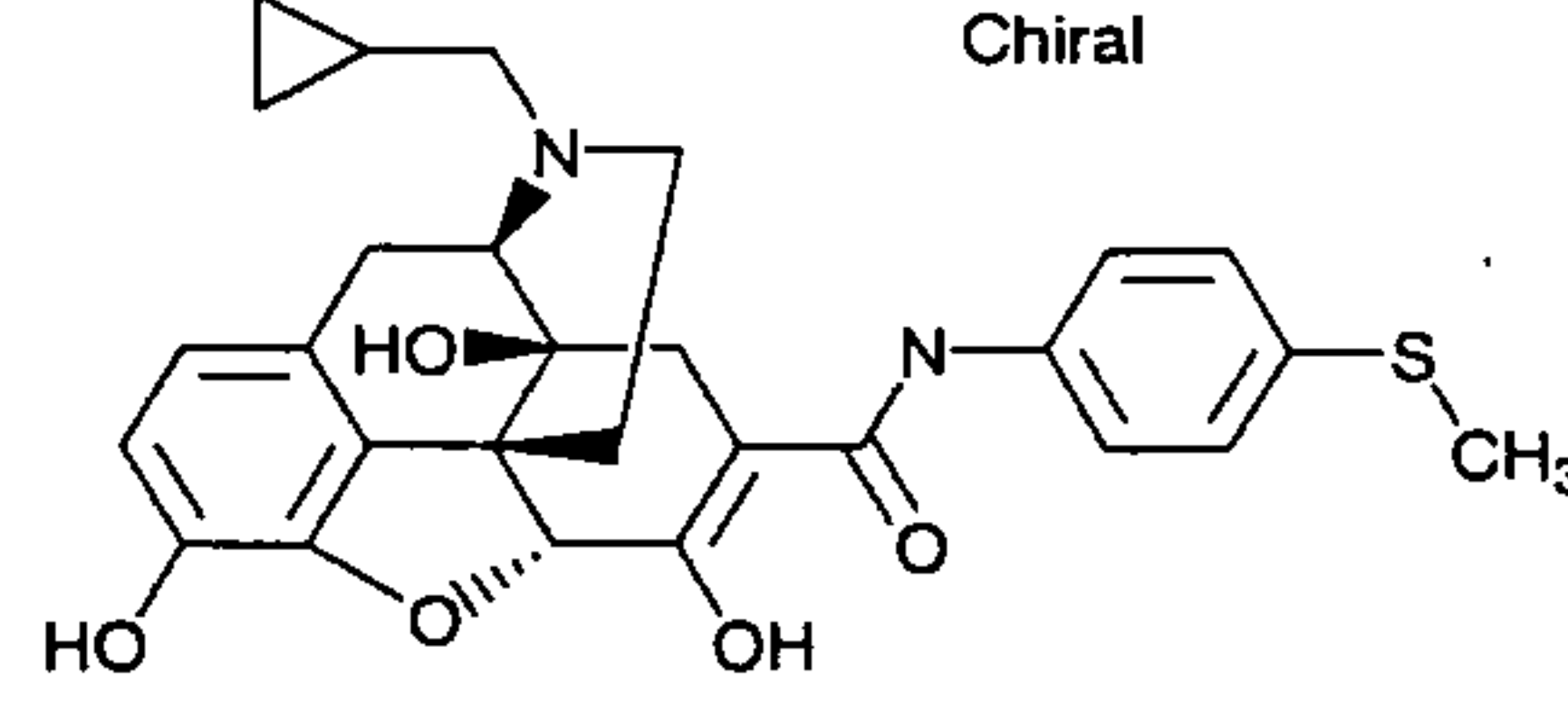
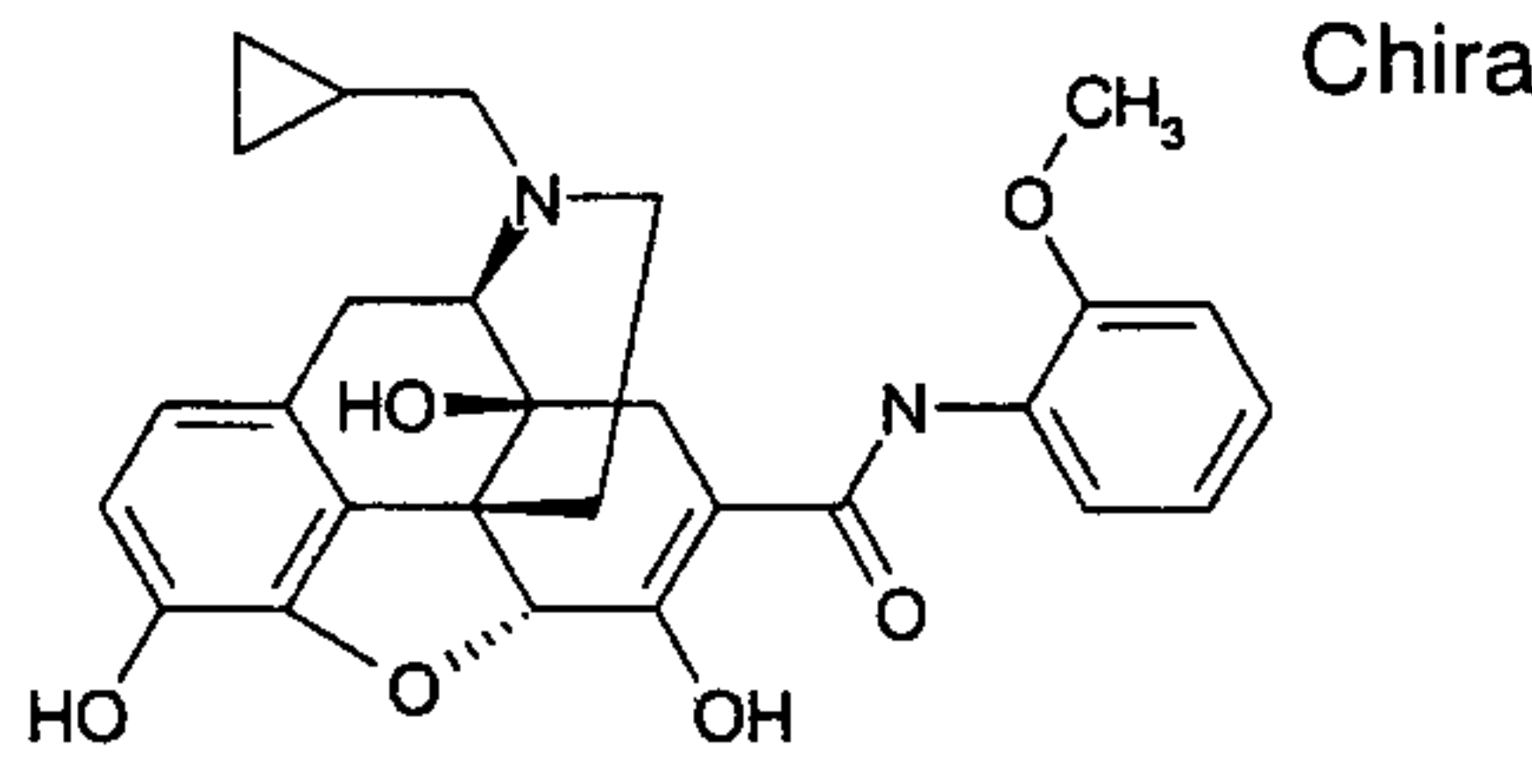
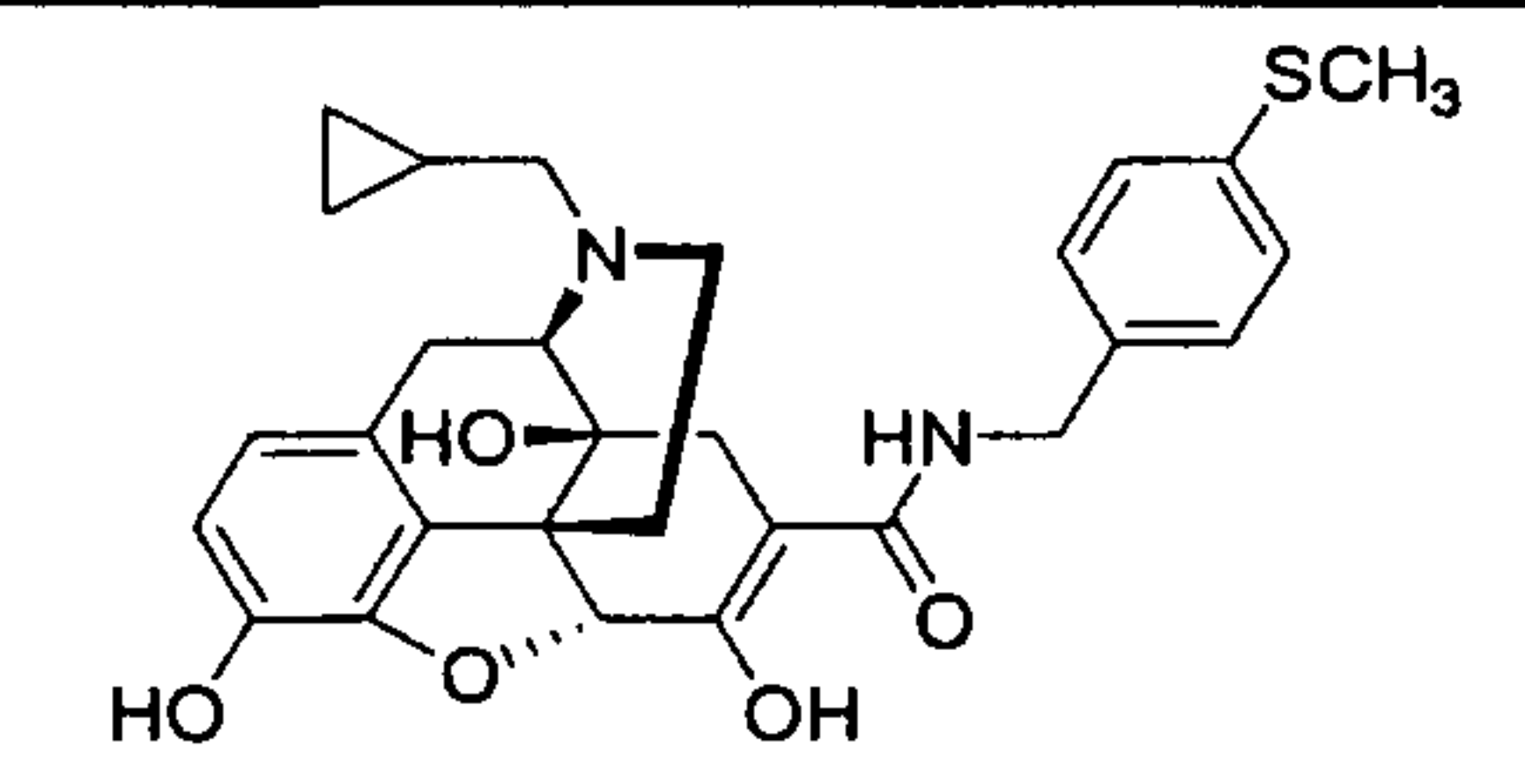
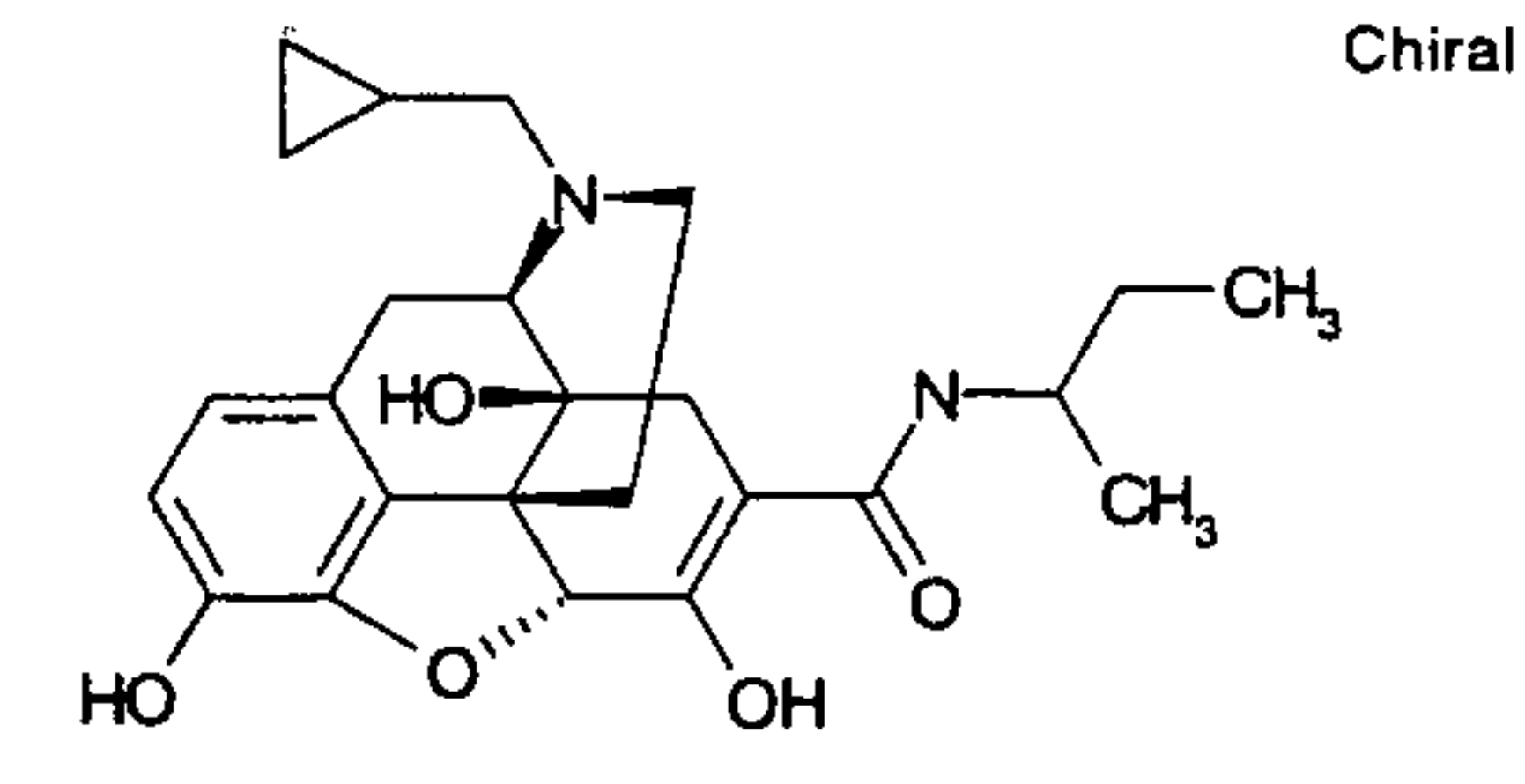
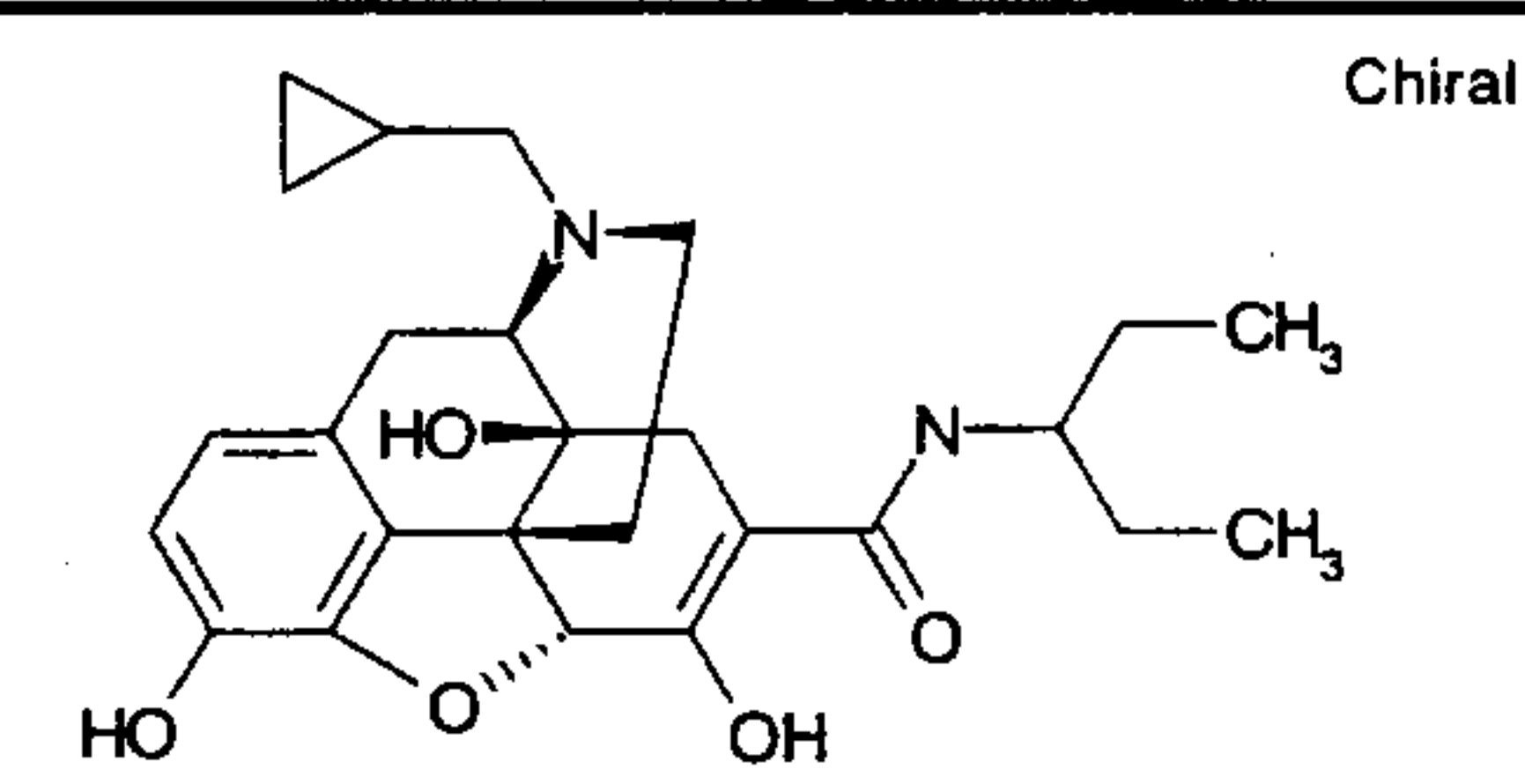
[0055]

[Table 10]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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	(CDCl ₃) 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, 1H), 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)
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 = 11.7 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)

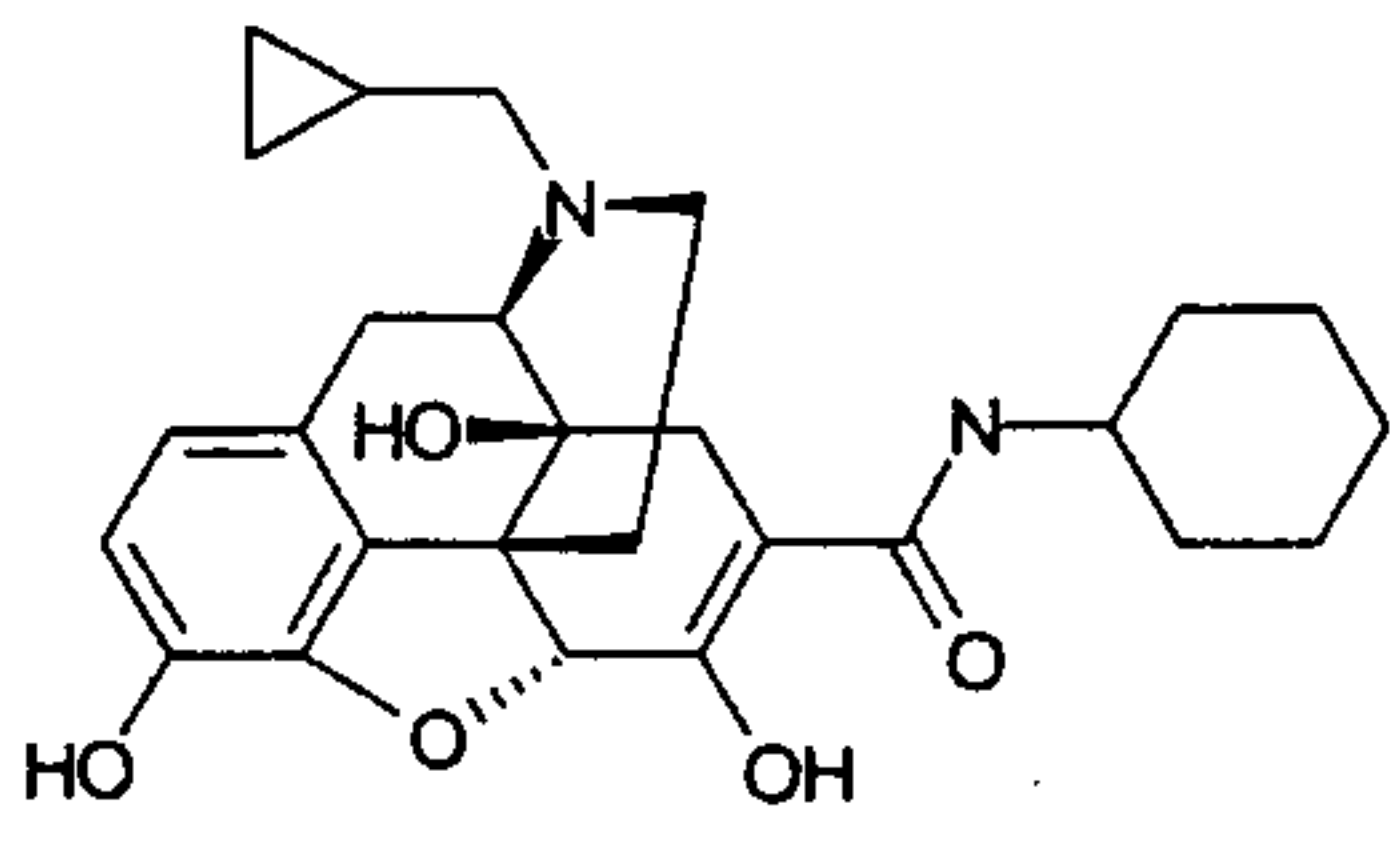
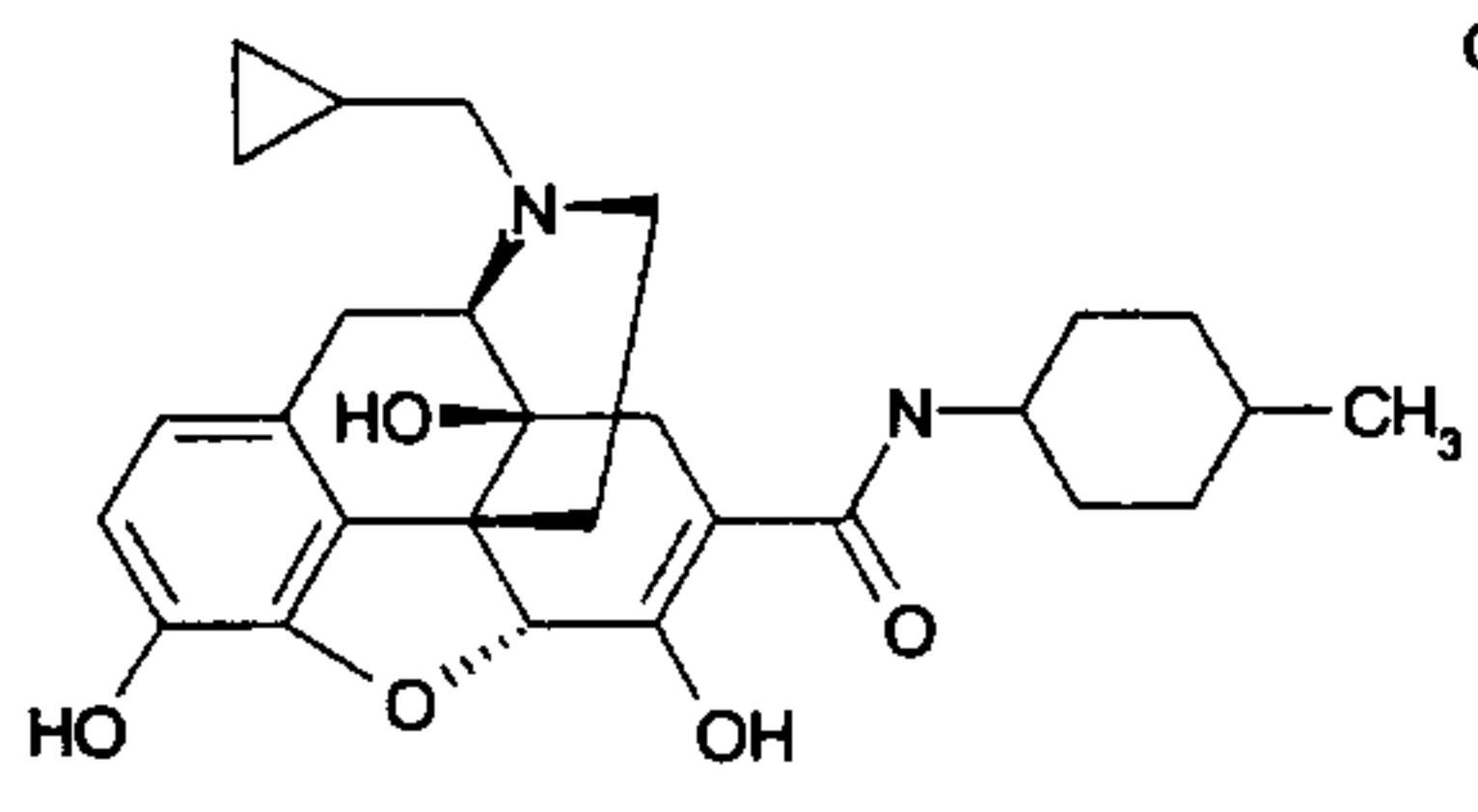
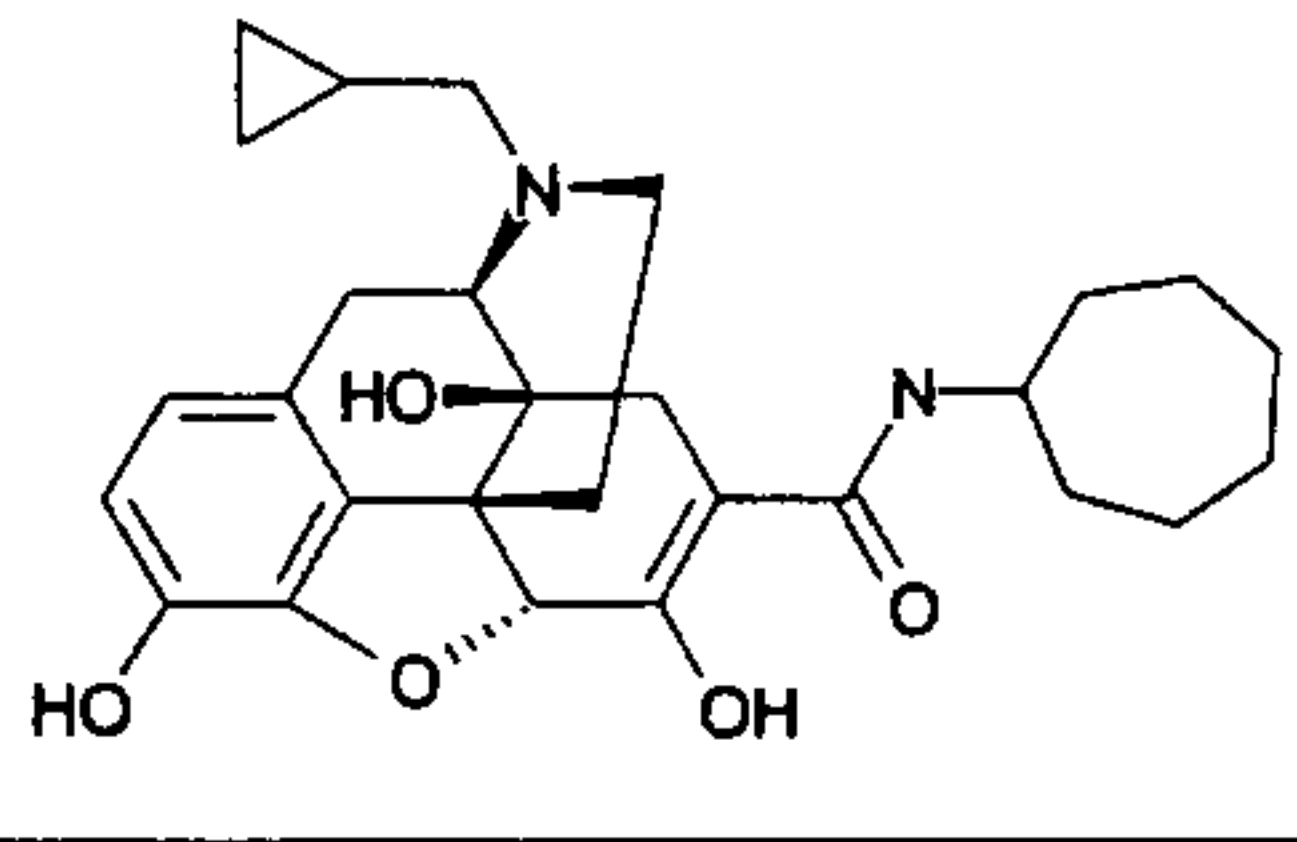
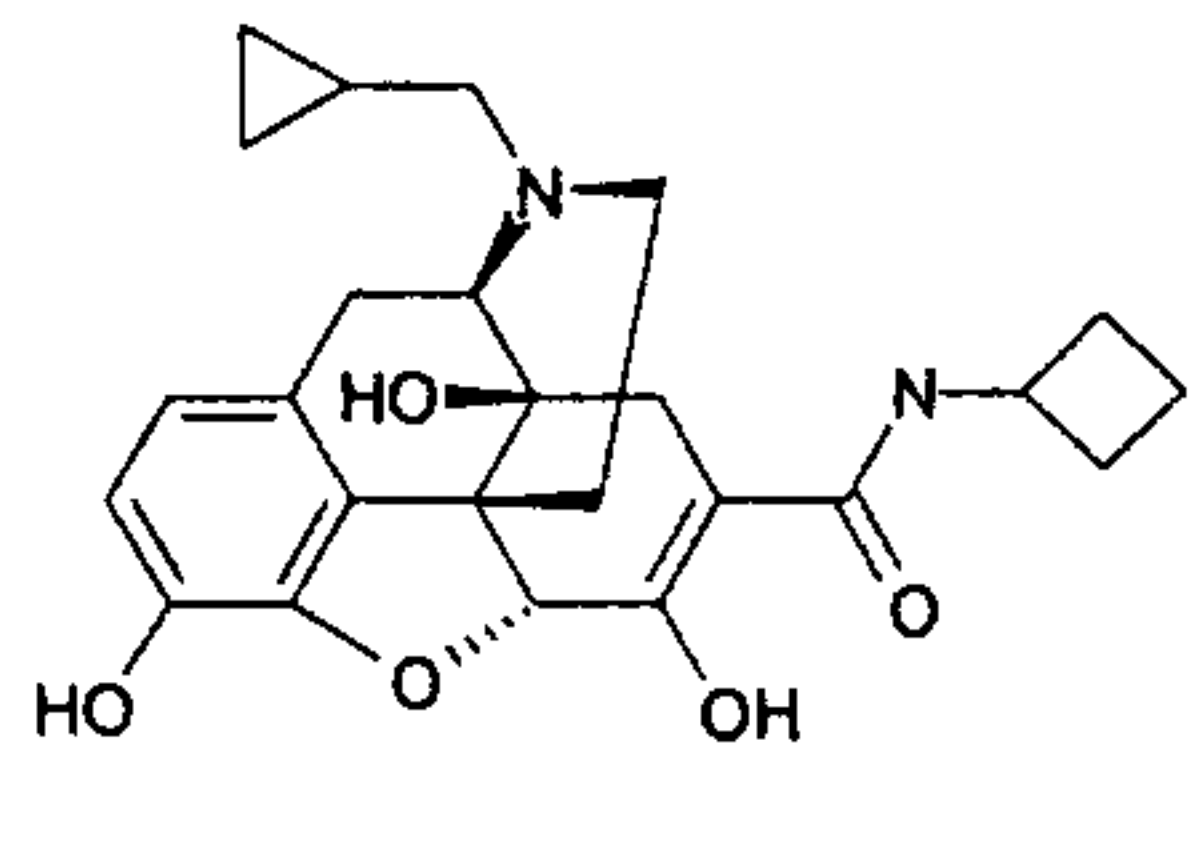
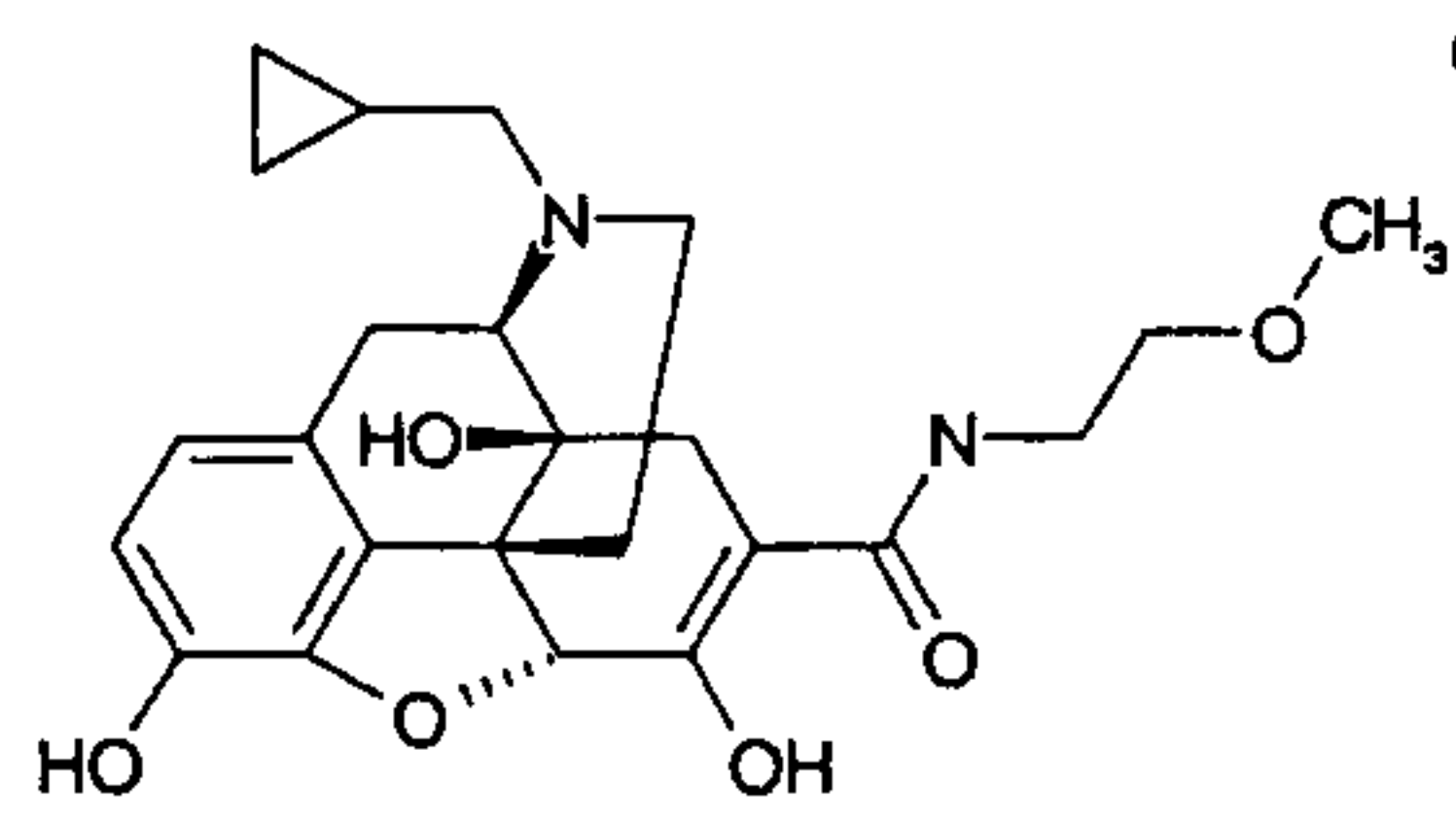
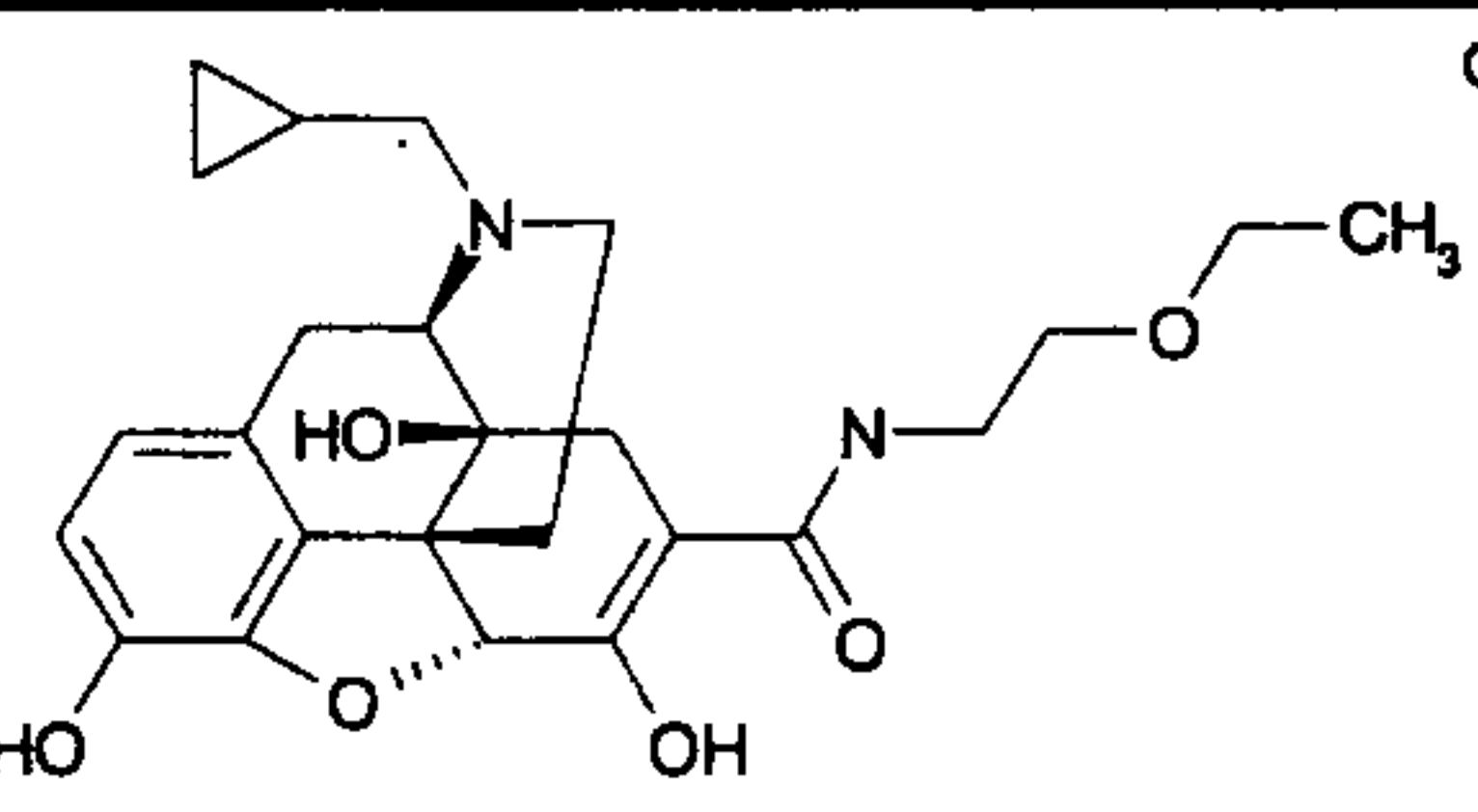
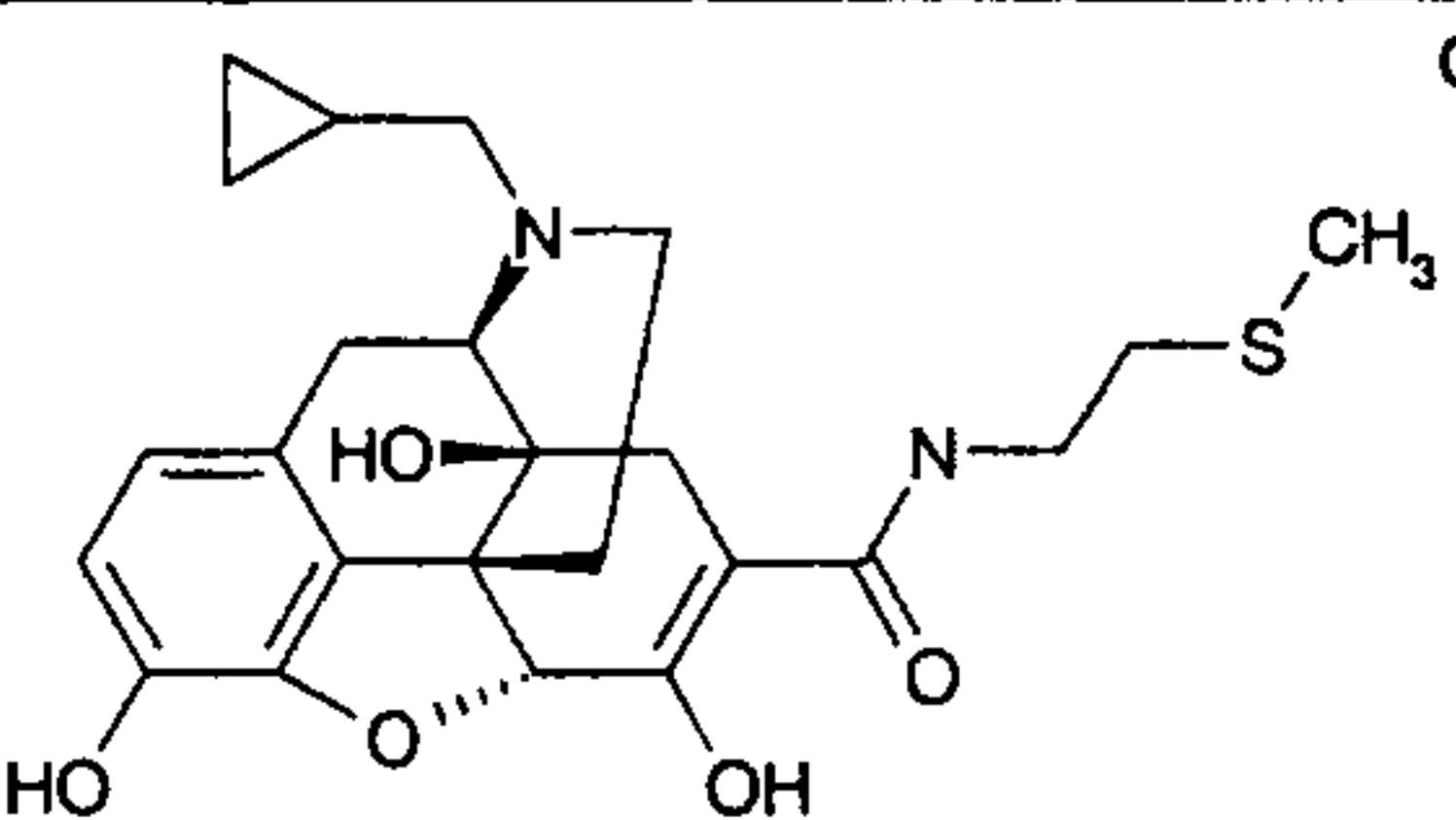
[0056]

[Table 11]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-15		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)
I-16		0.10-0.25 (m, 2H), 0.40-0.60 (m, 2H), 0.90 (m, 1H), 1.45 (d, J = 10.8 Hz, 1H), 1.70-3.40 (m, 10H), 4.77 (s, 1H), 4.84 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 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		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, 1H), 13.90 (br s, 1H)
I-18		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		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)
I-21		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)

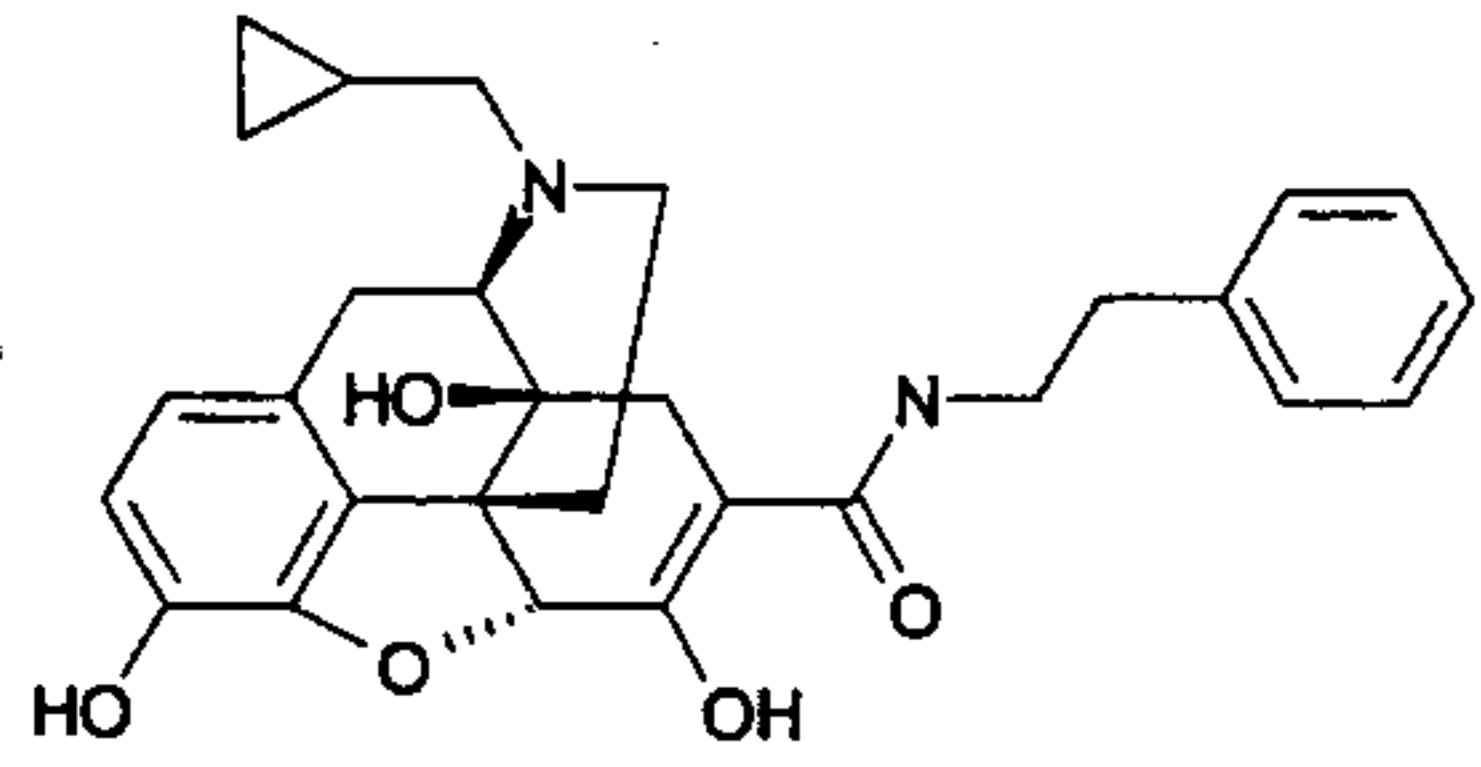
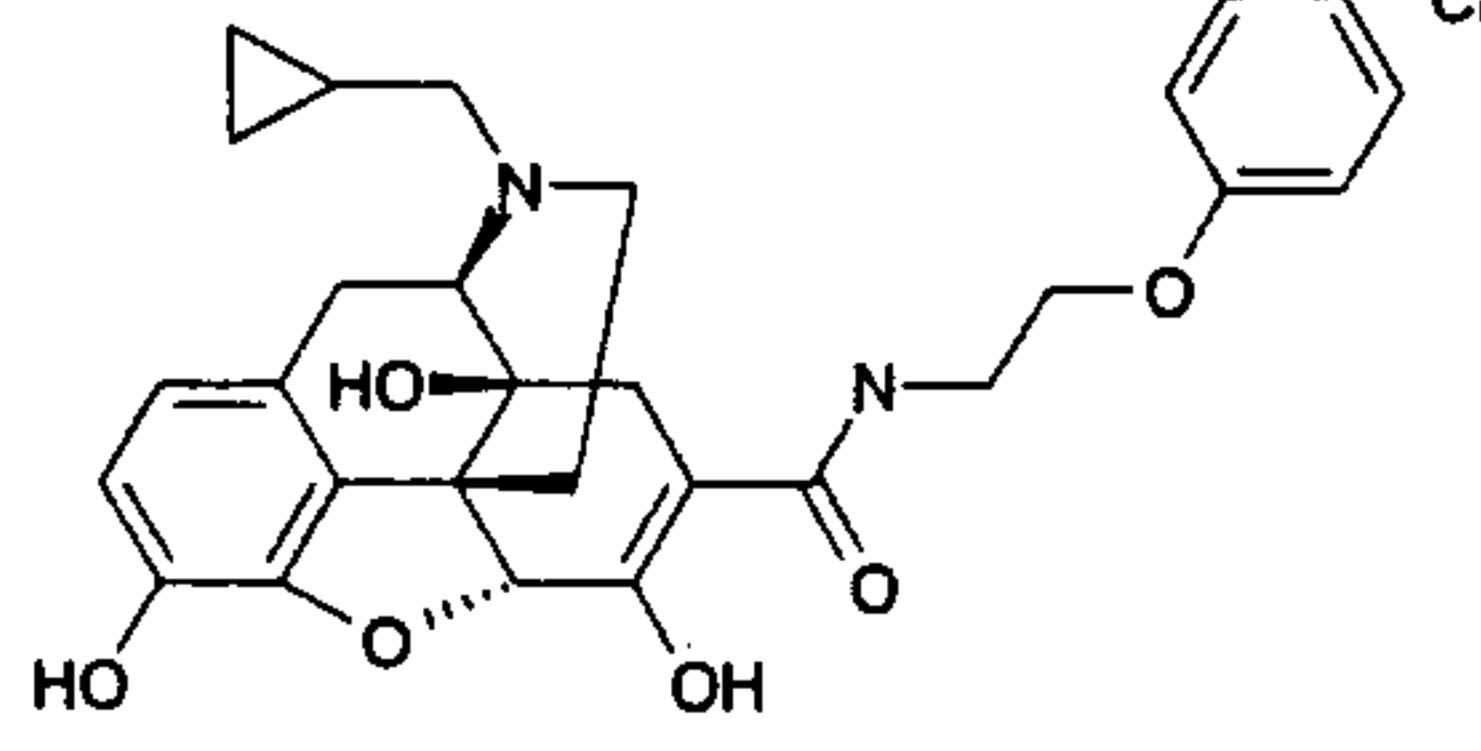
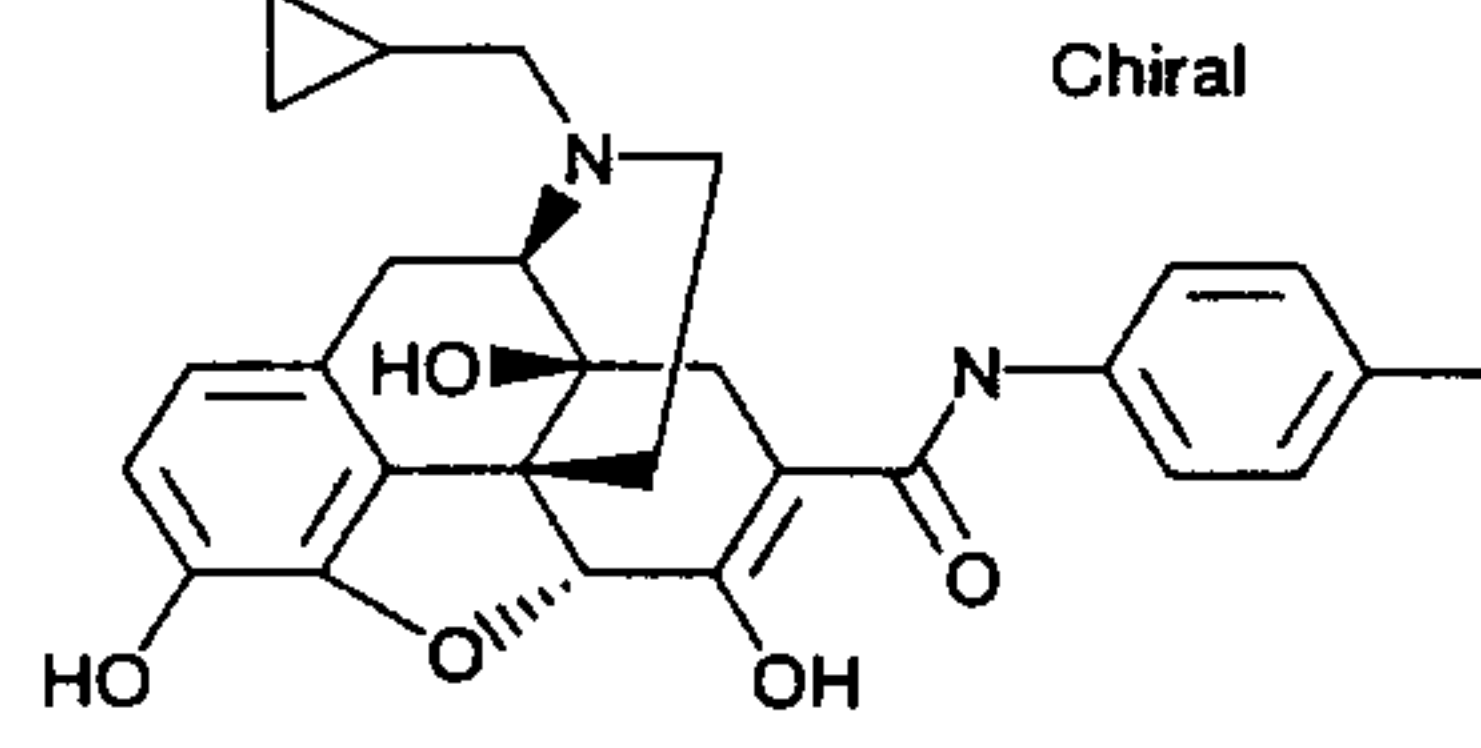
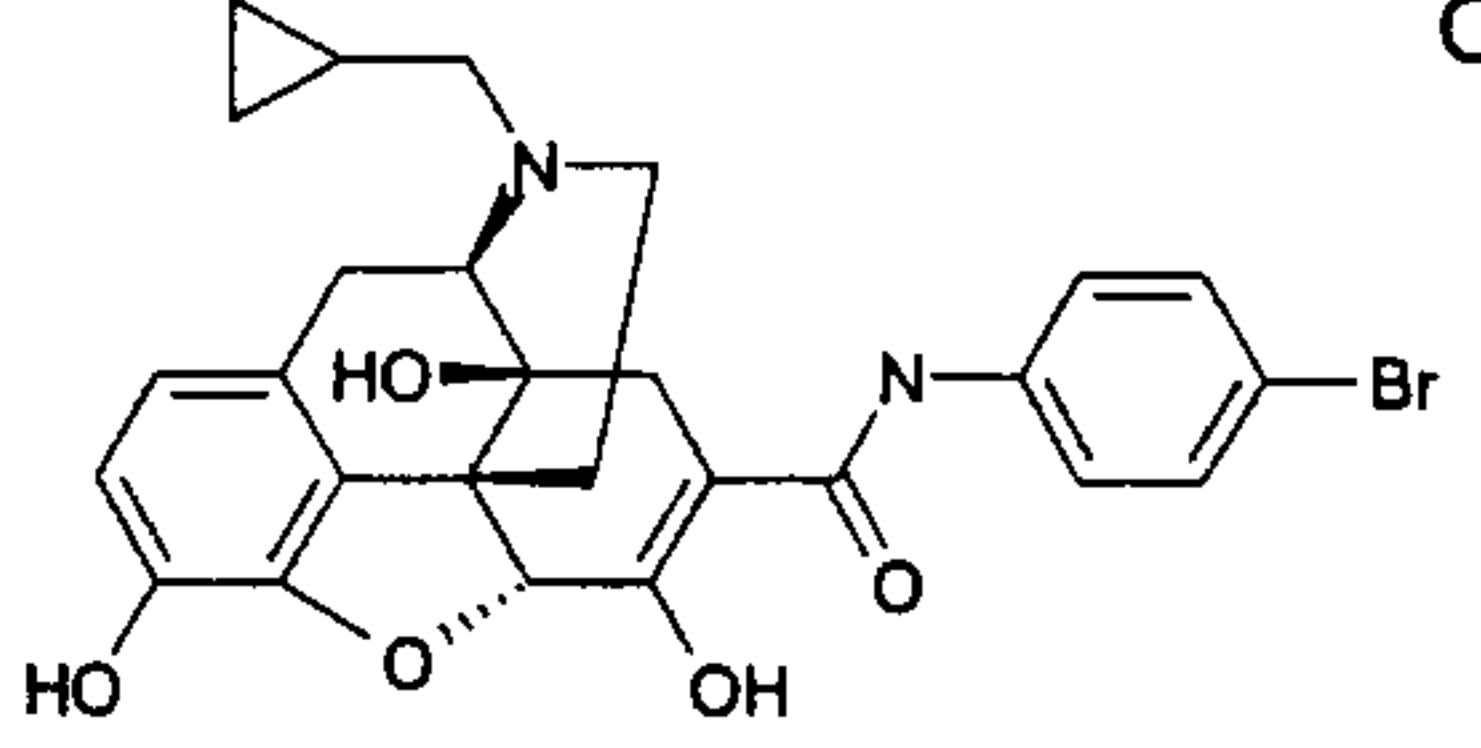
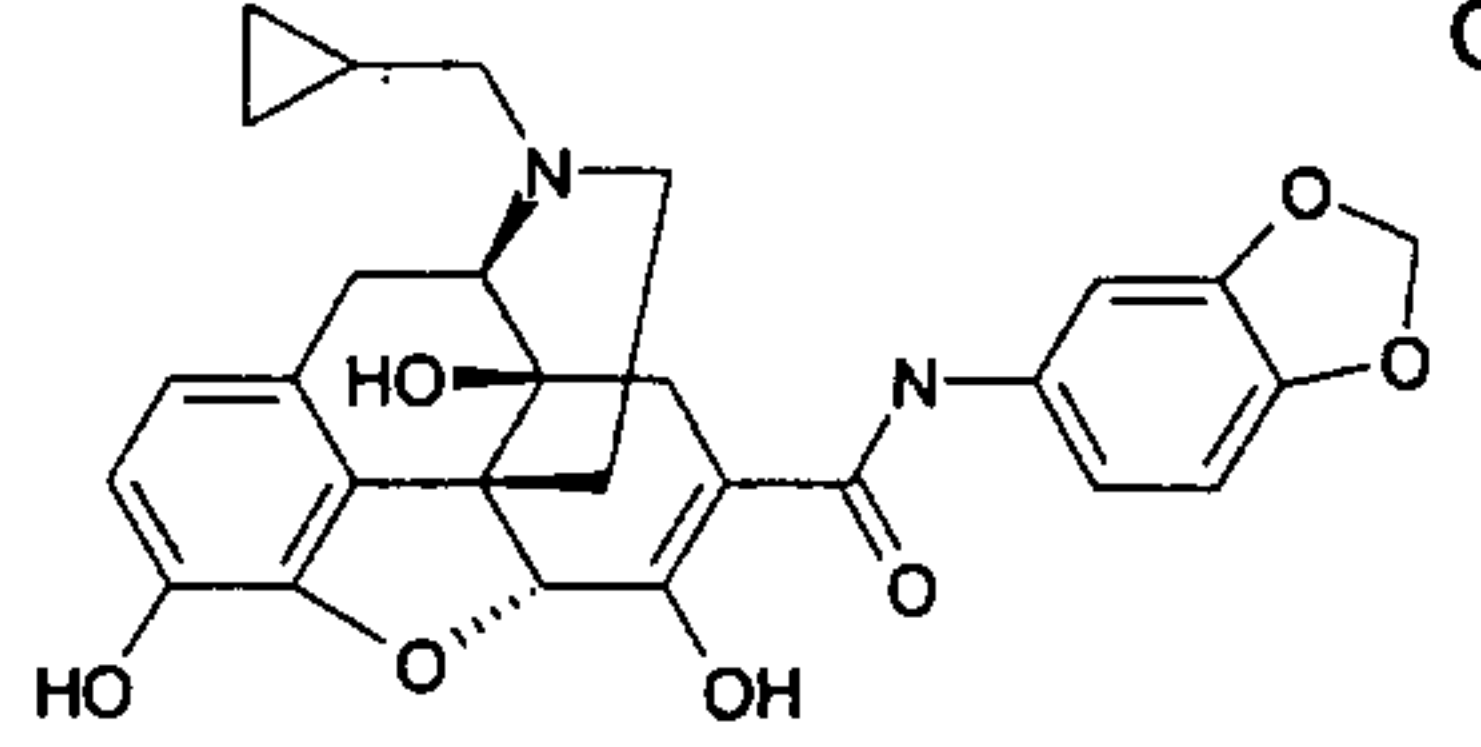
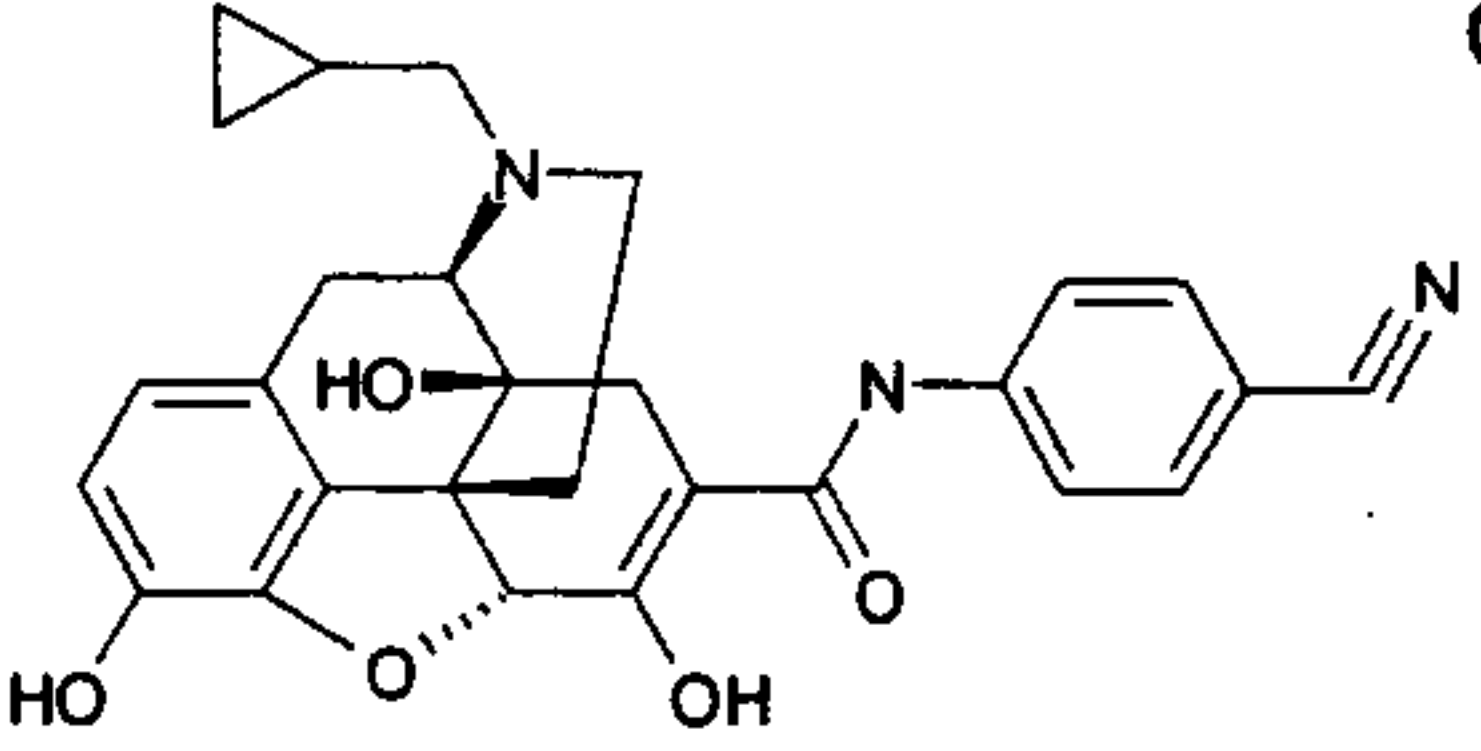
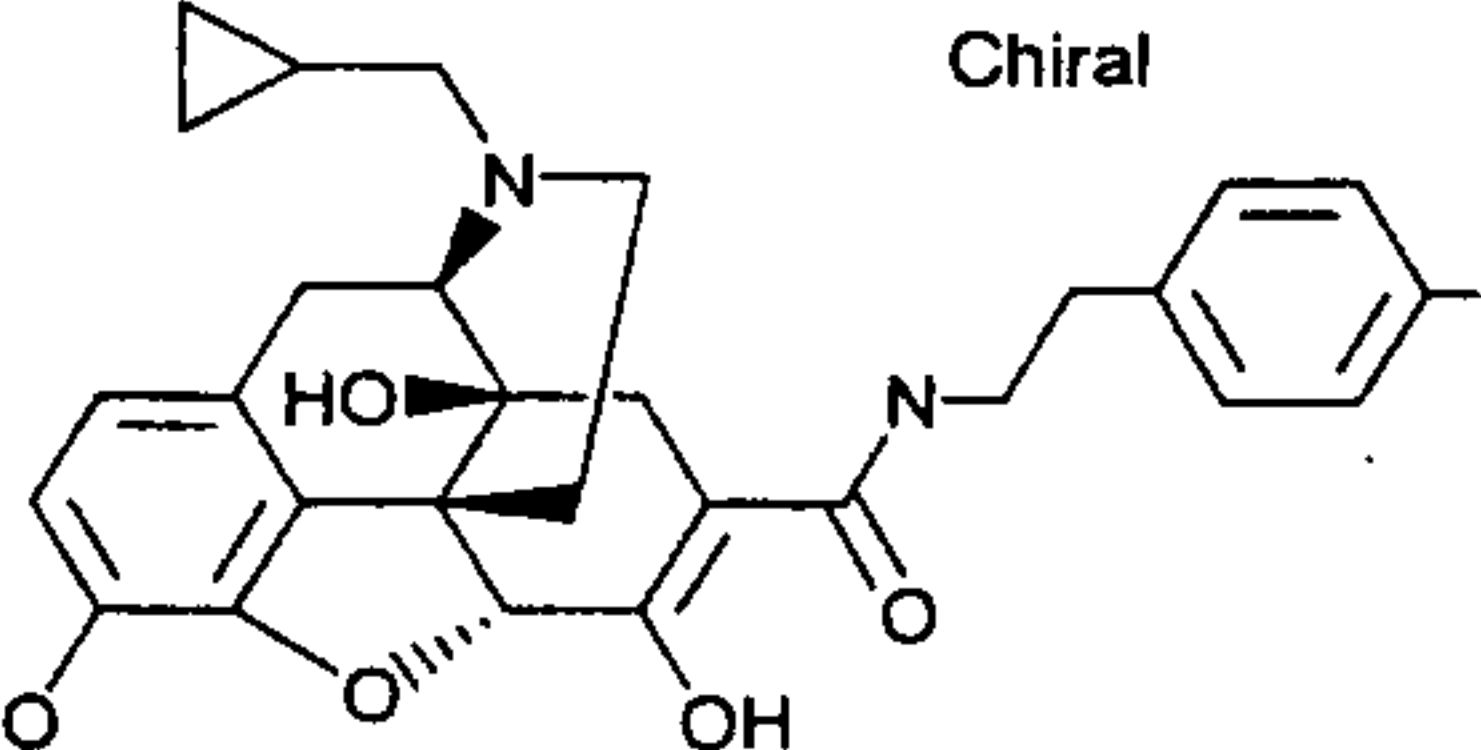
[0057]

[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)
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).

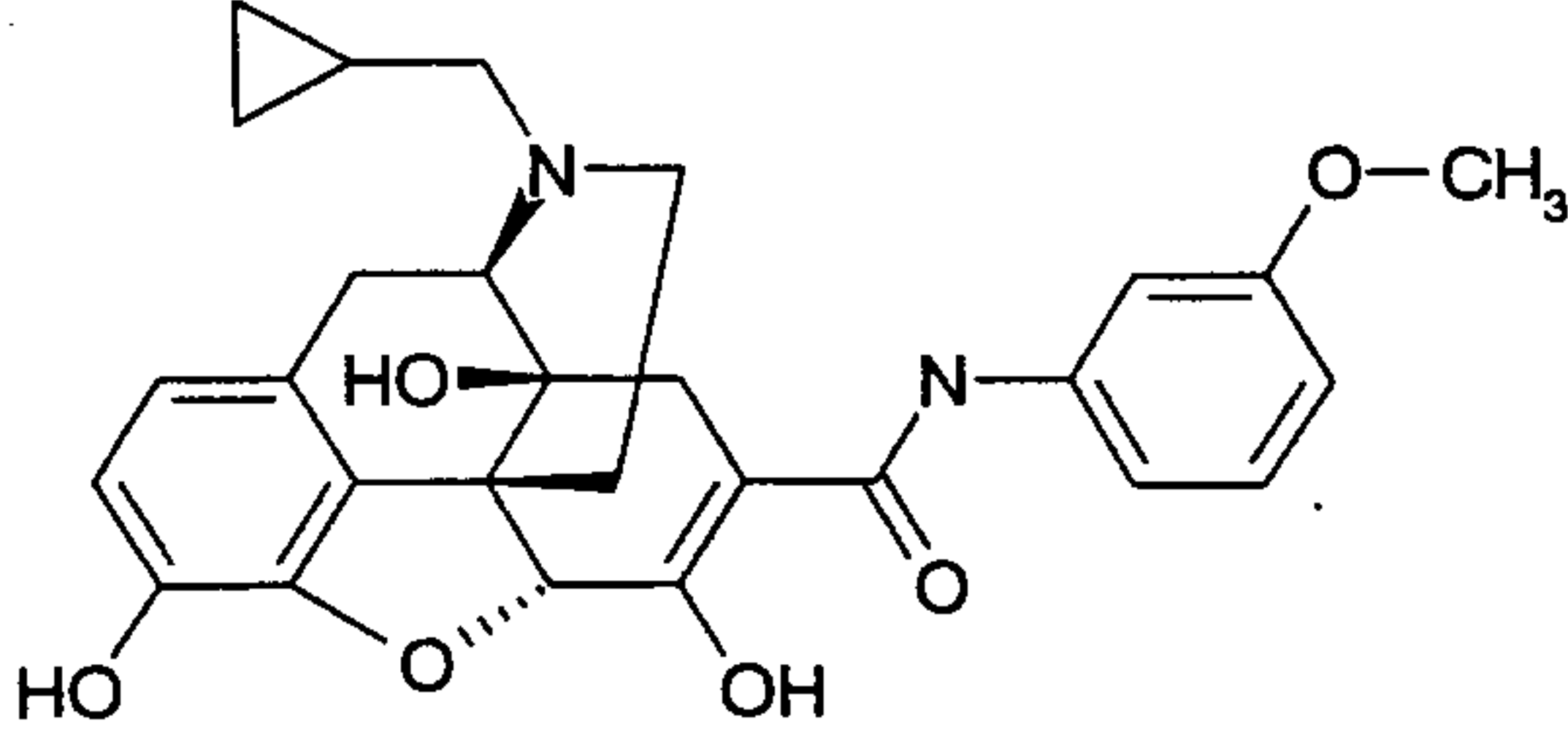
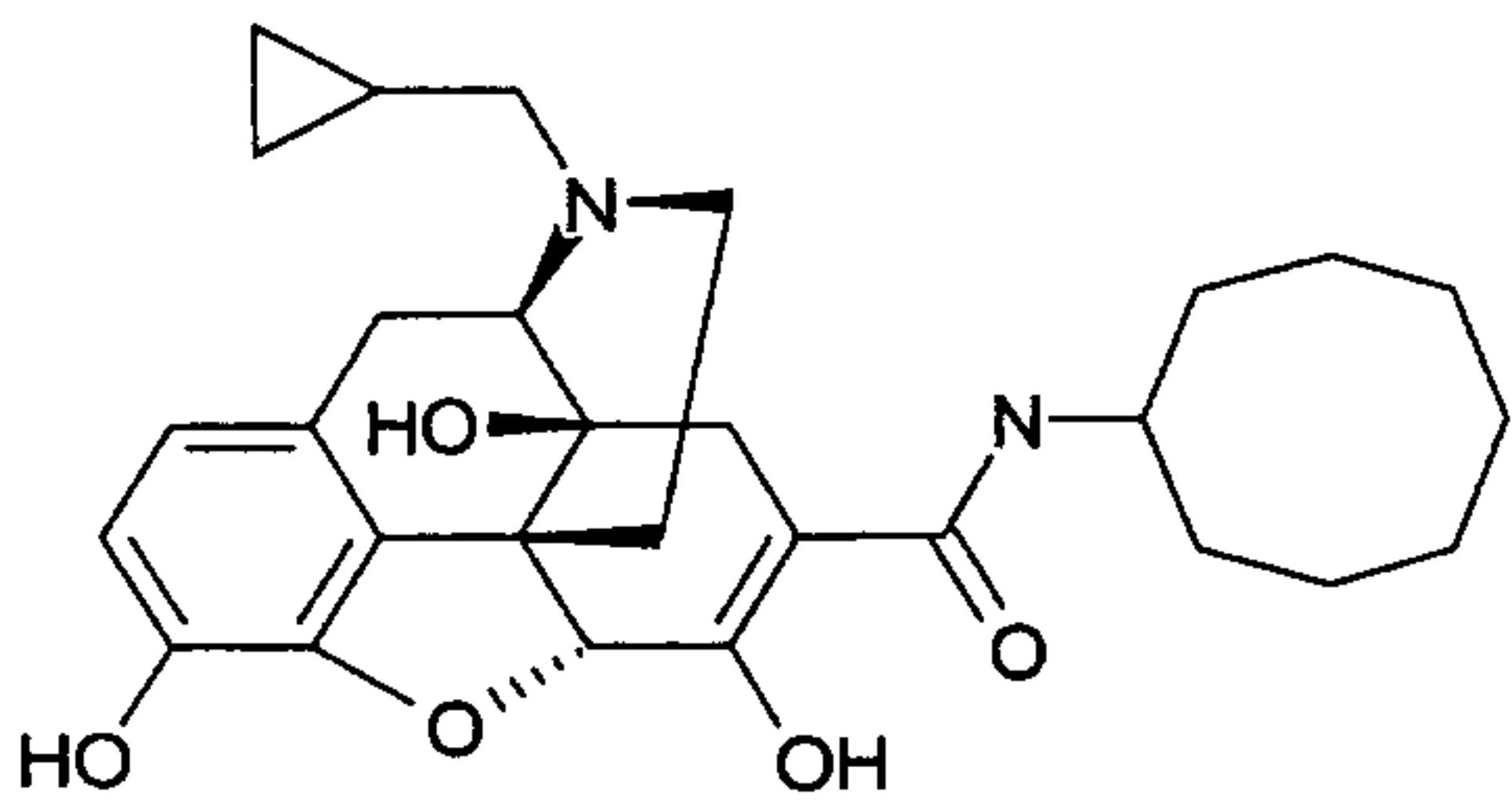
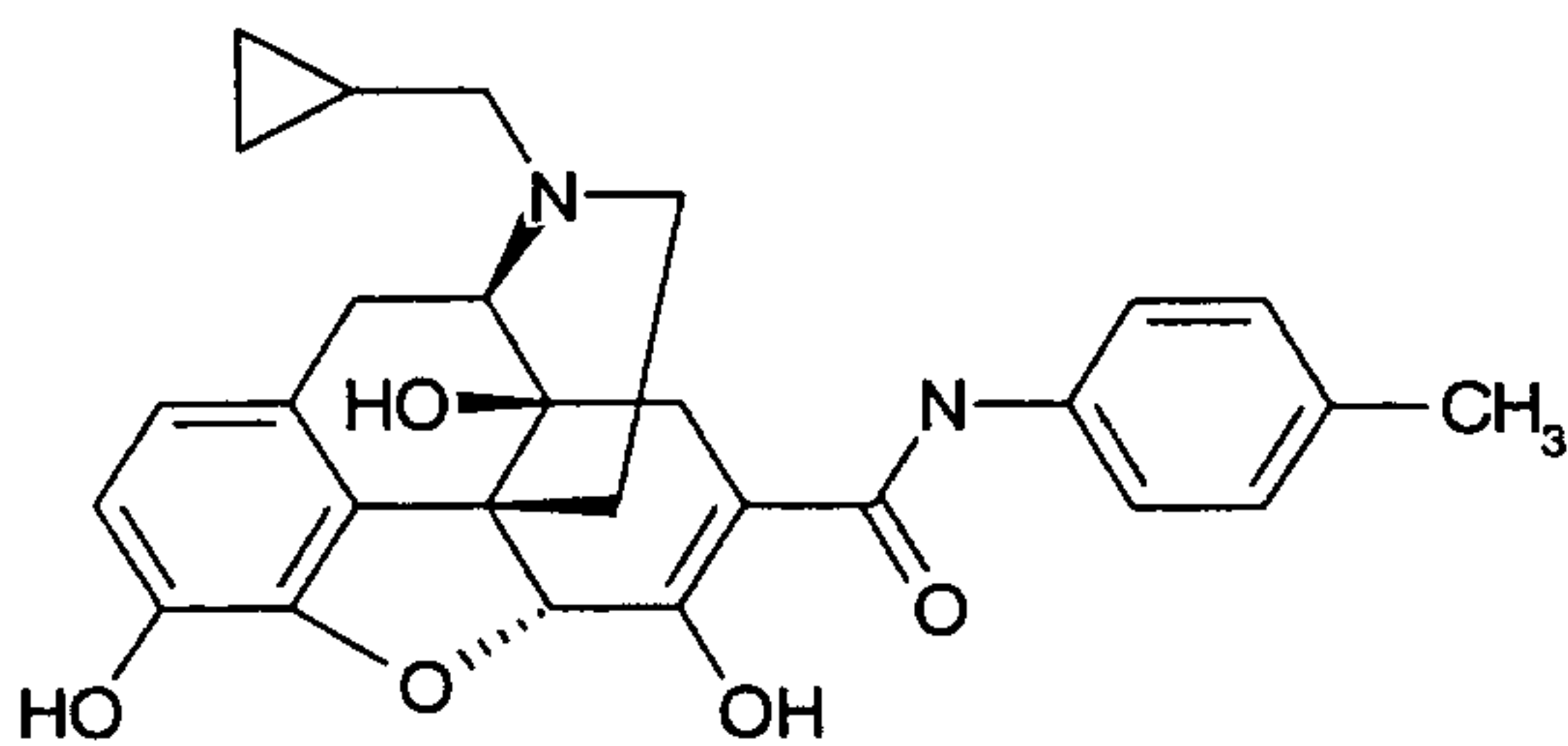
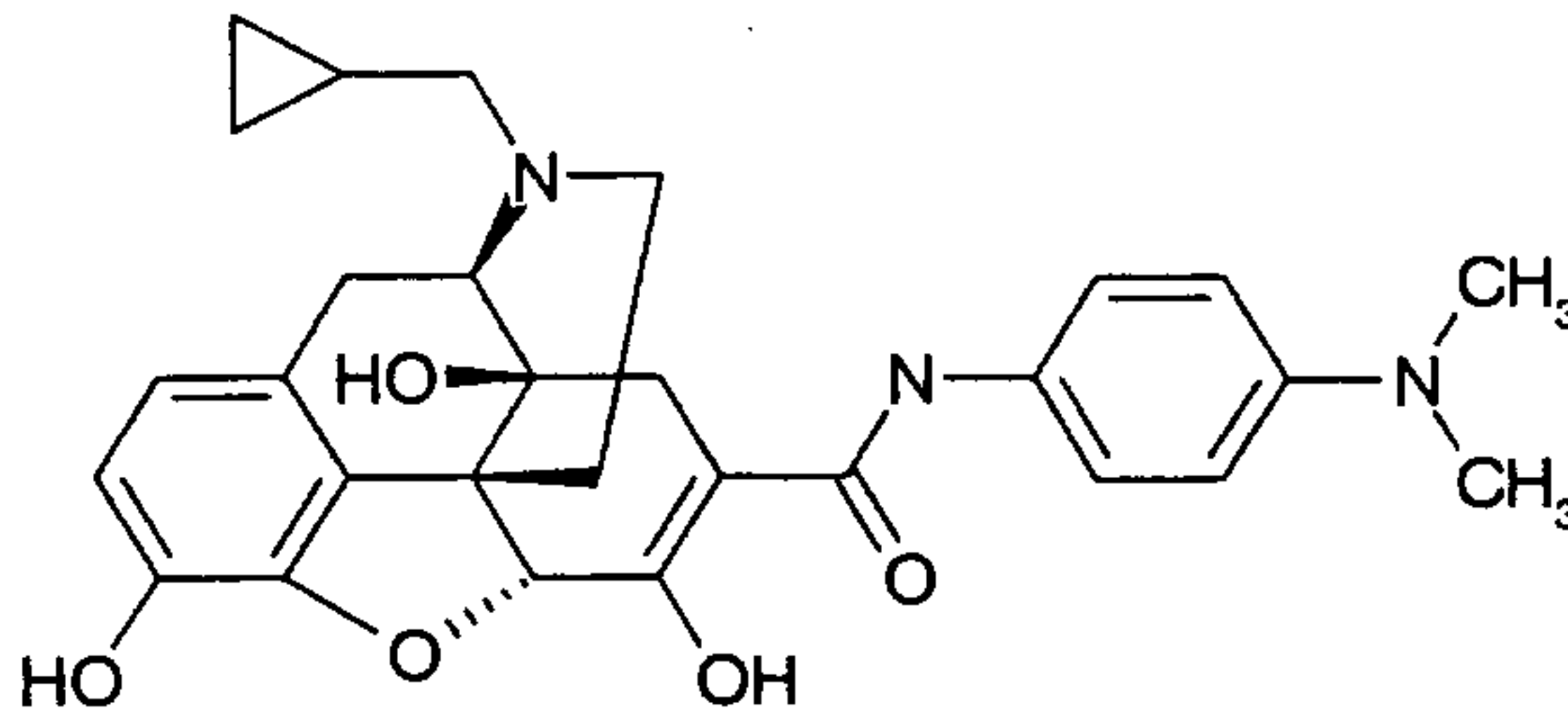
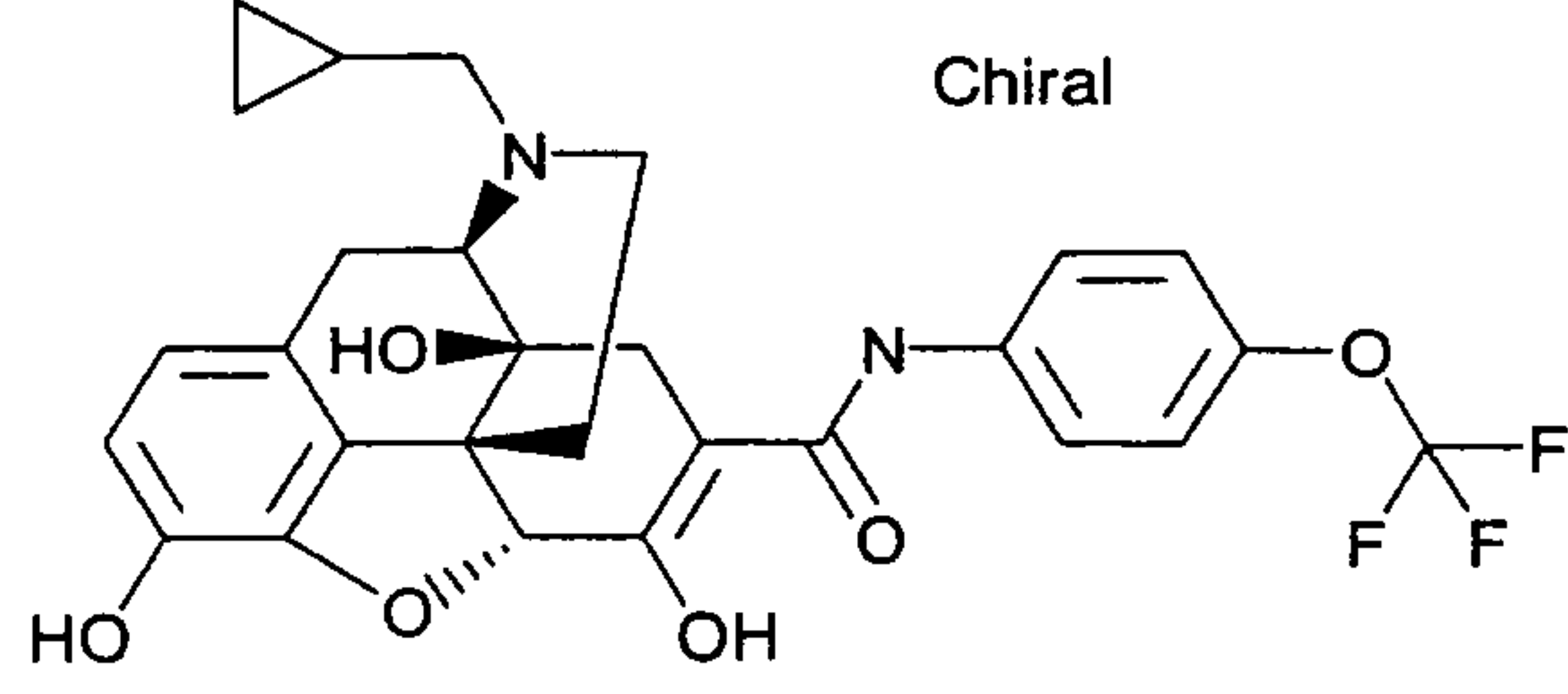
[0058]

[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).
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)

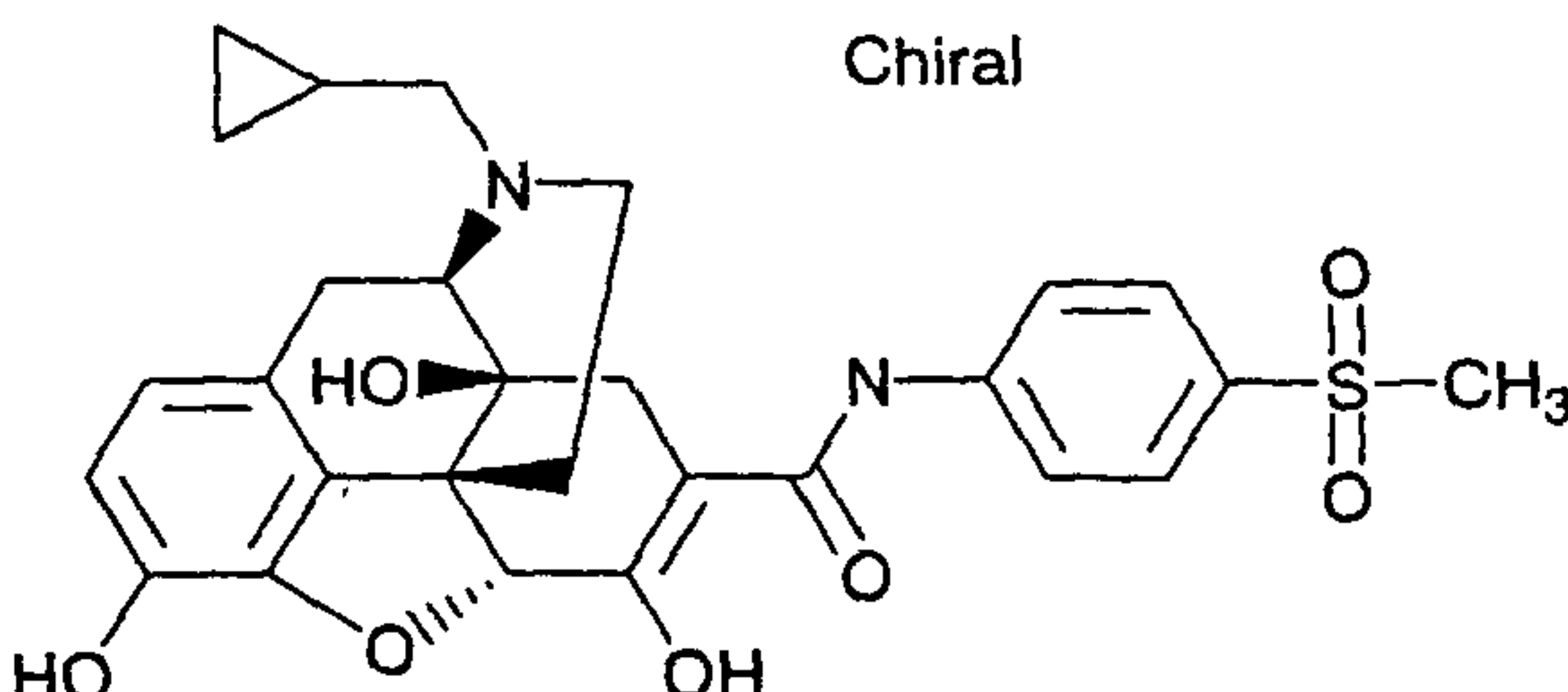
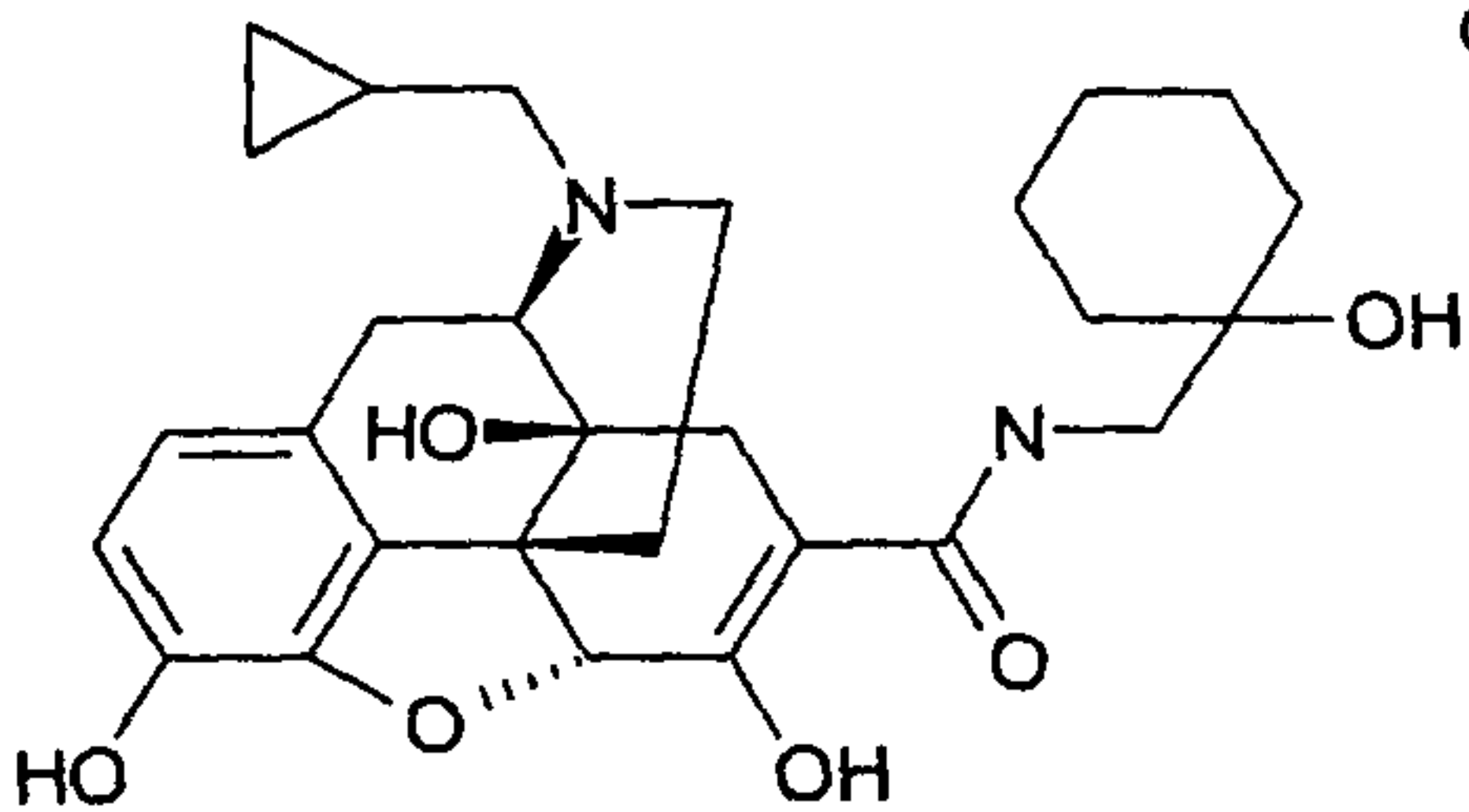
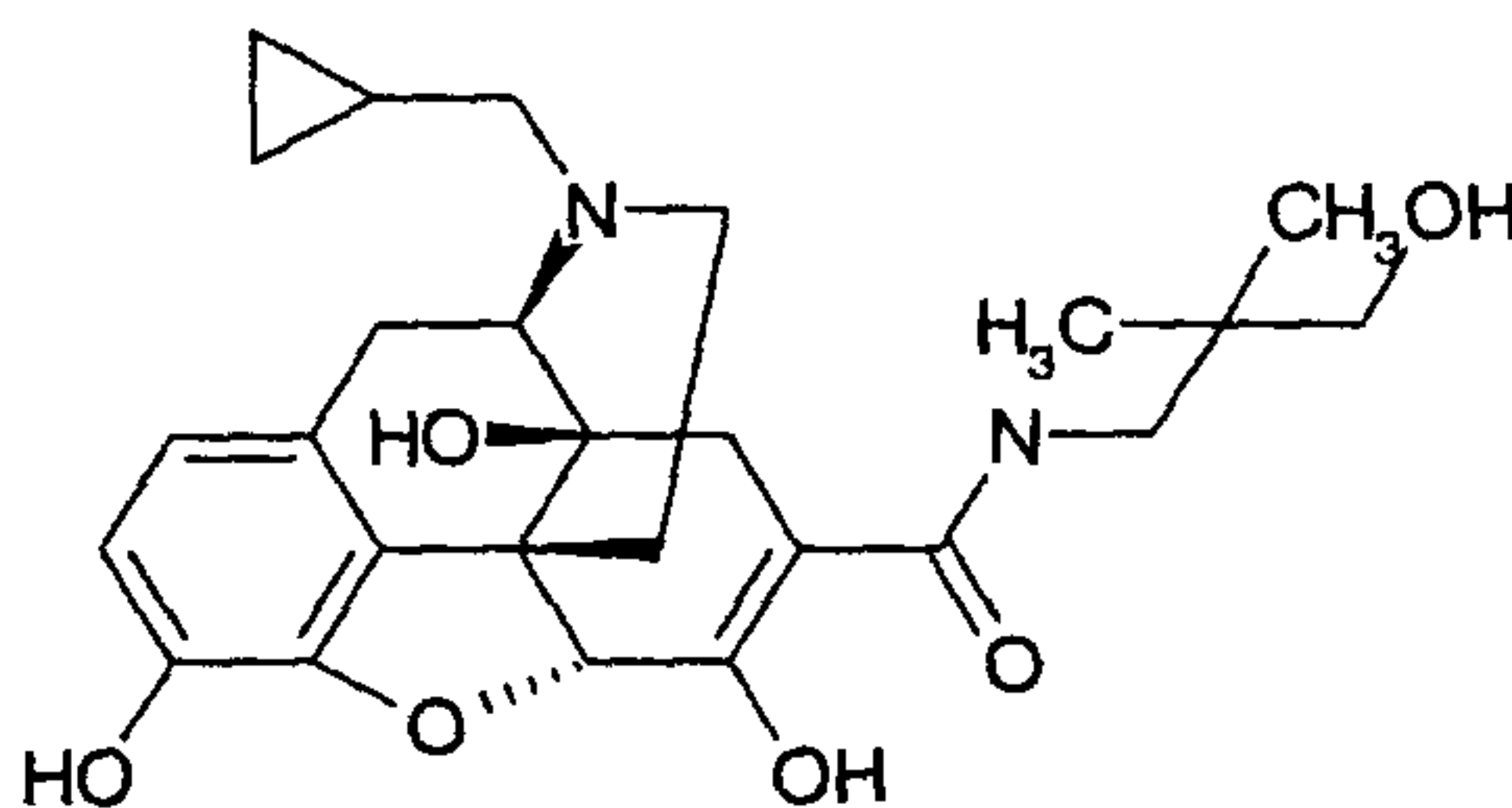
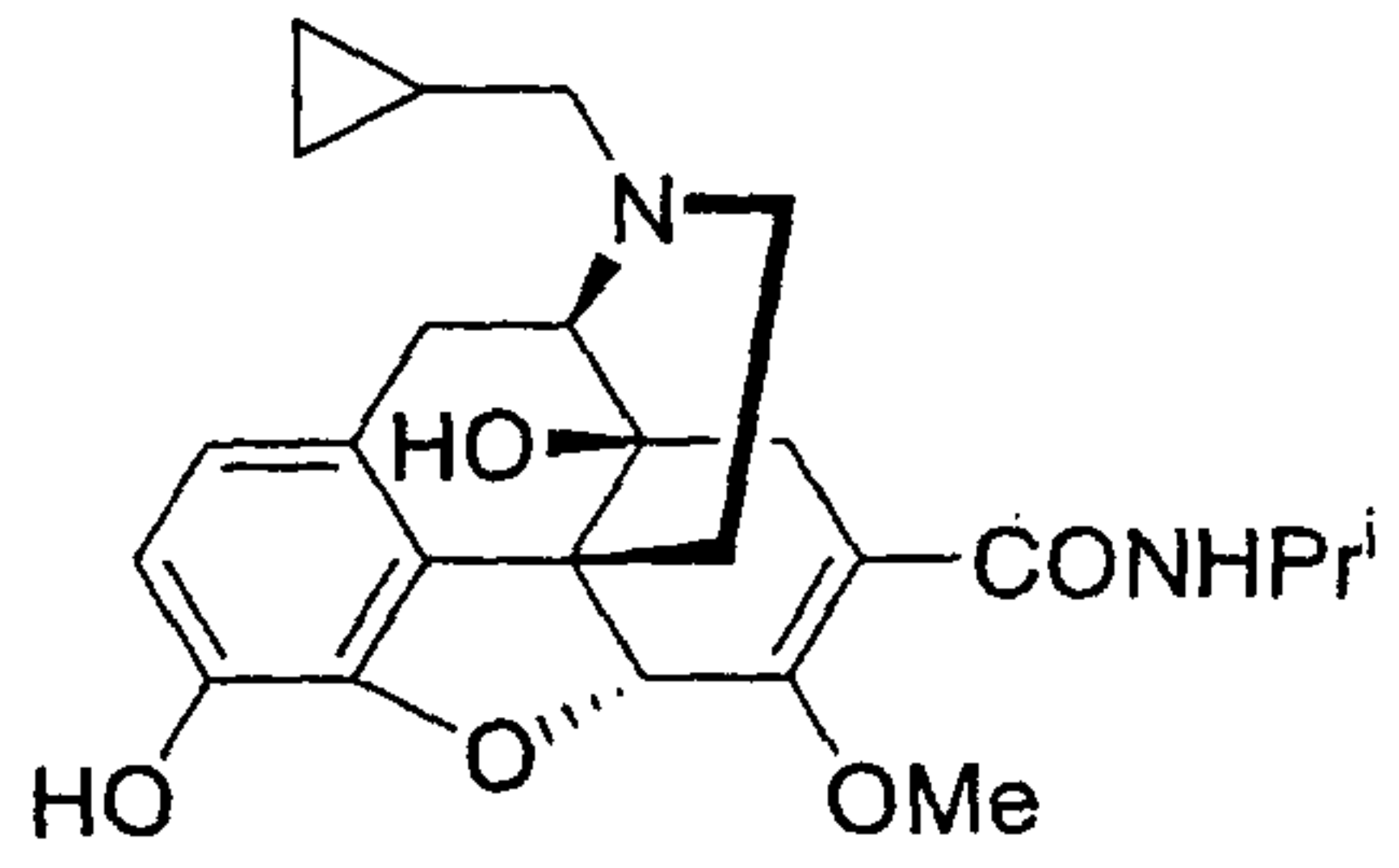
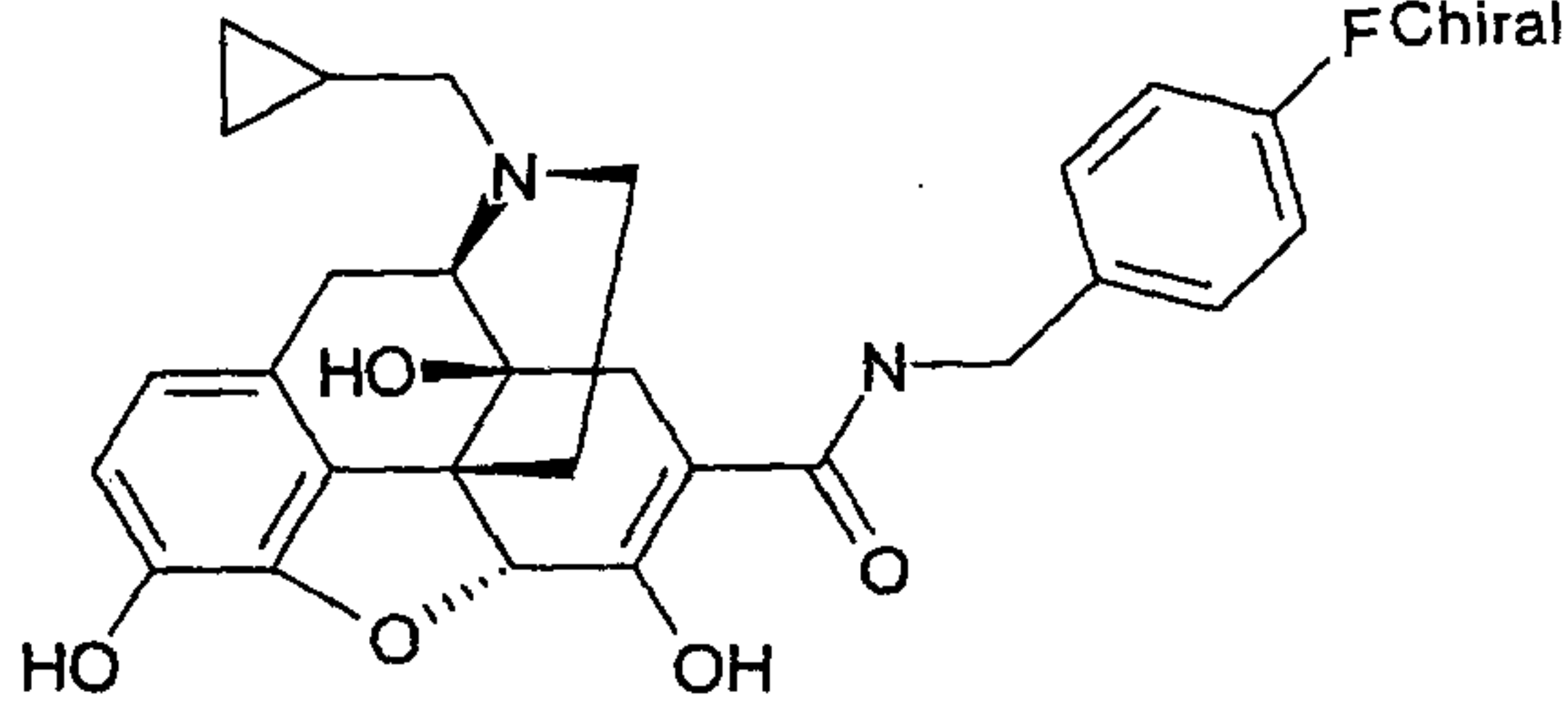
[0059]

[Table 14]

Compound No.	Chemical structure	NMR (¹ H-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, 1H)

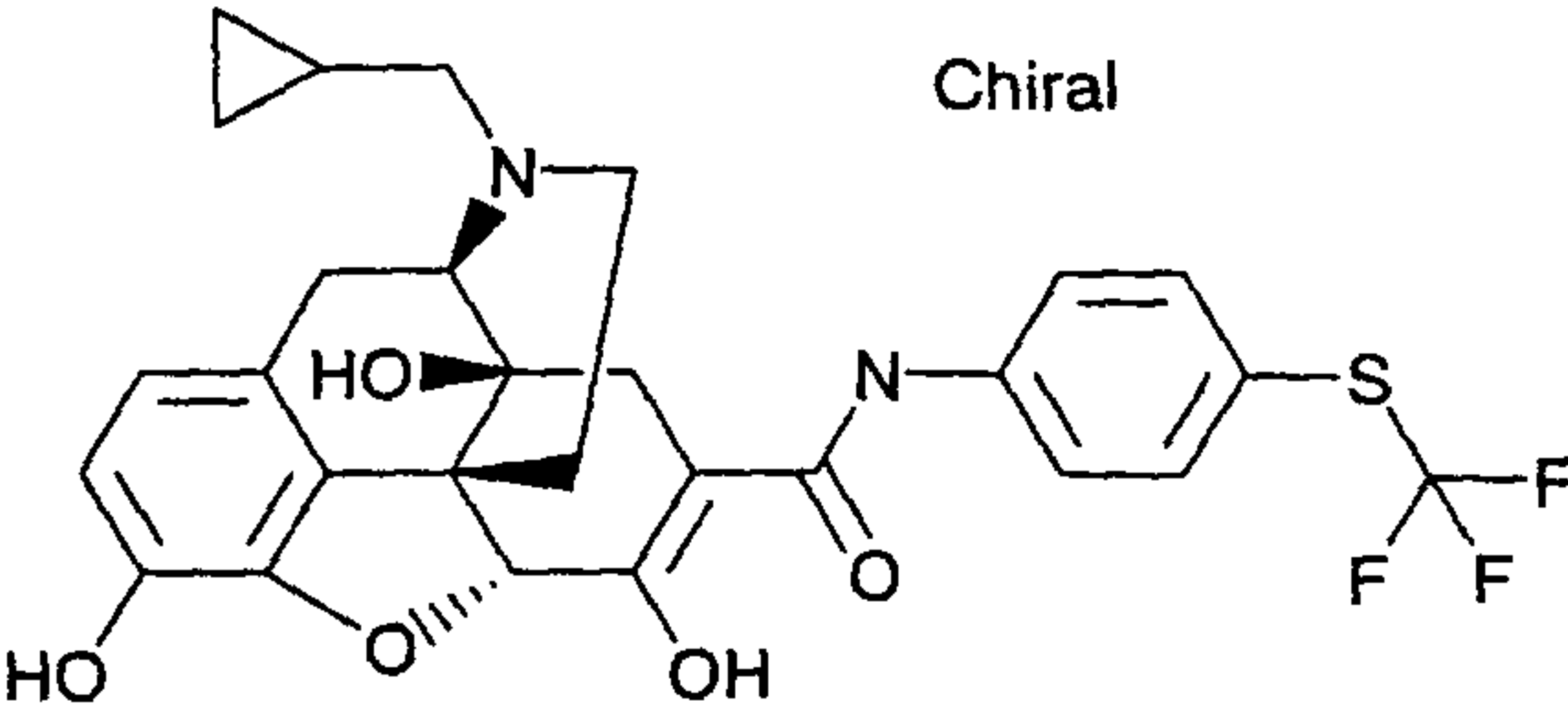
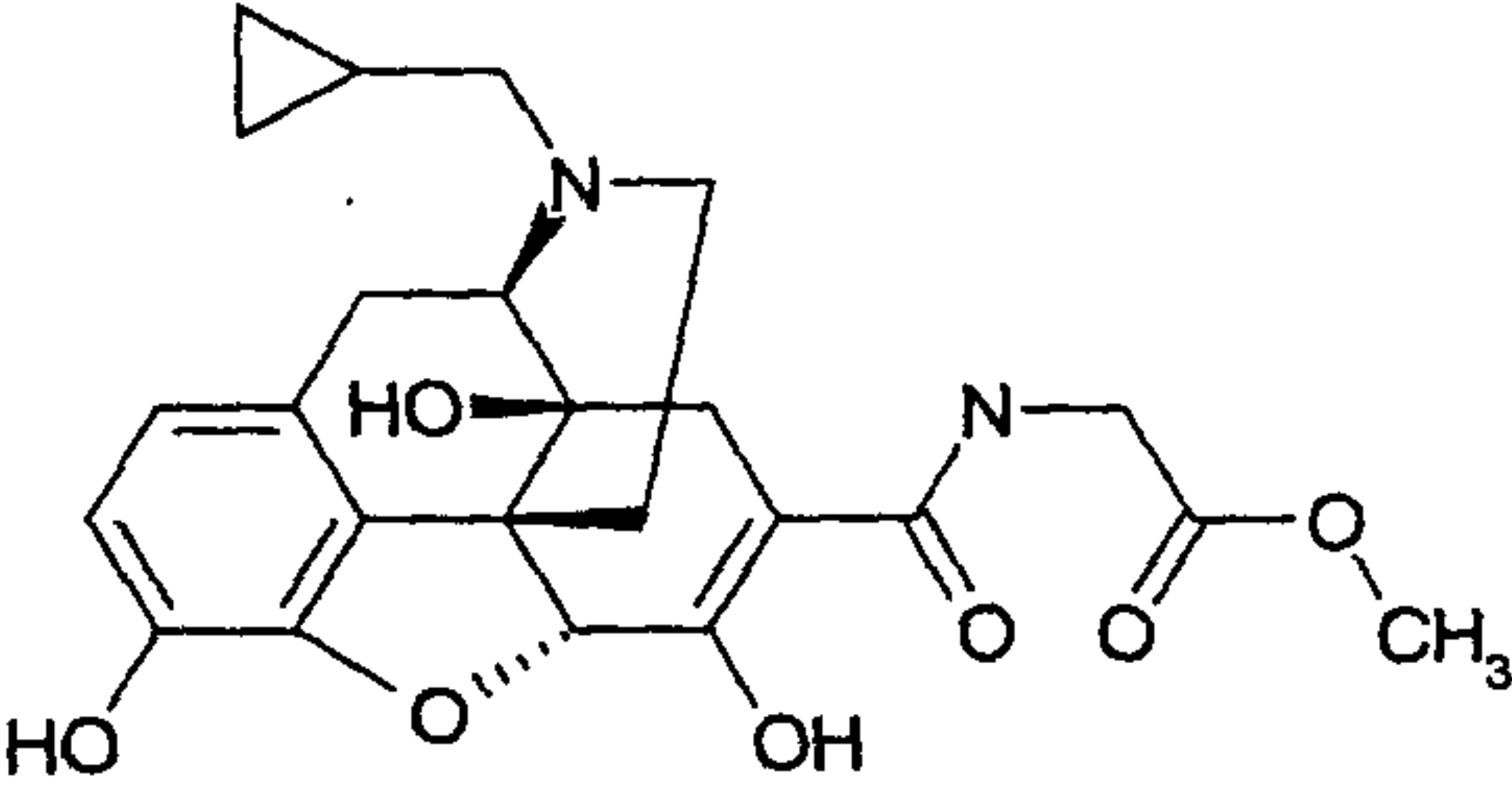
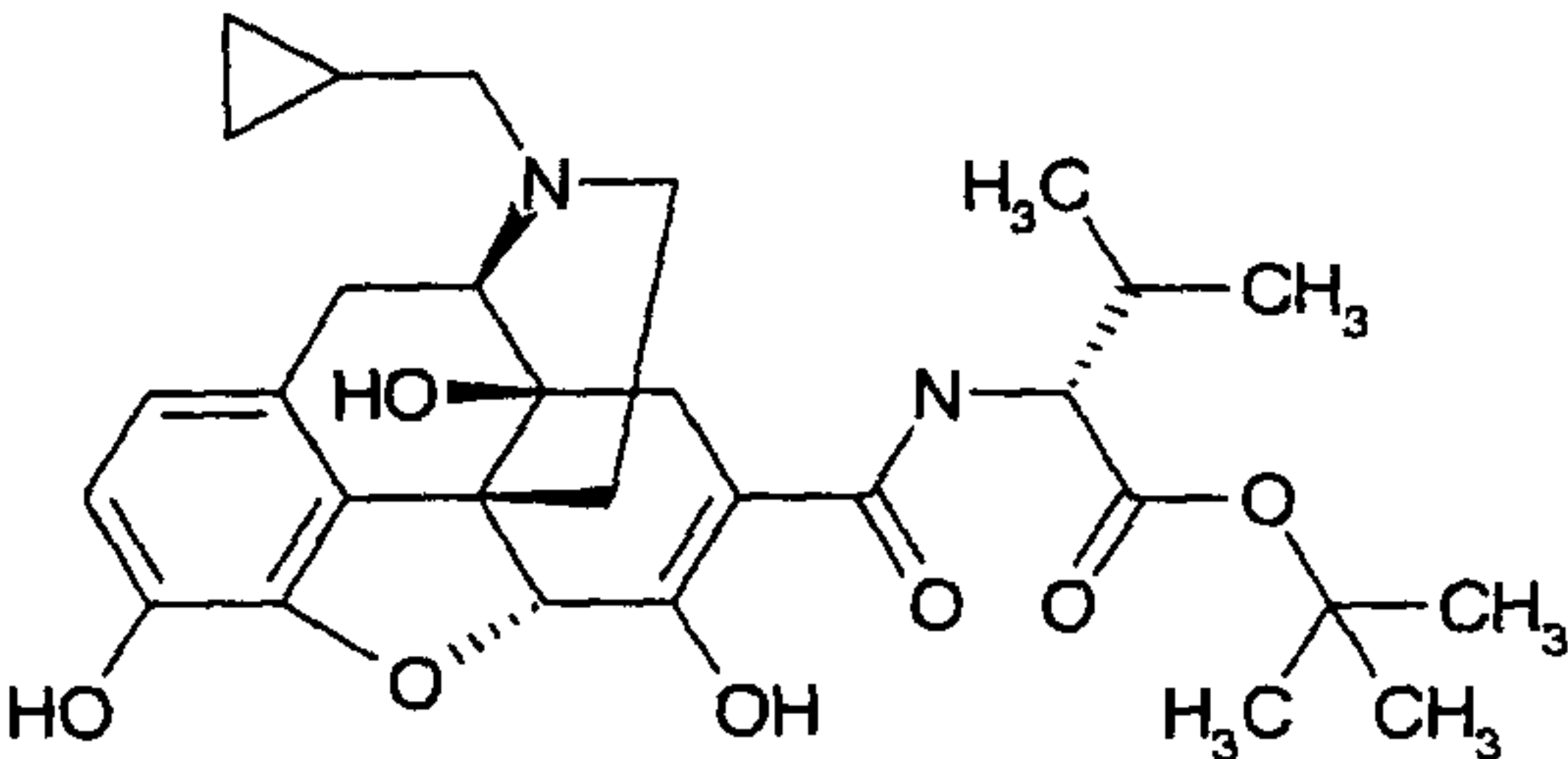
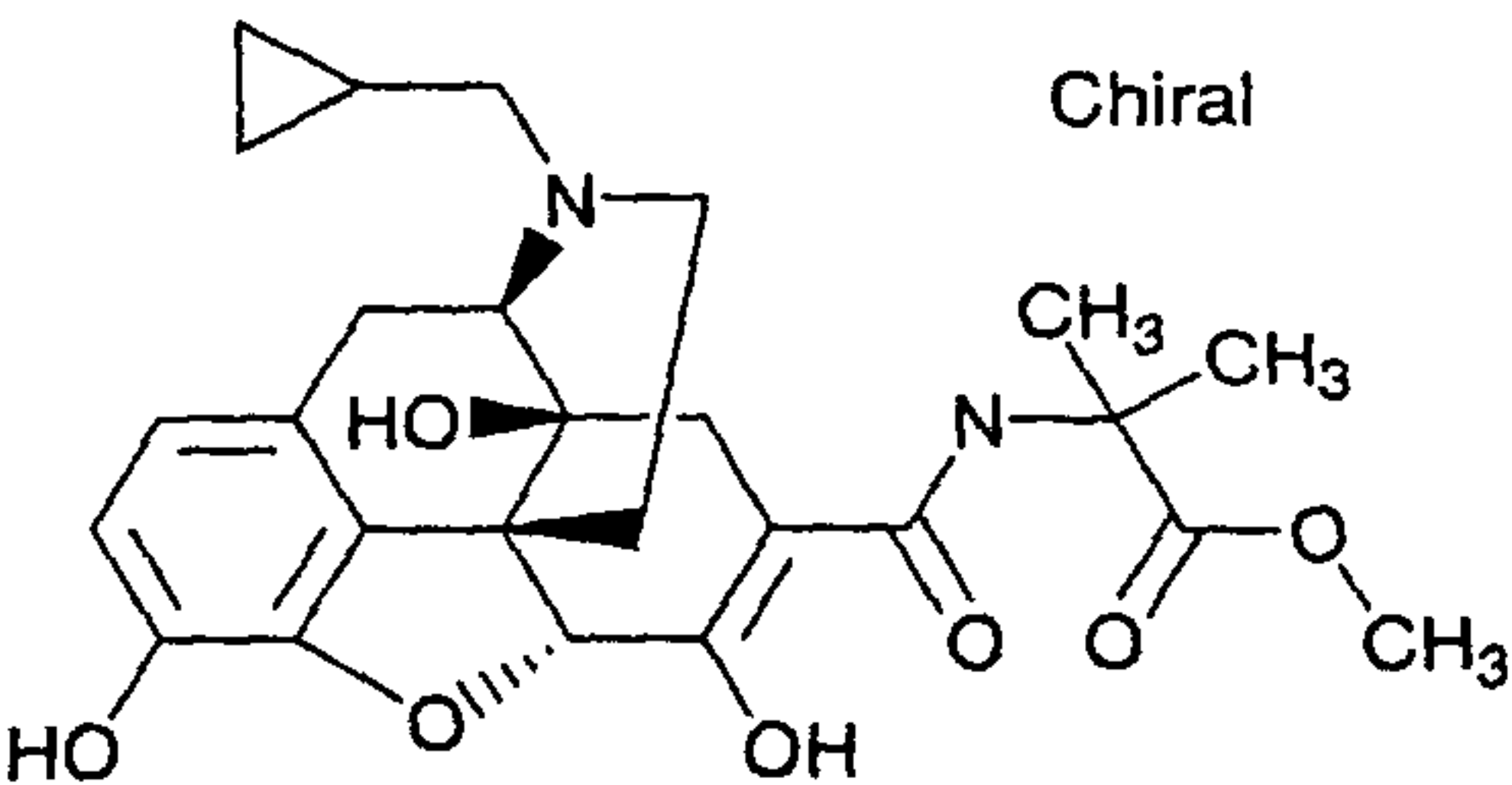
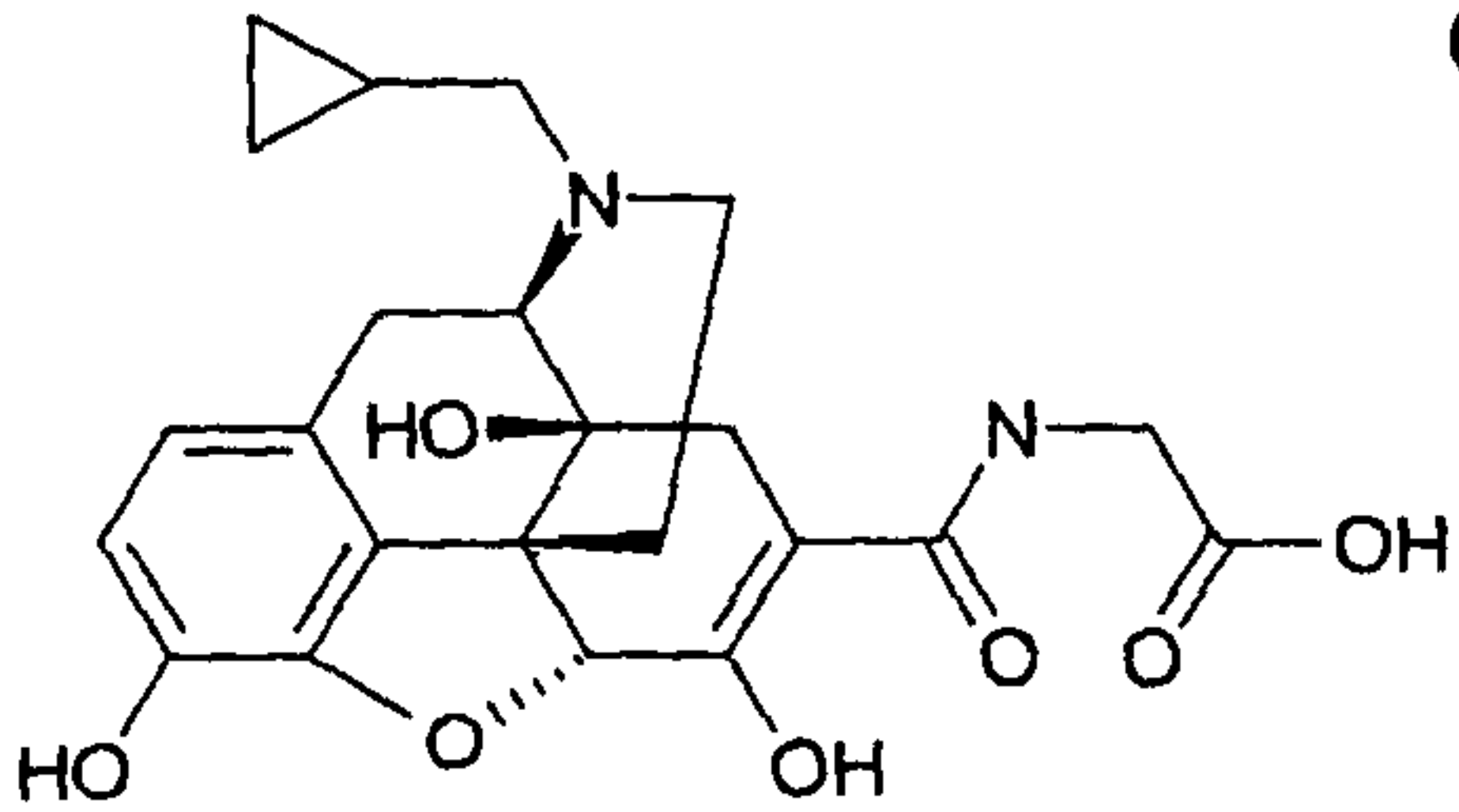
[0060]

[Table 15]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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	FChiral 	

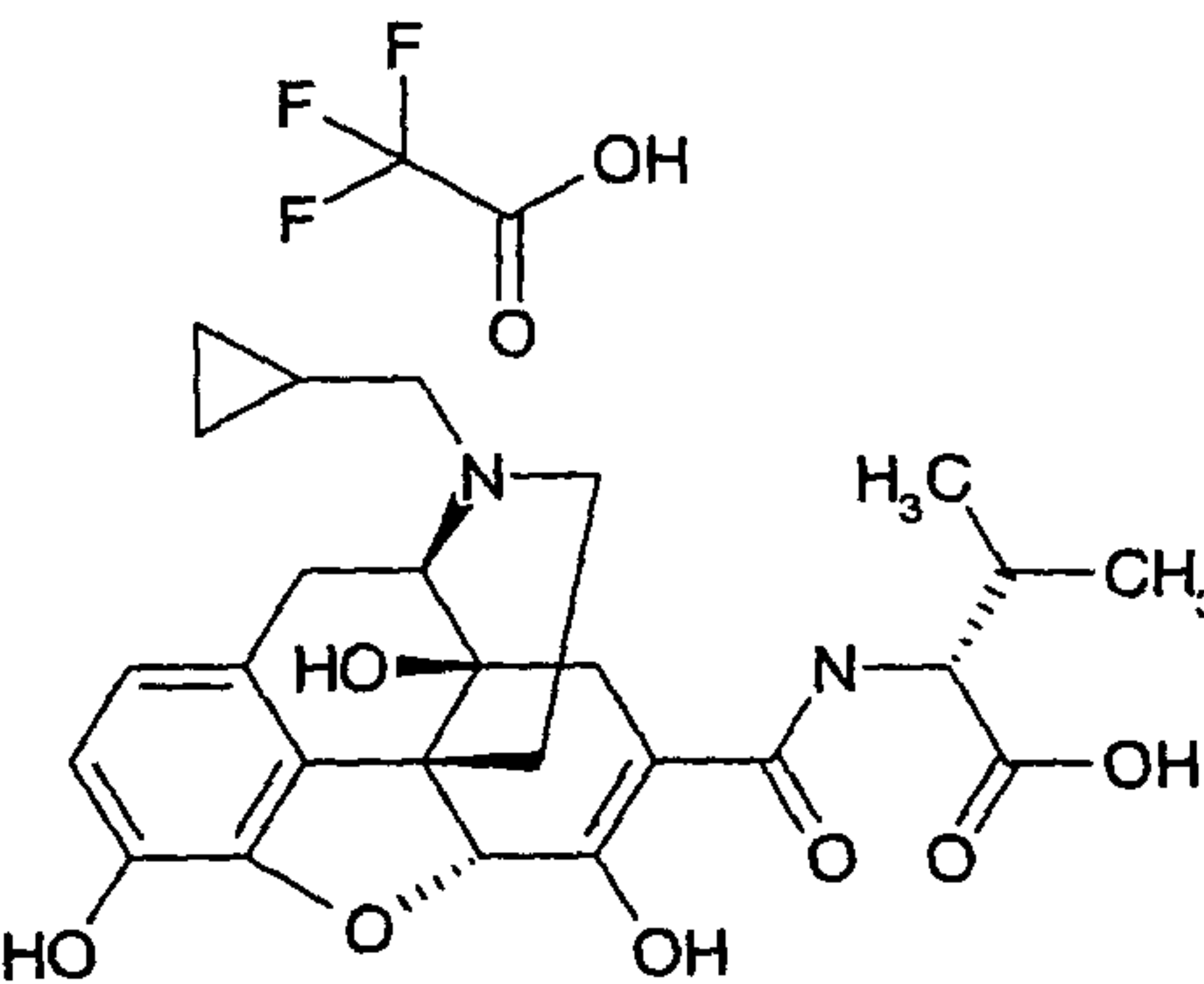
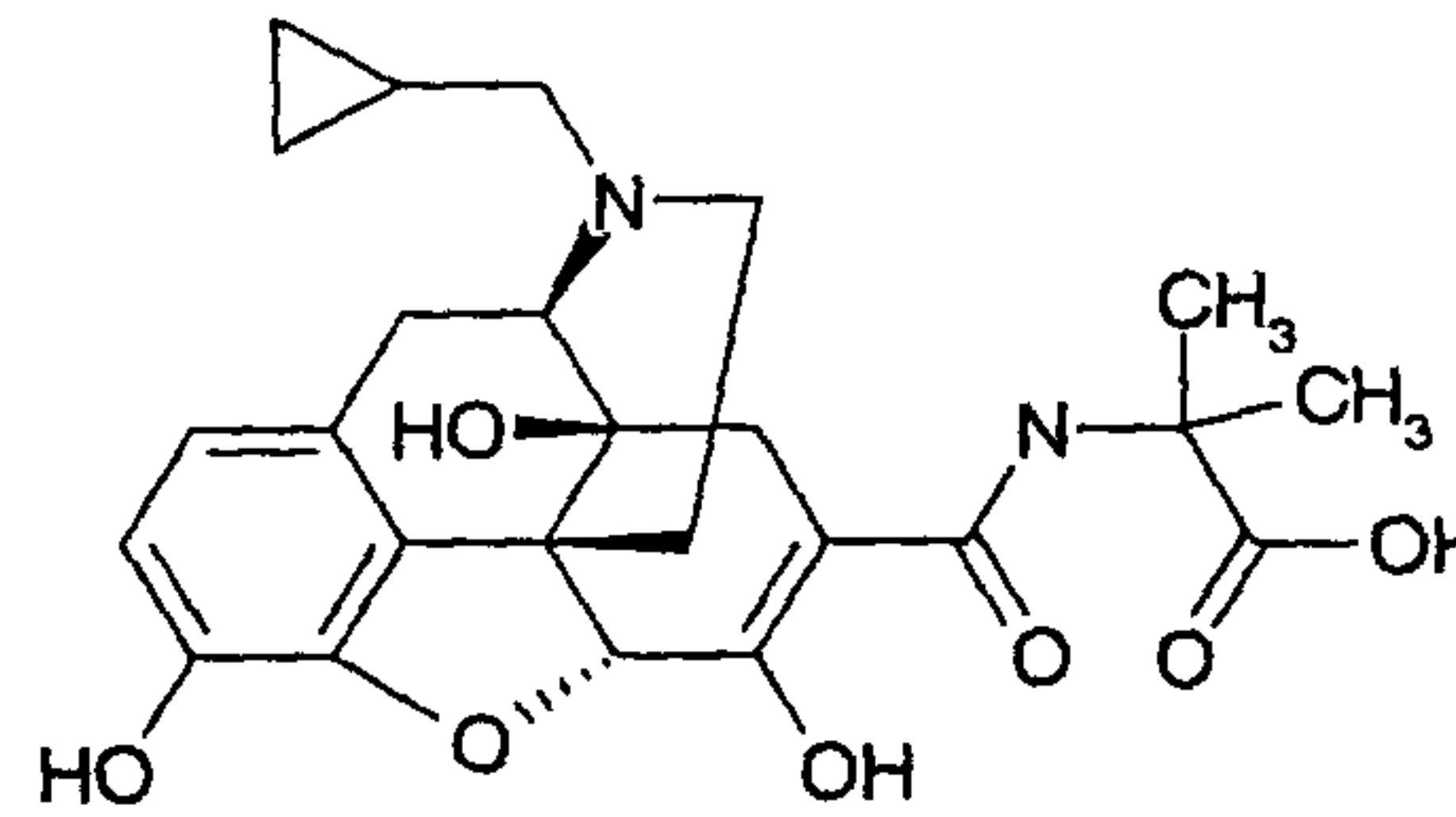
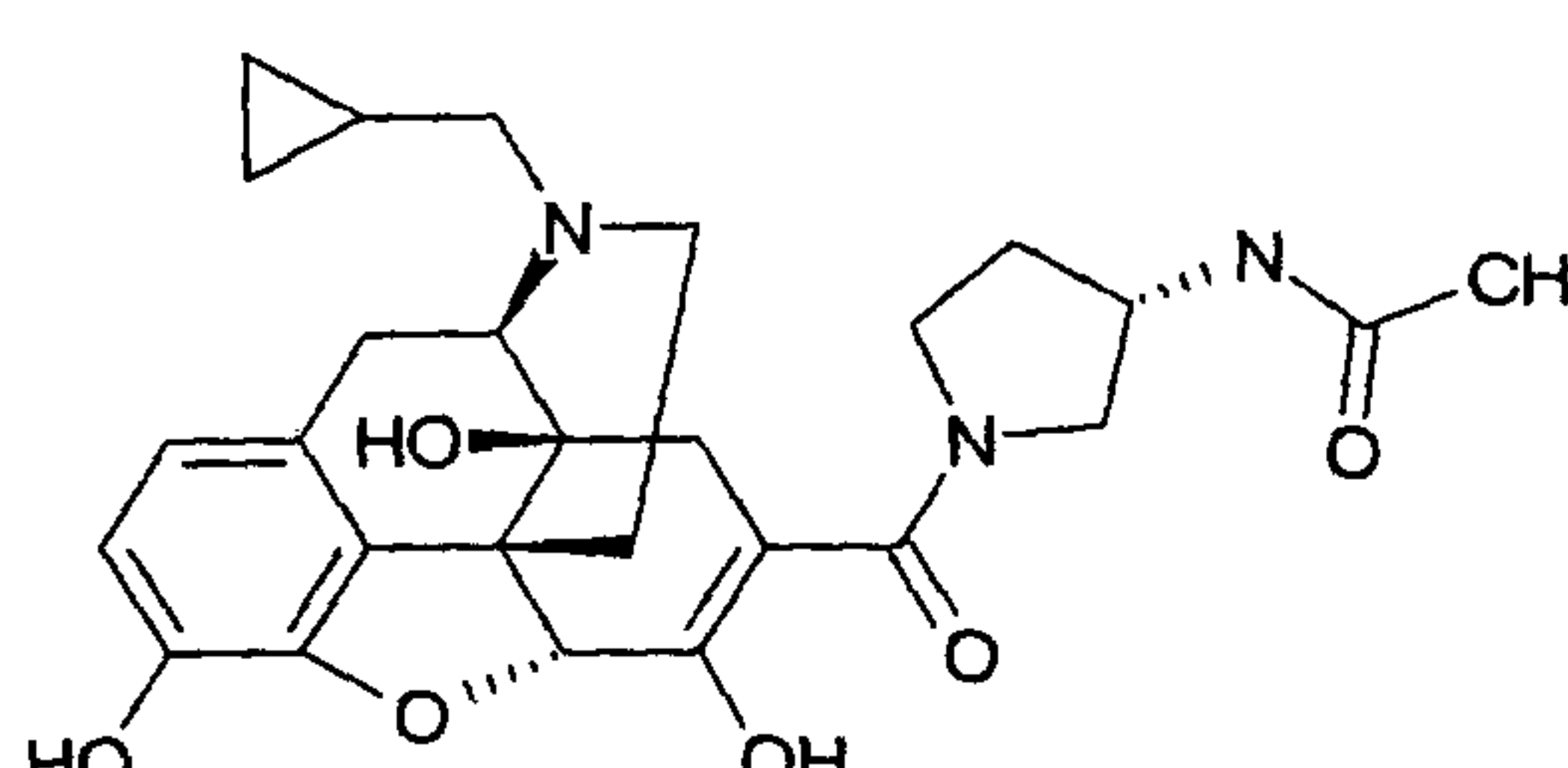
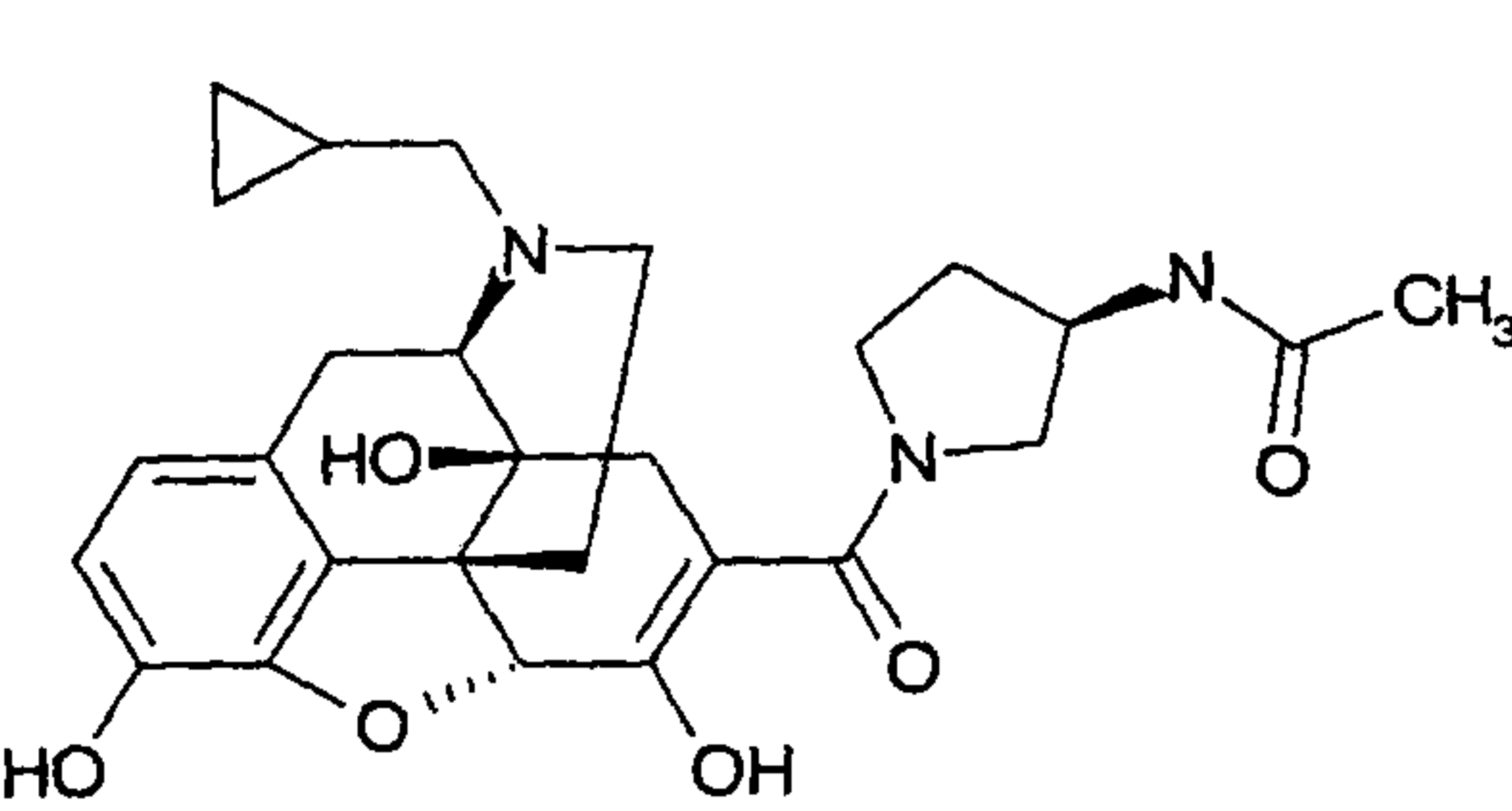
[0061]

[Table 16]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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)

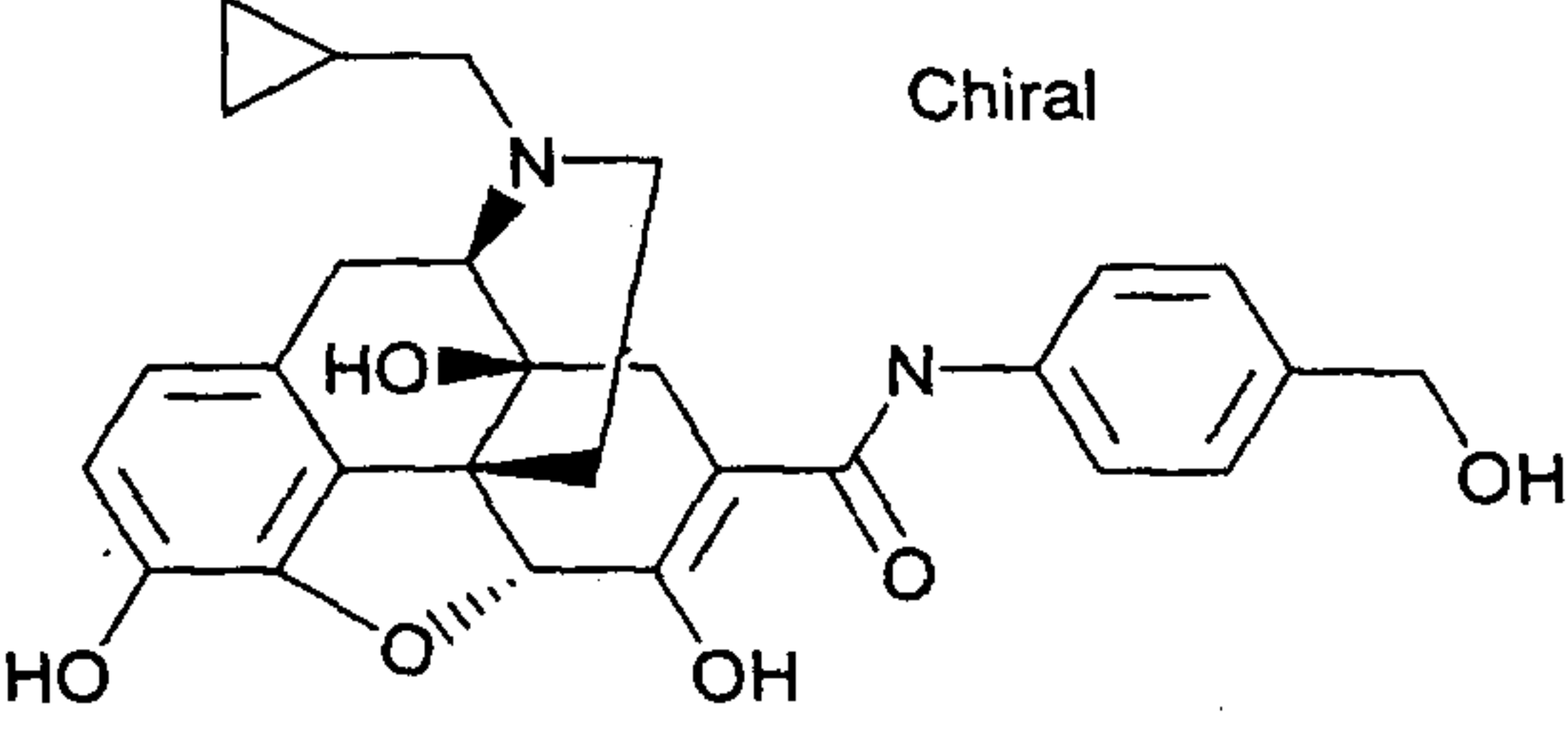
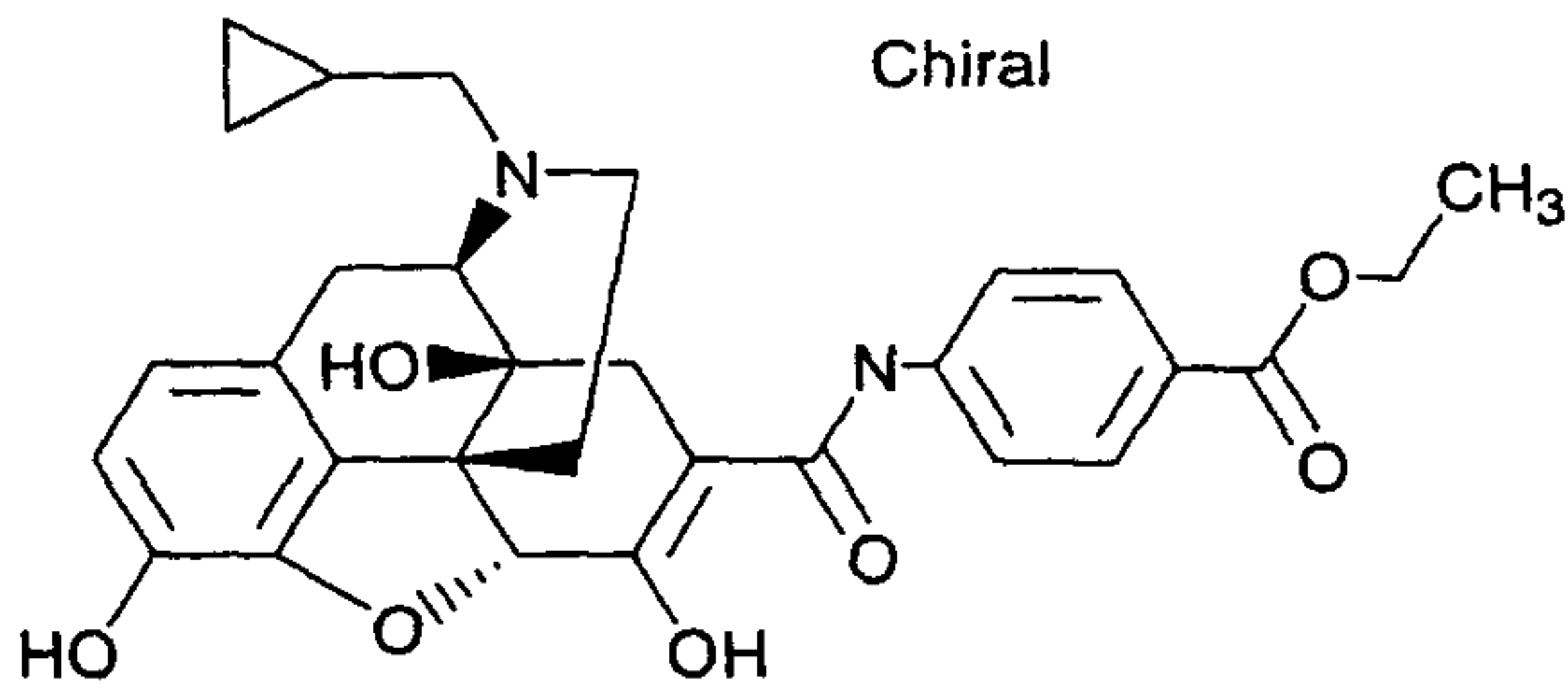
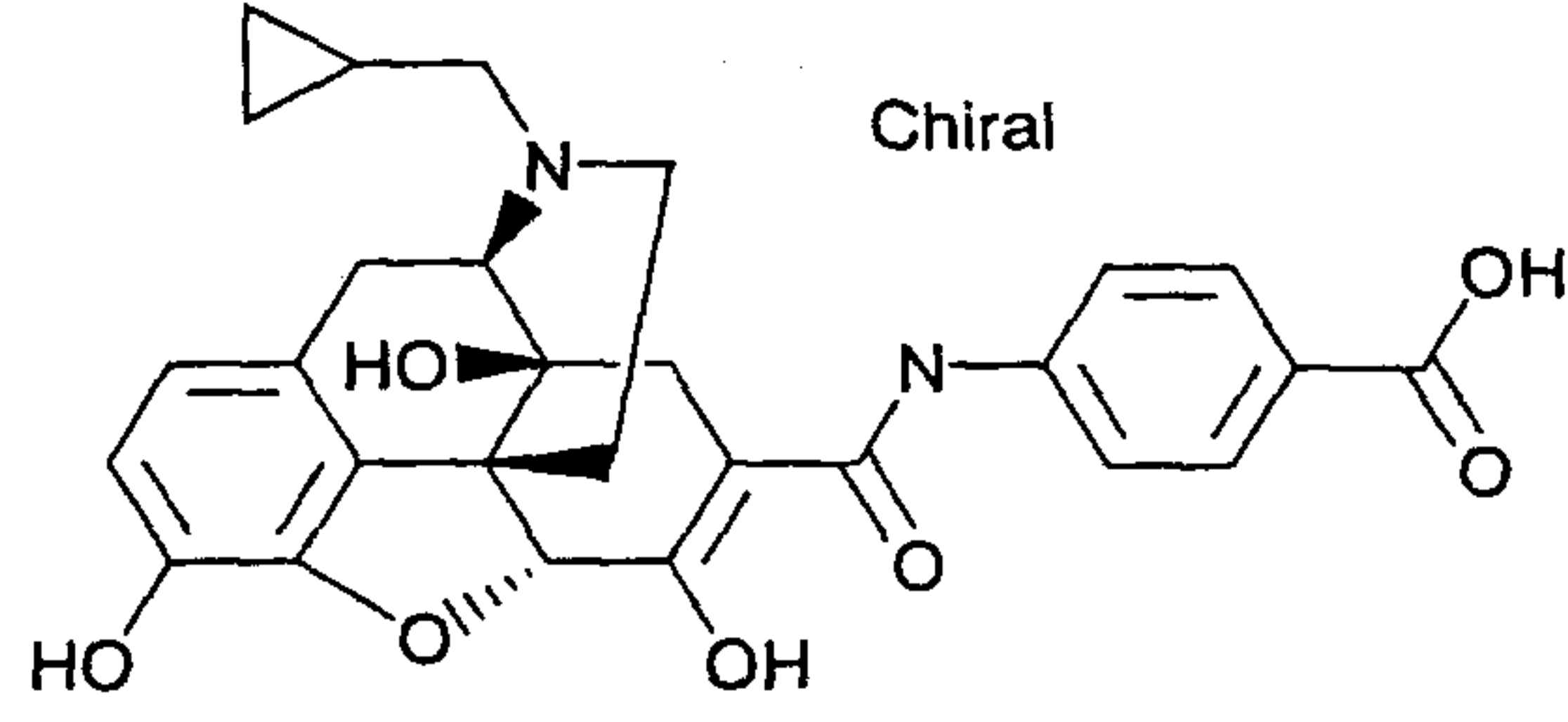
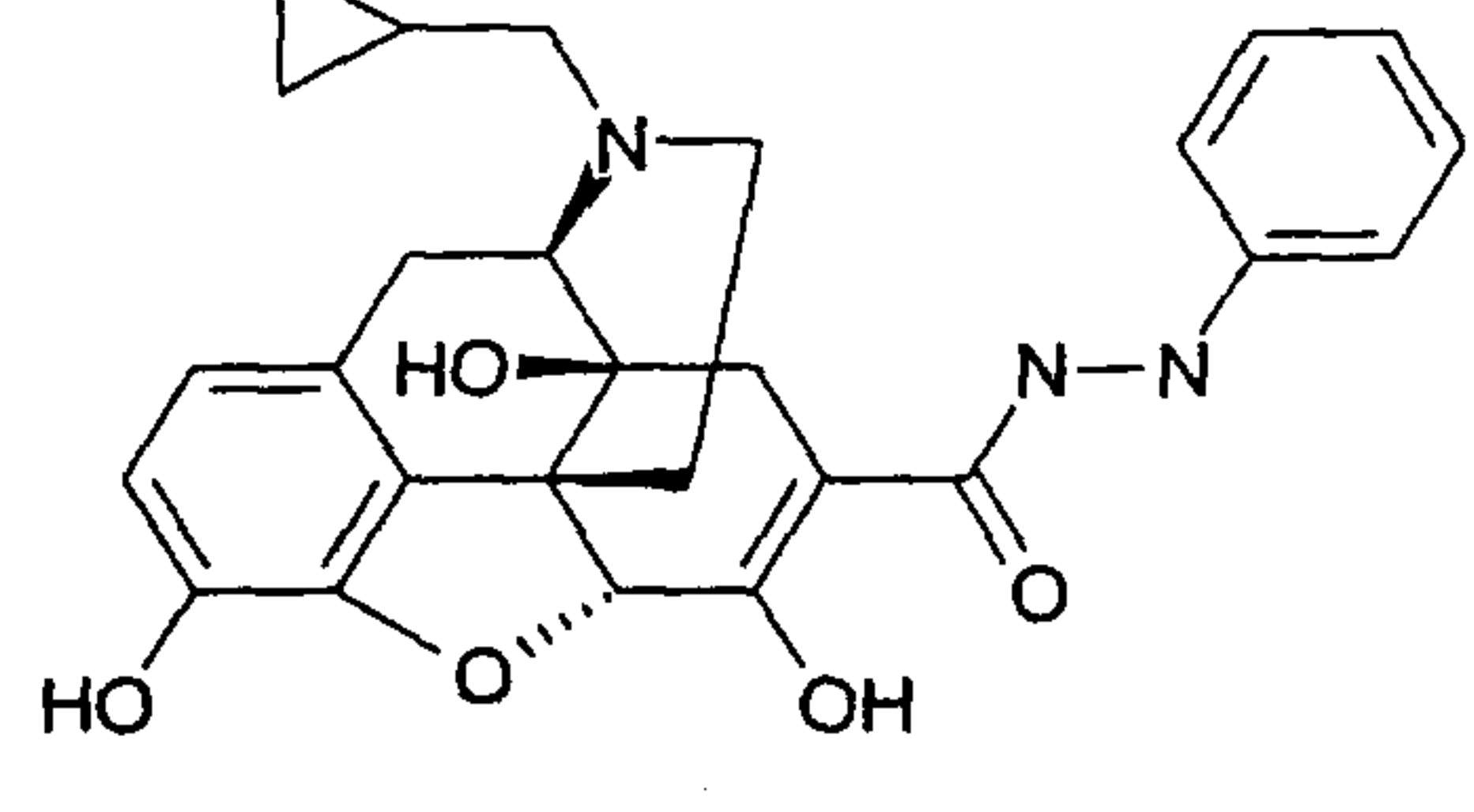
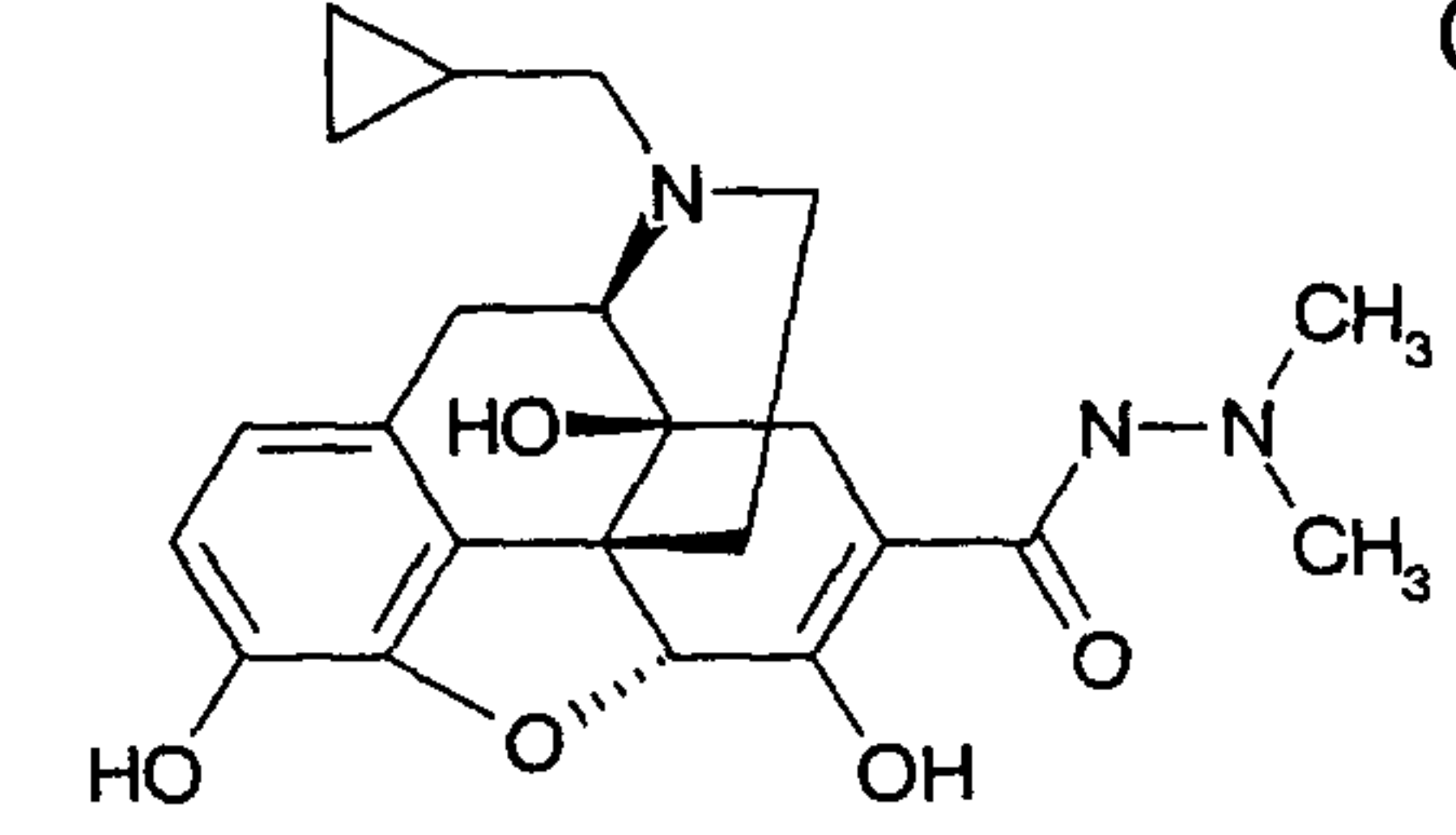
[0062]

[Table 17]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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).

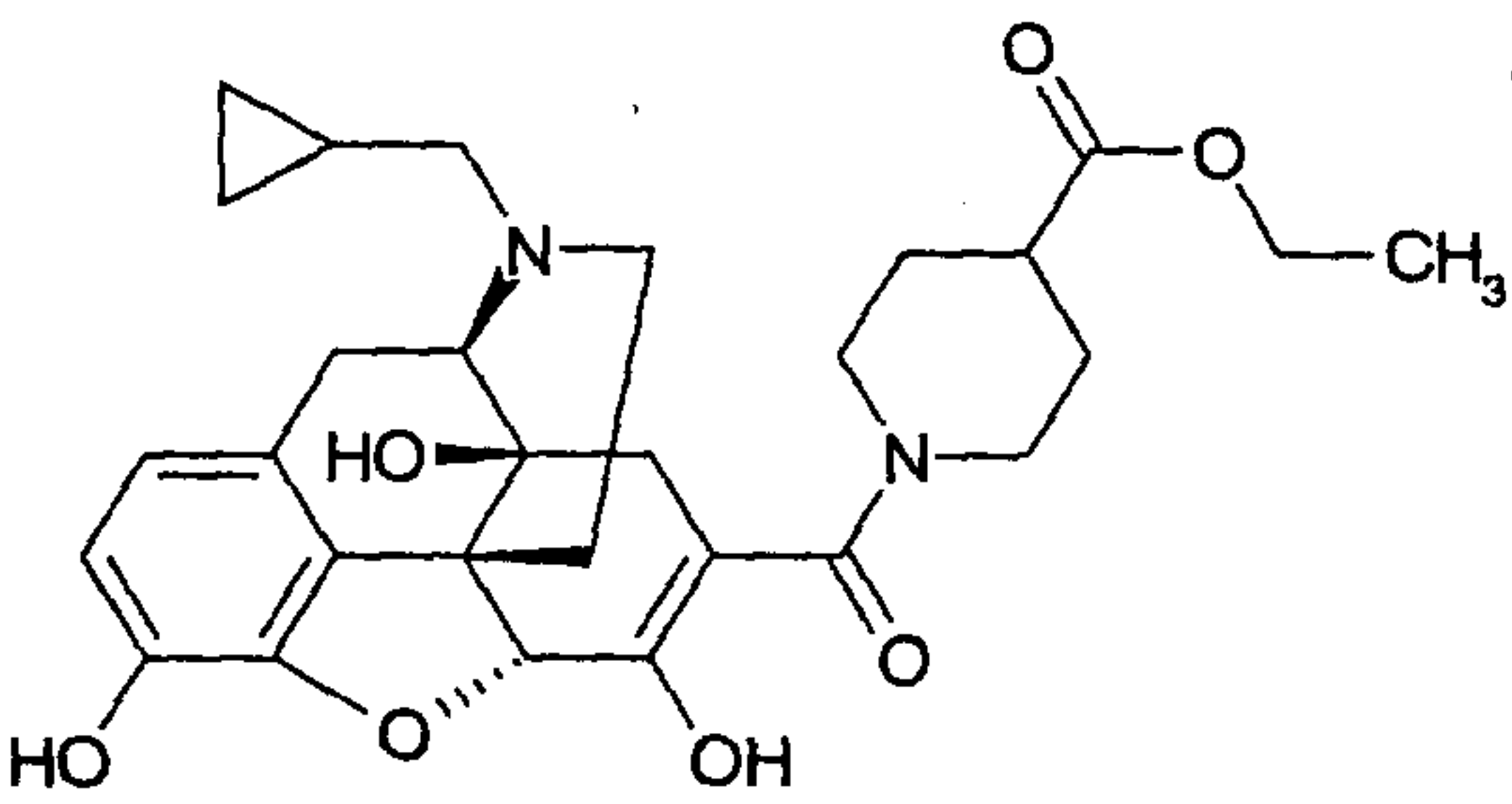
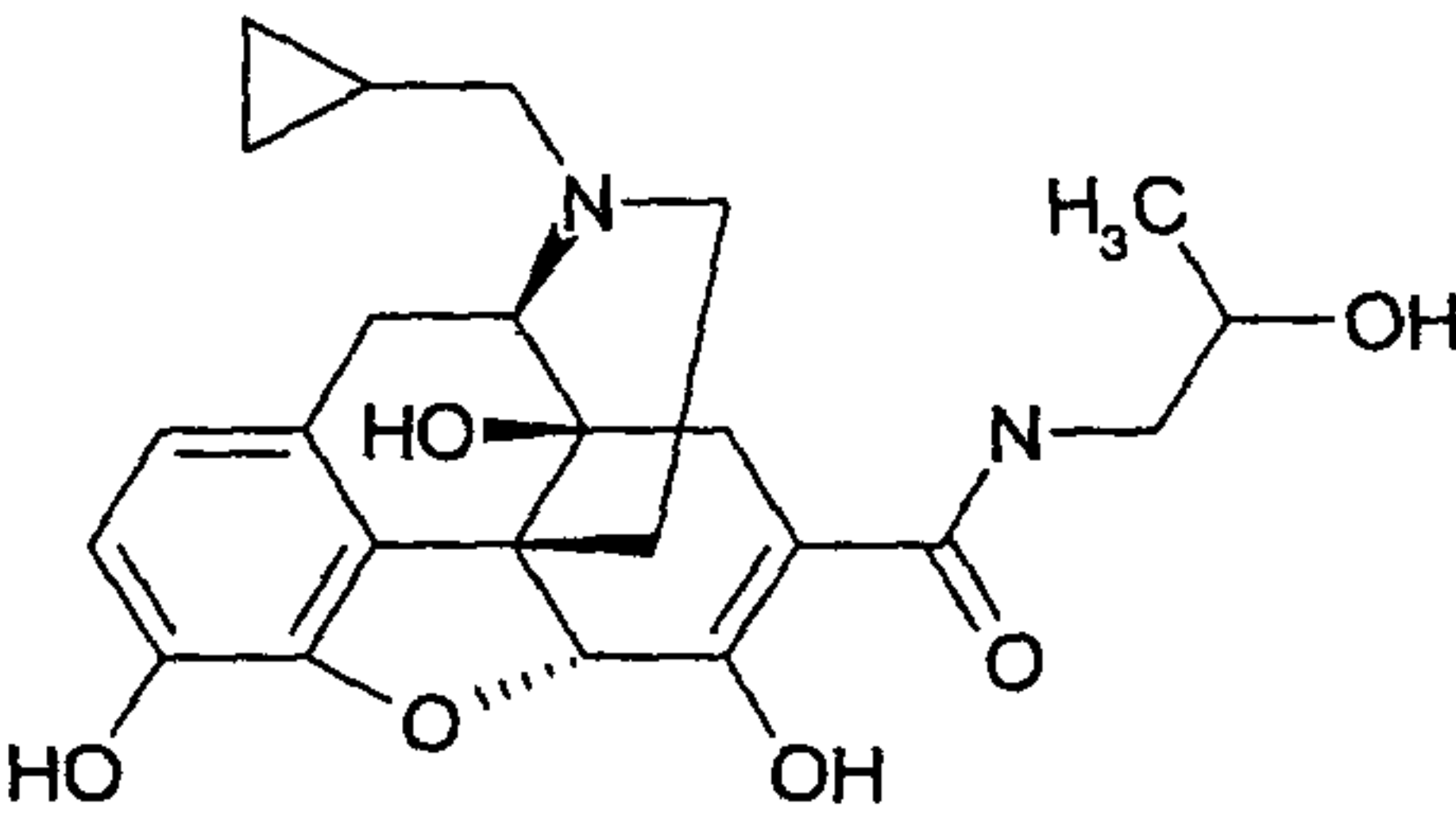
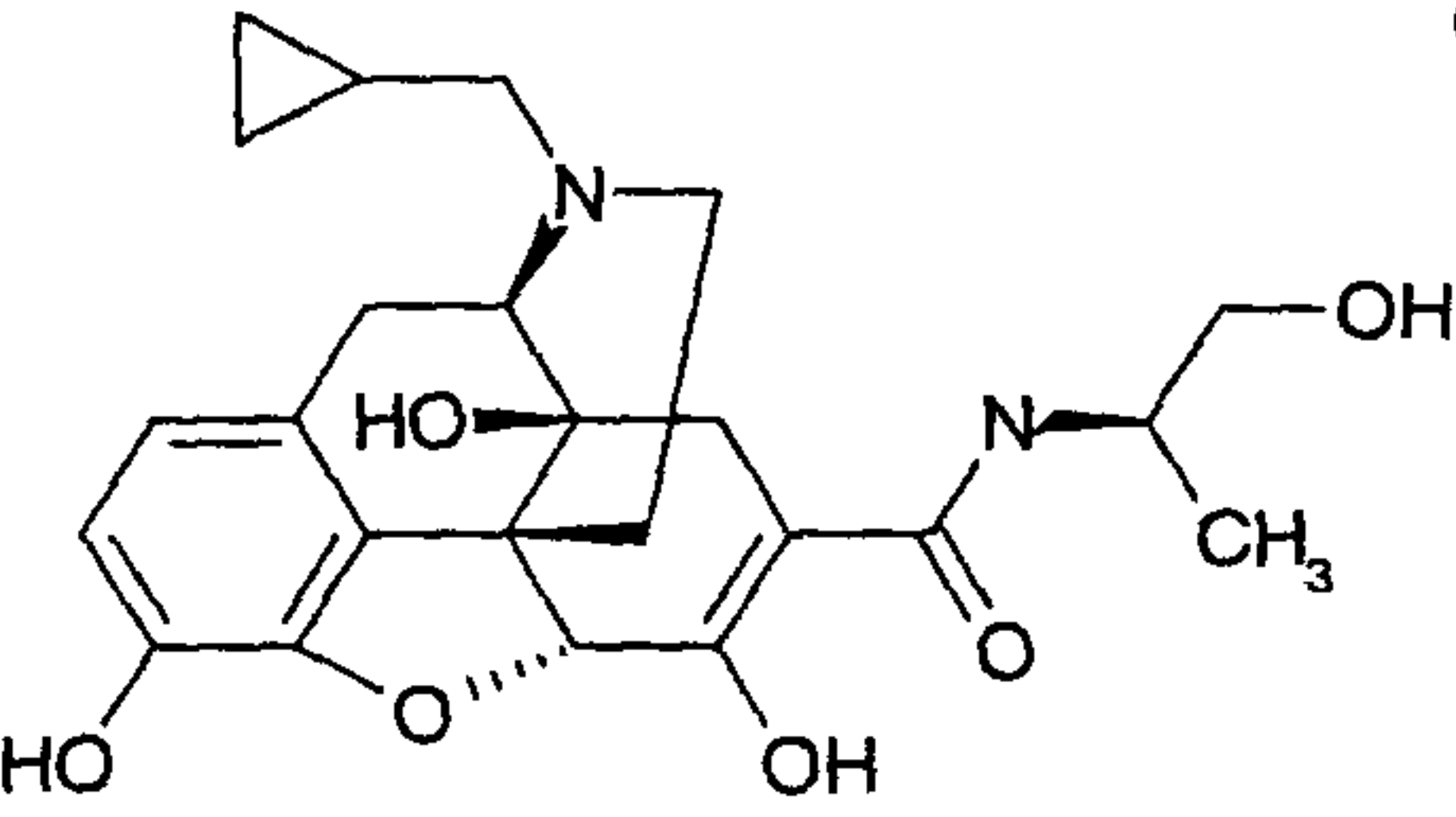
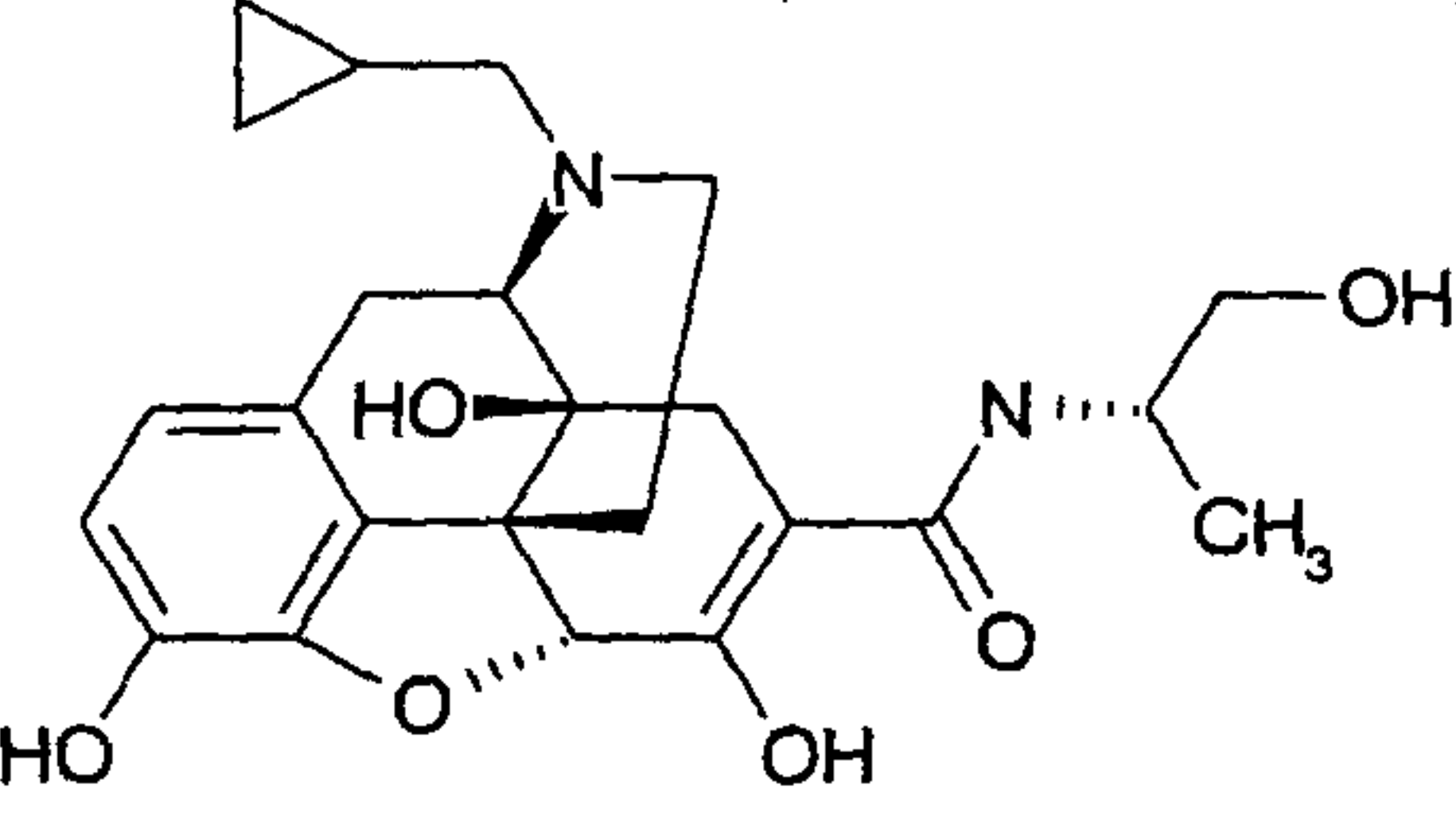
[0063]

[Table 18]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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)

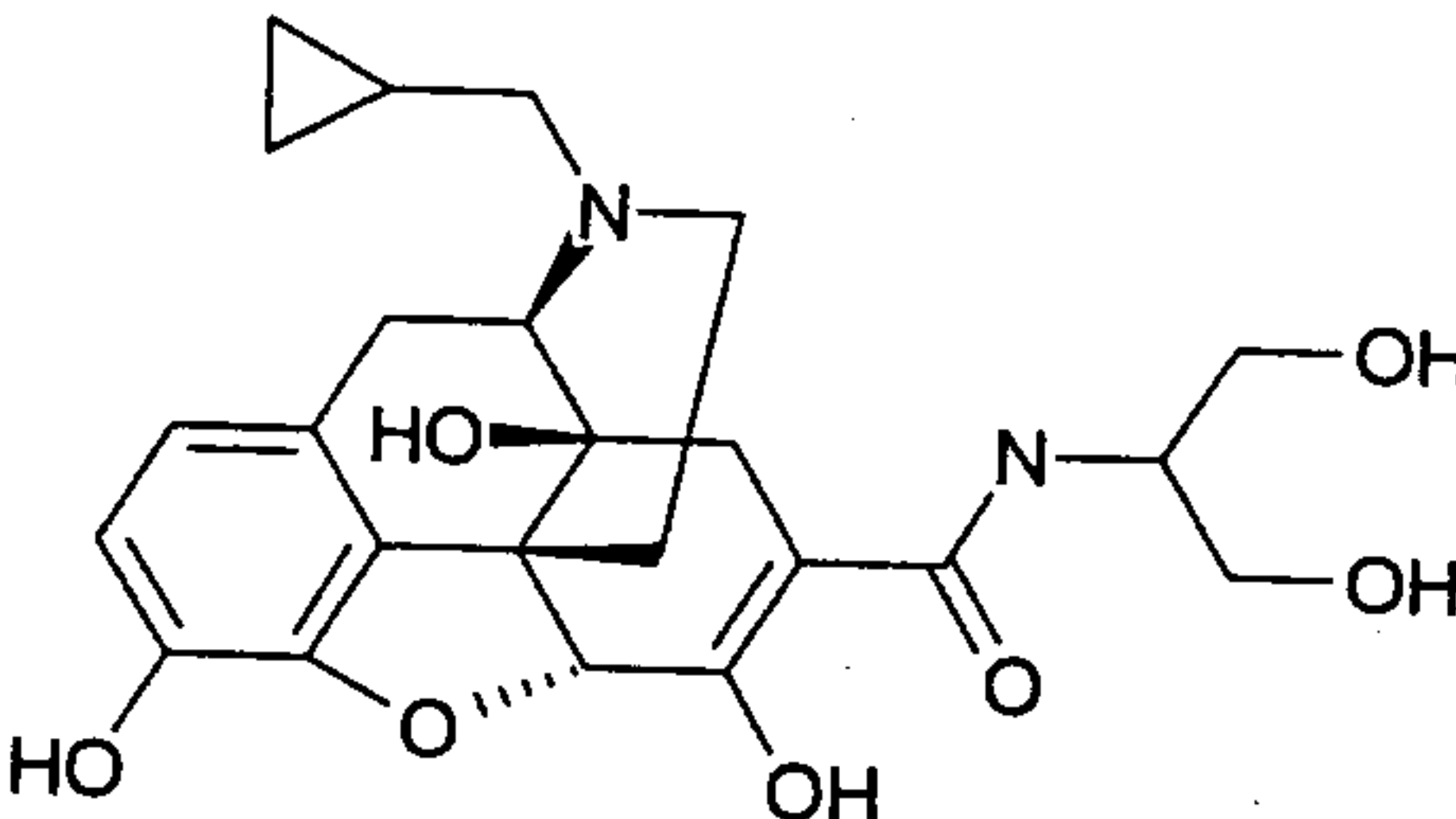
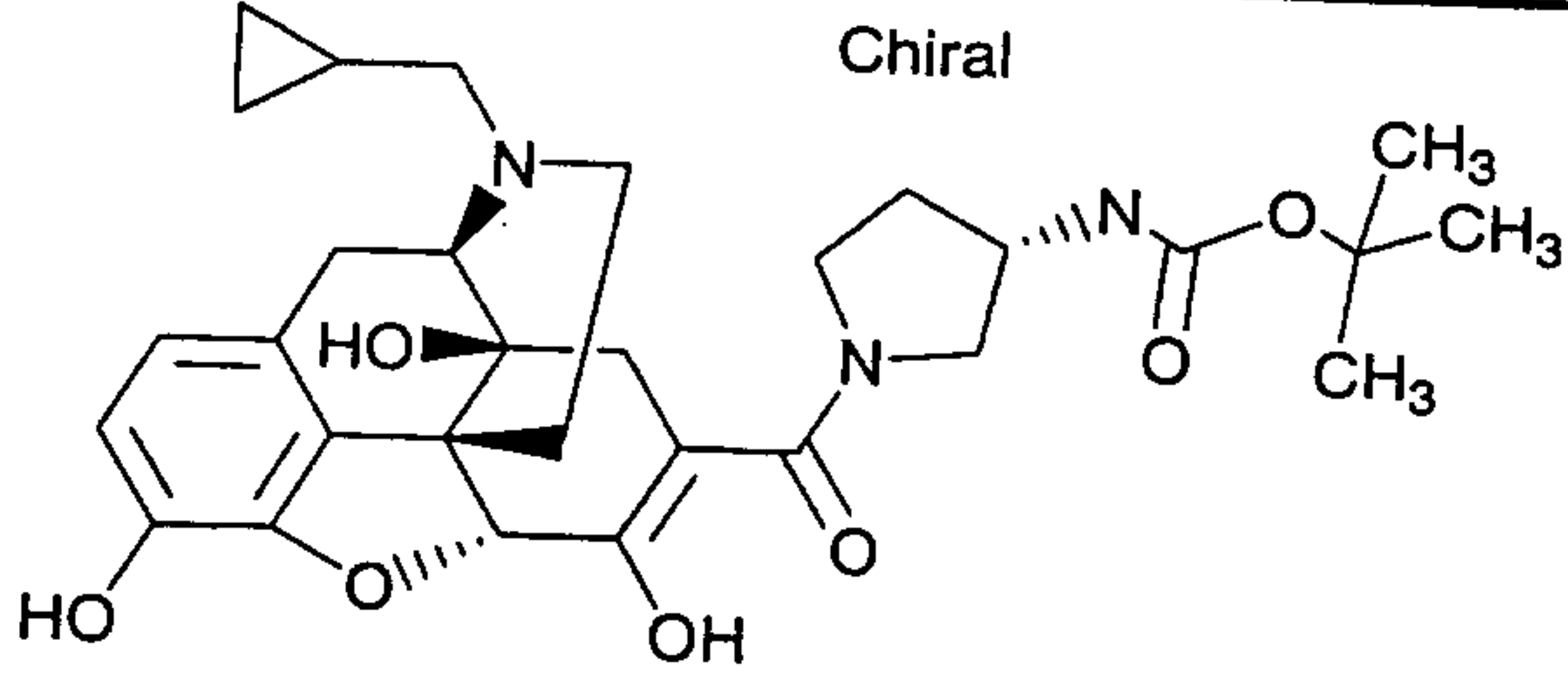
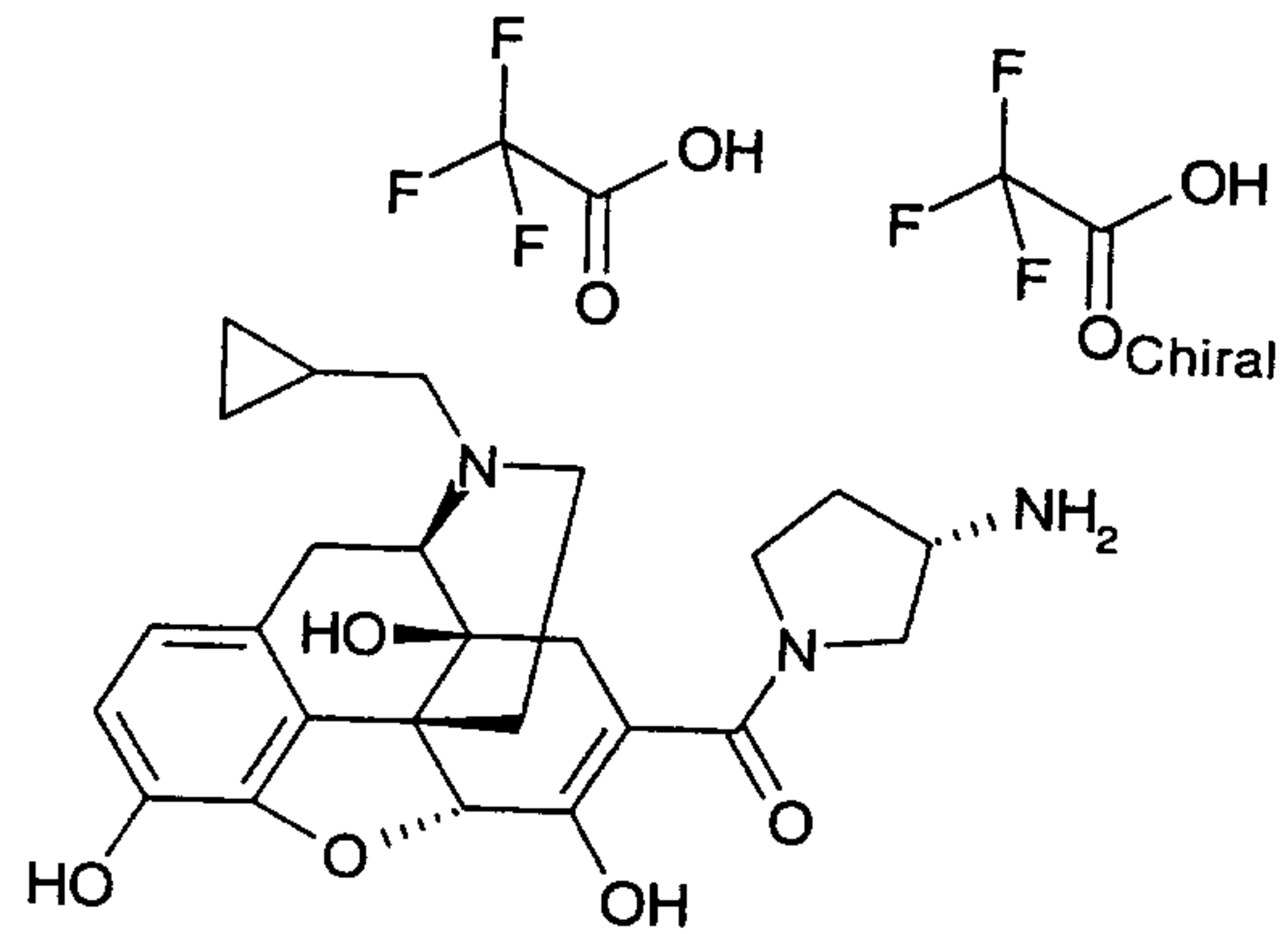
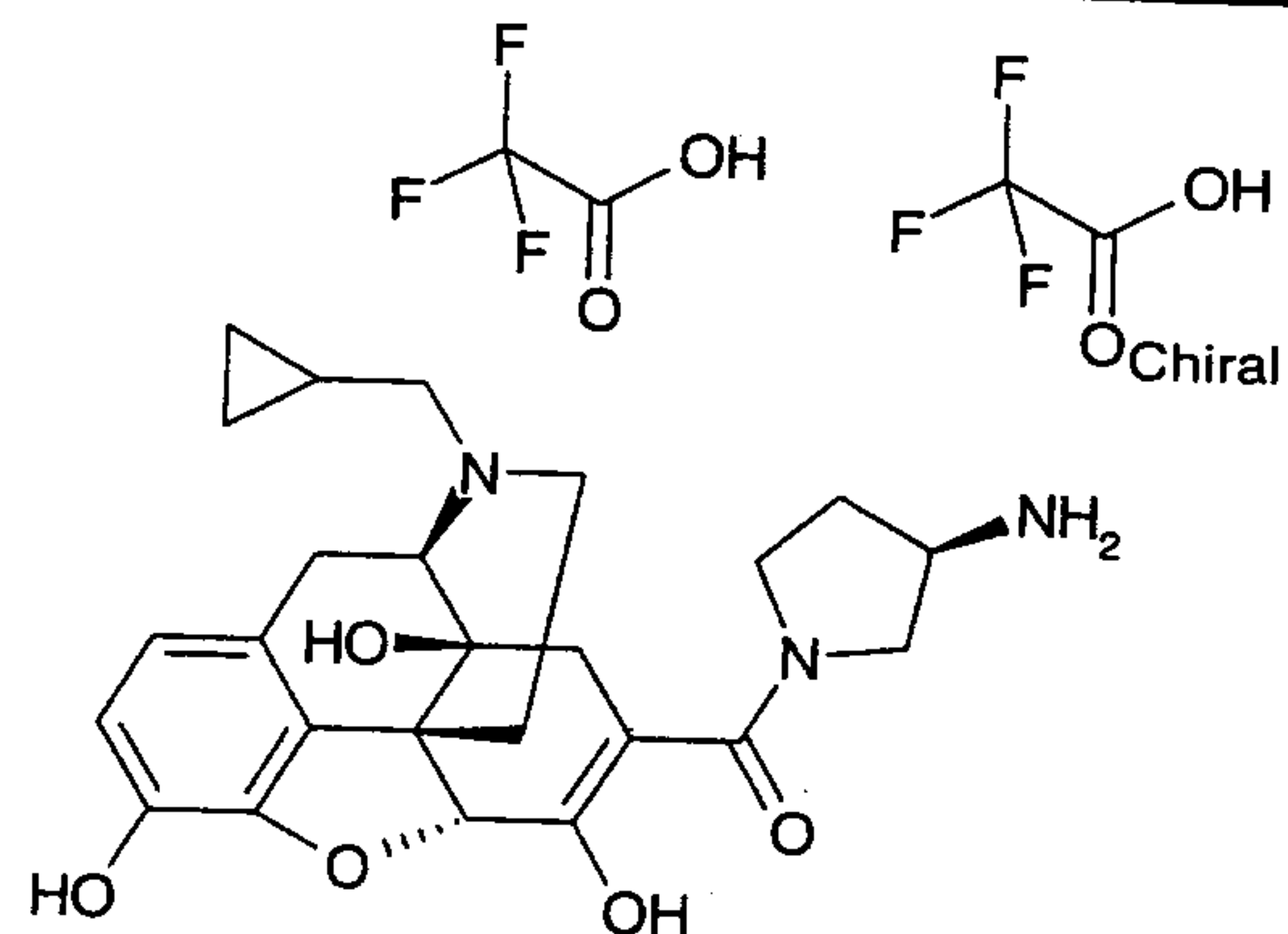
[0064]

[Table 19]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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)

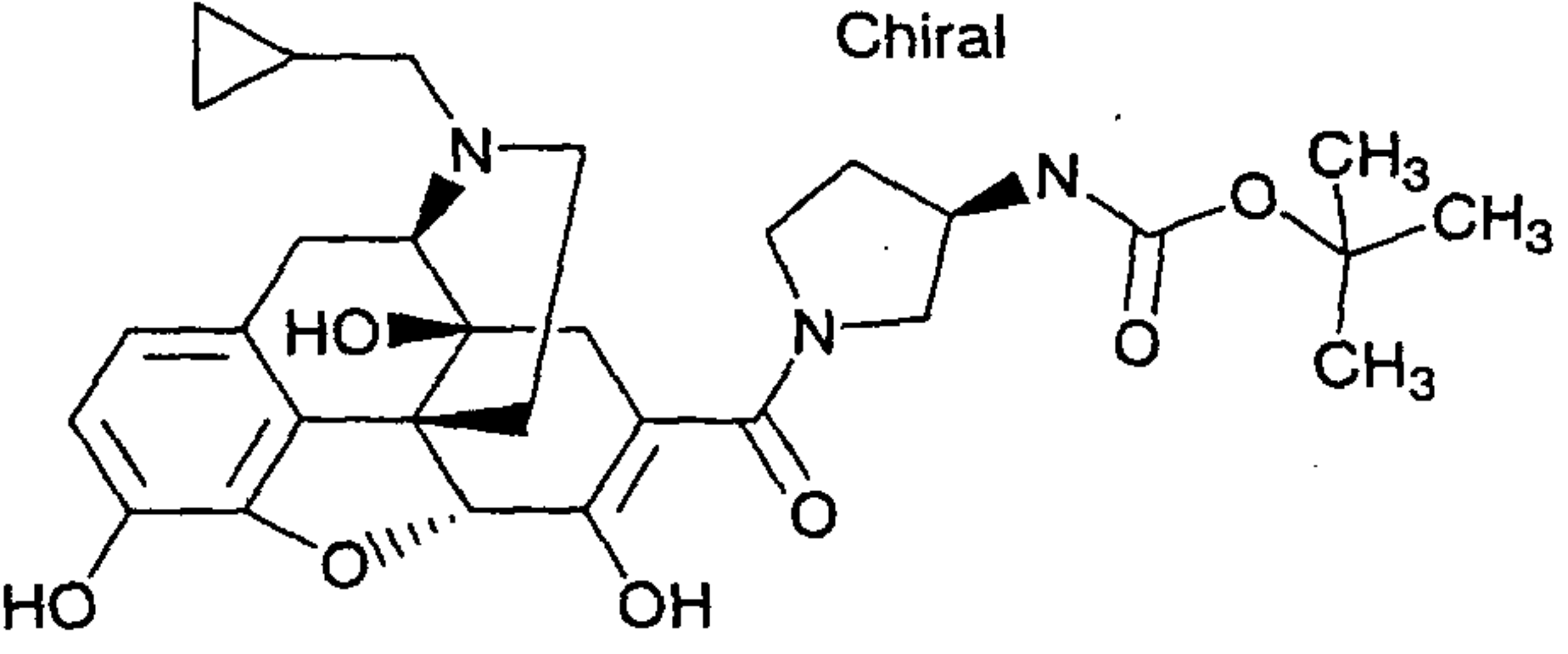
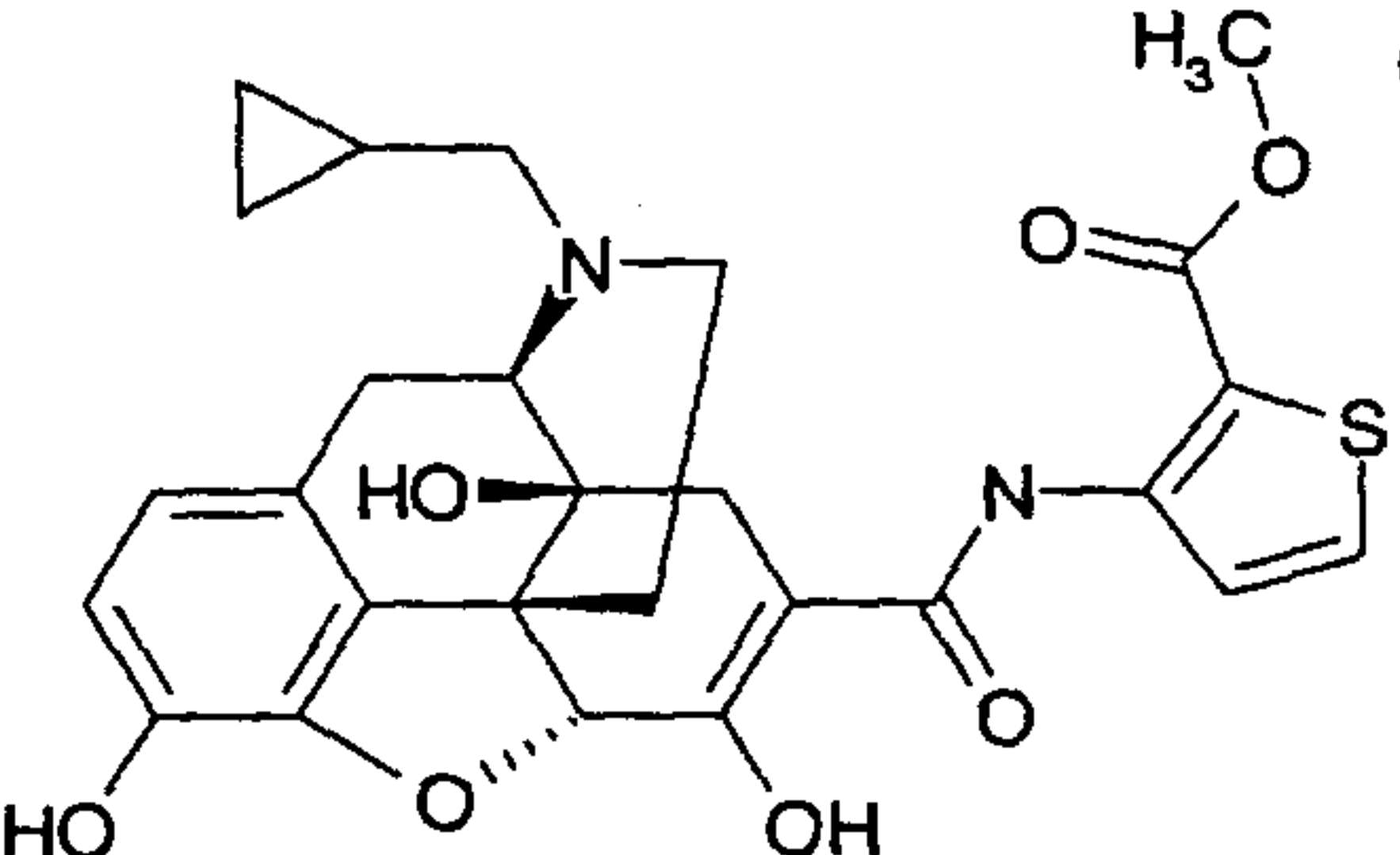
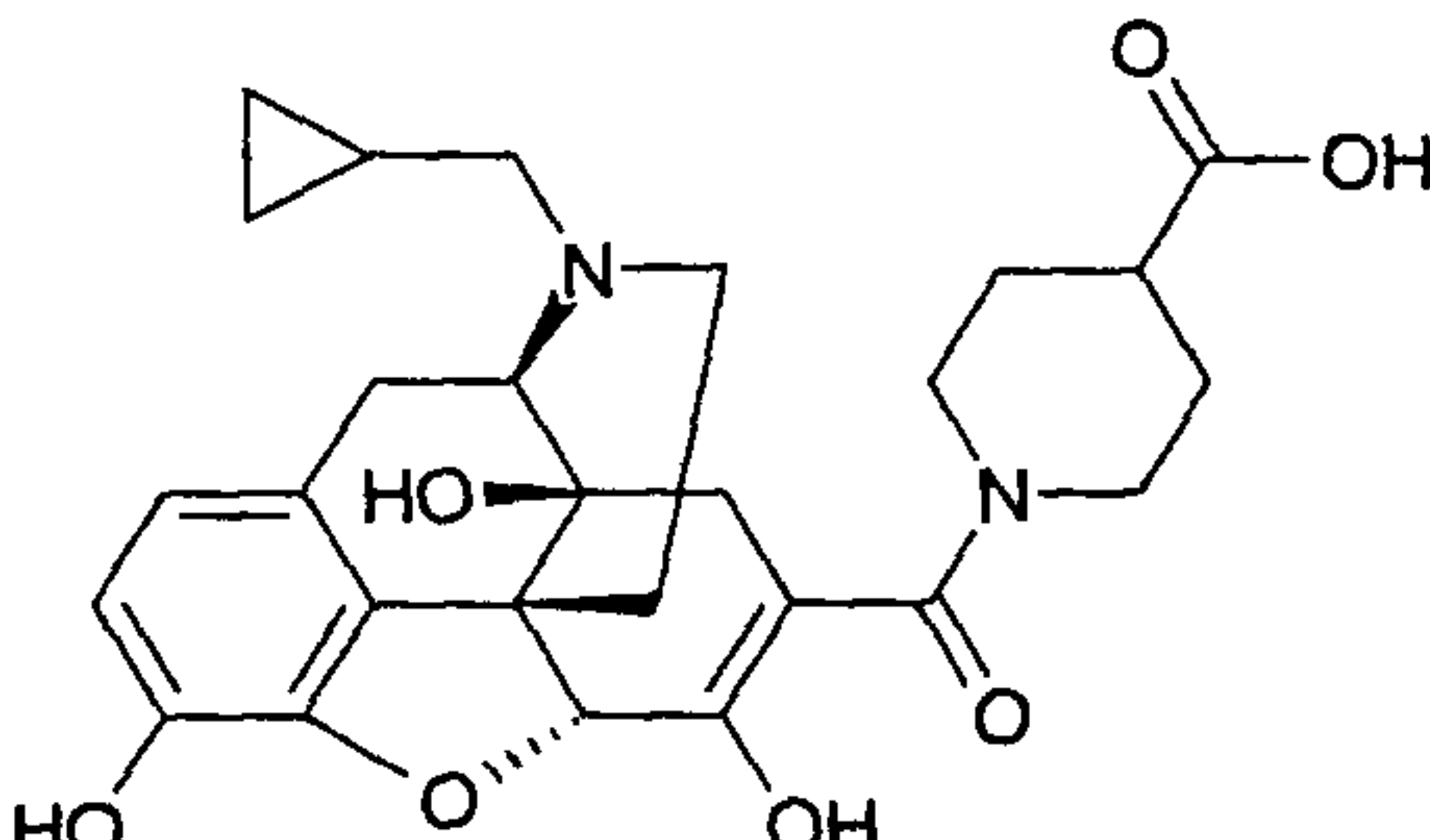
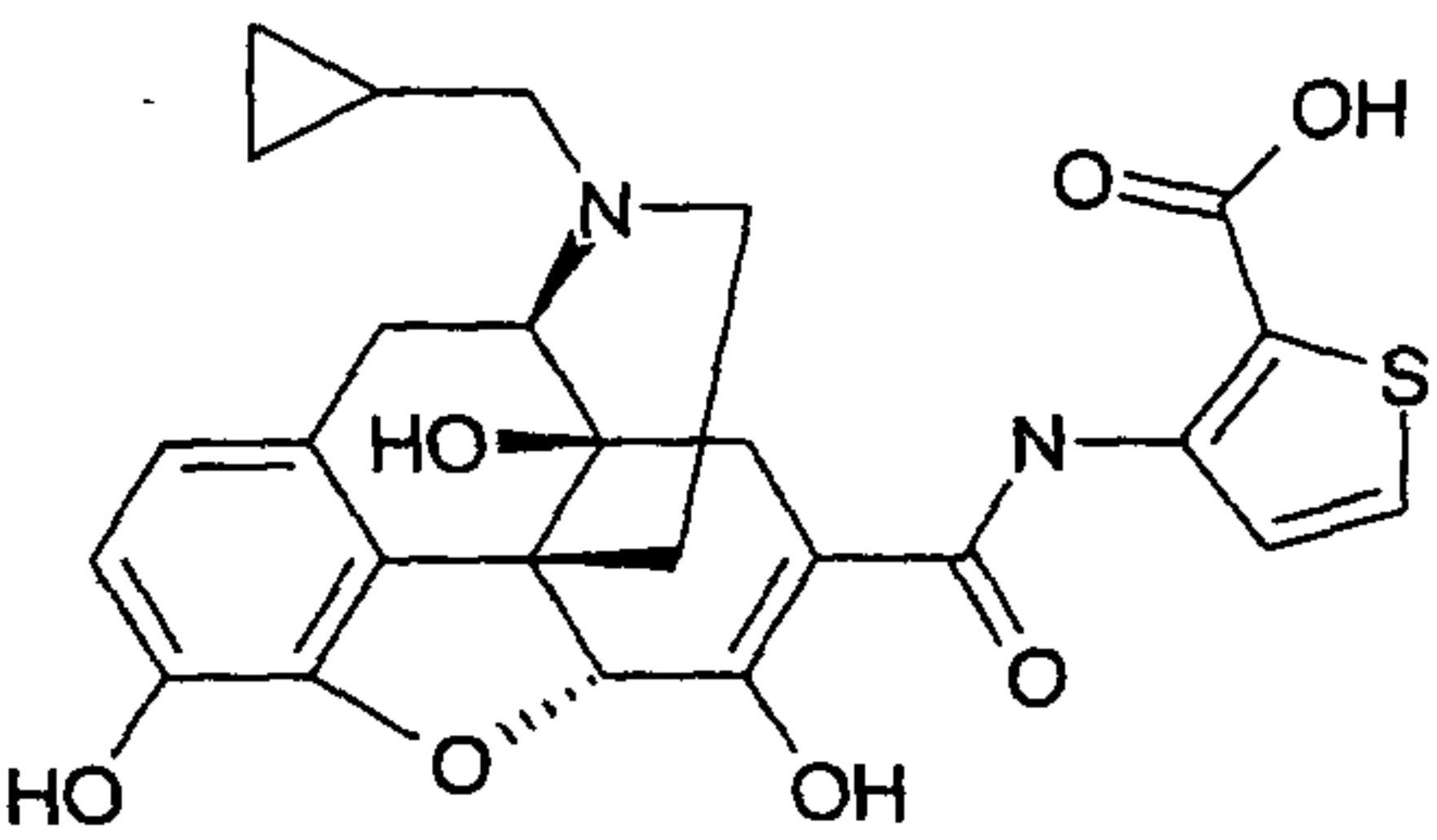
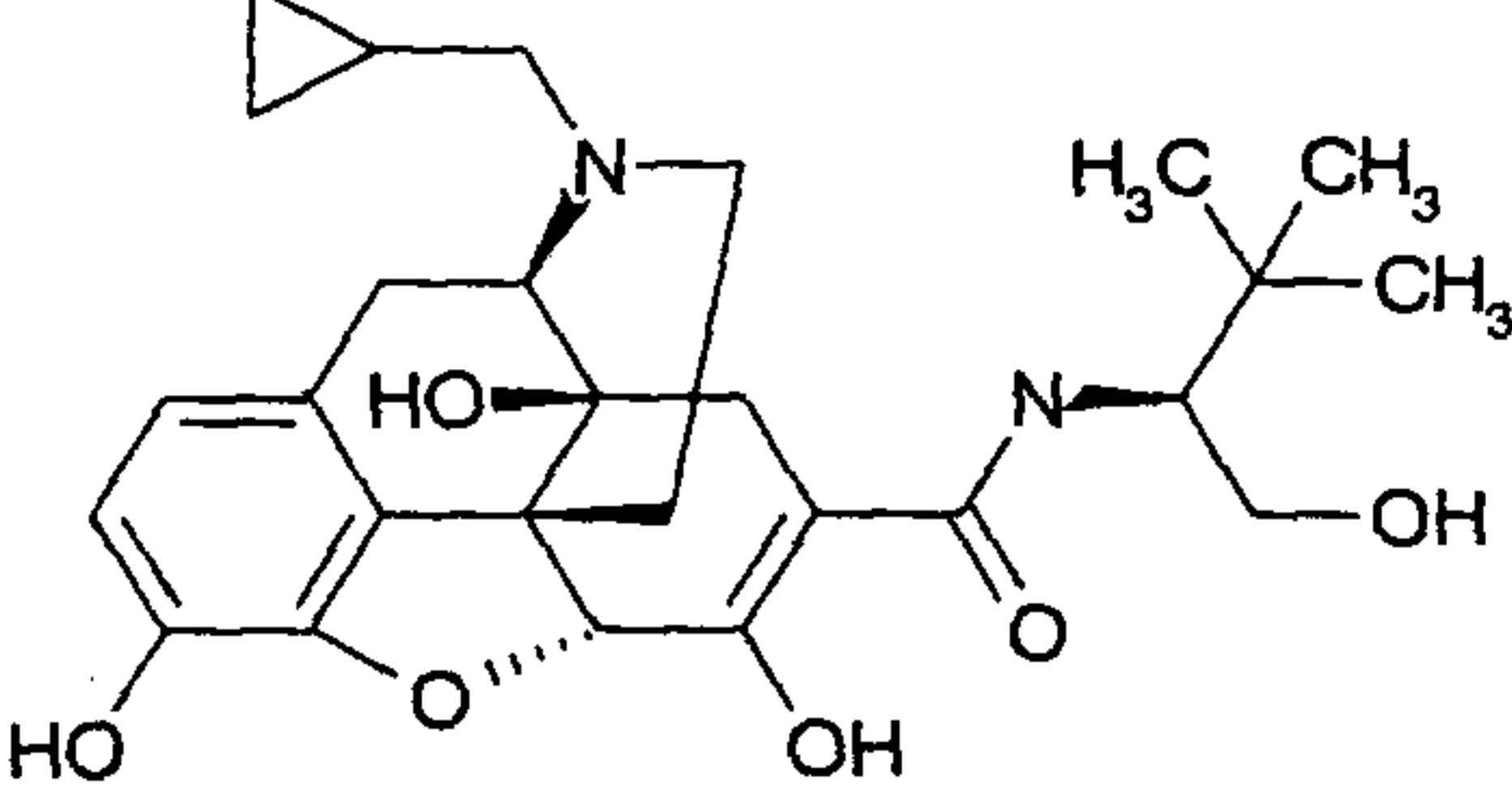
[0065]

[Table 20]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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)
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).

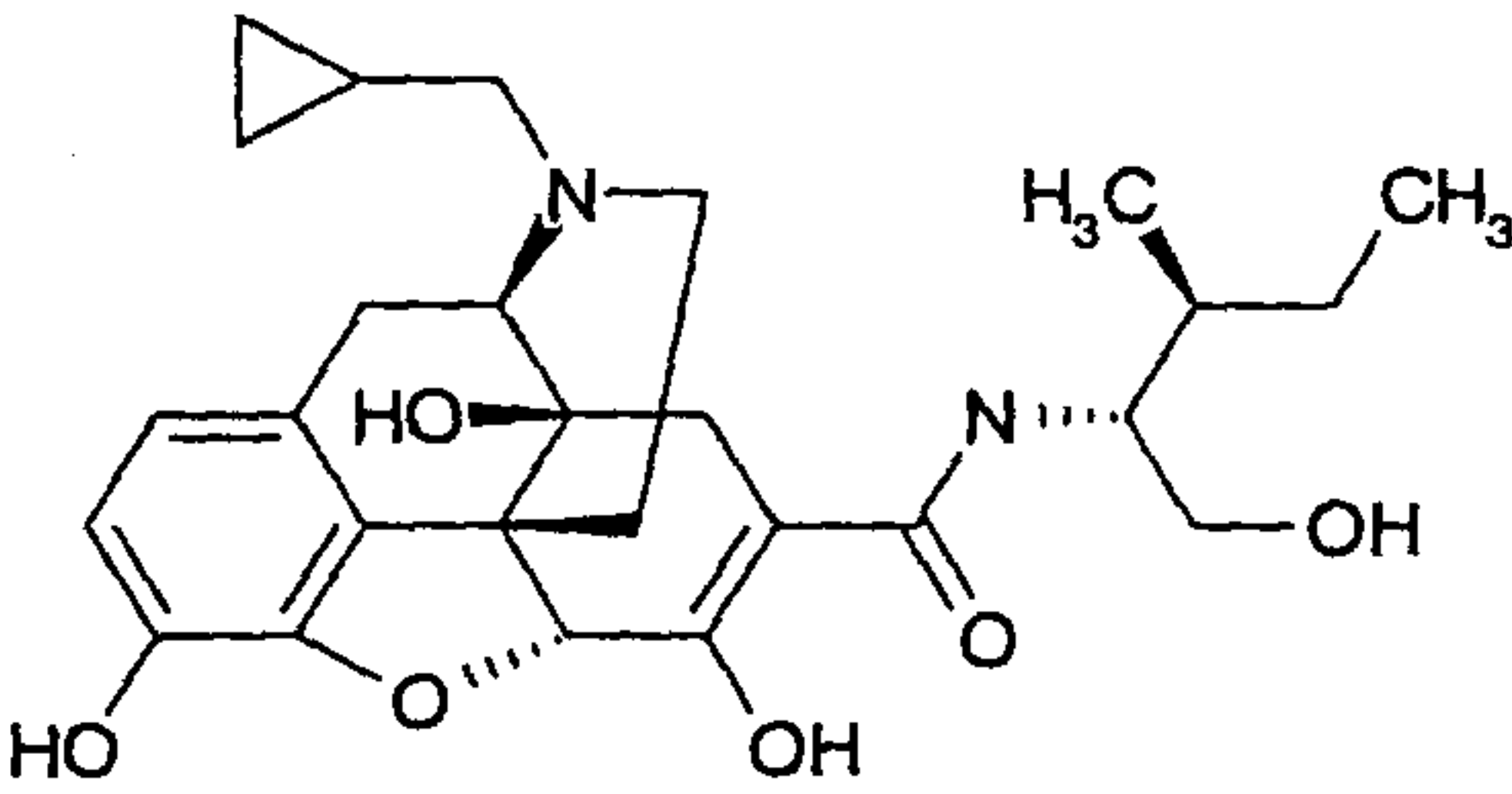
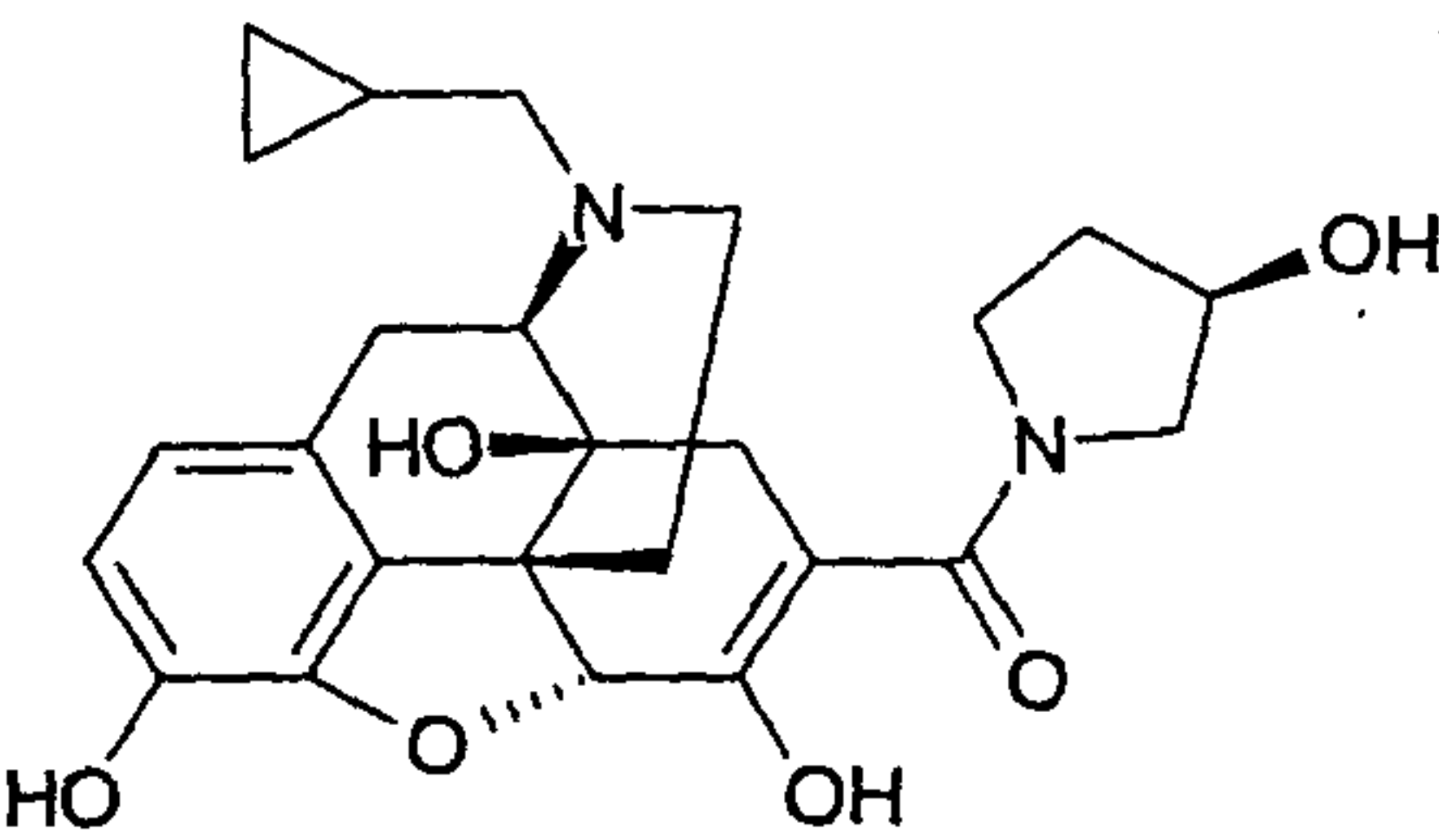
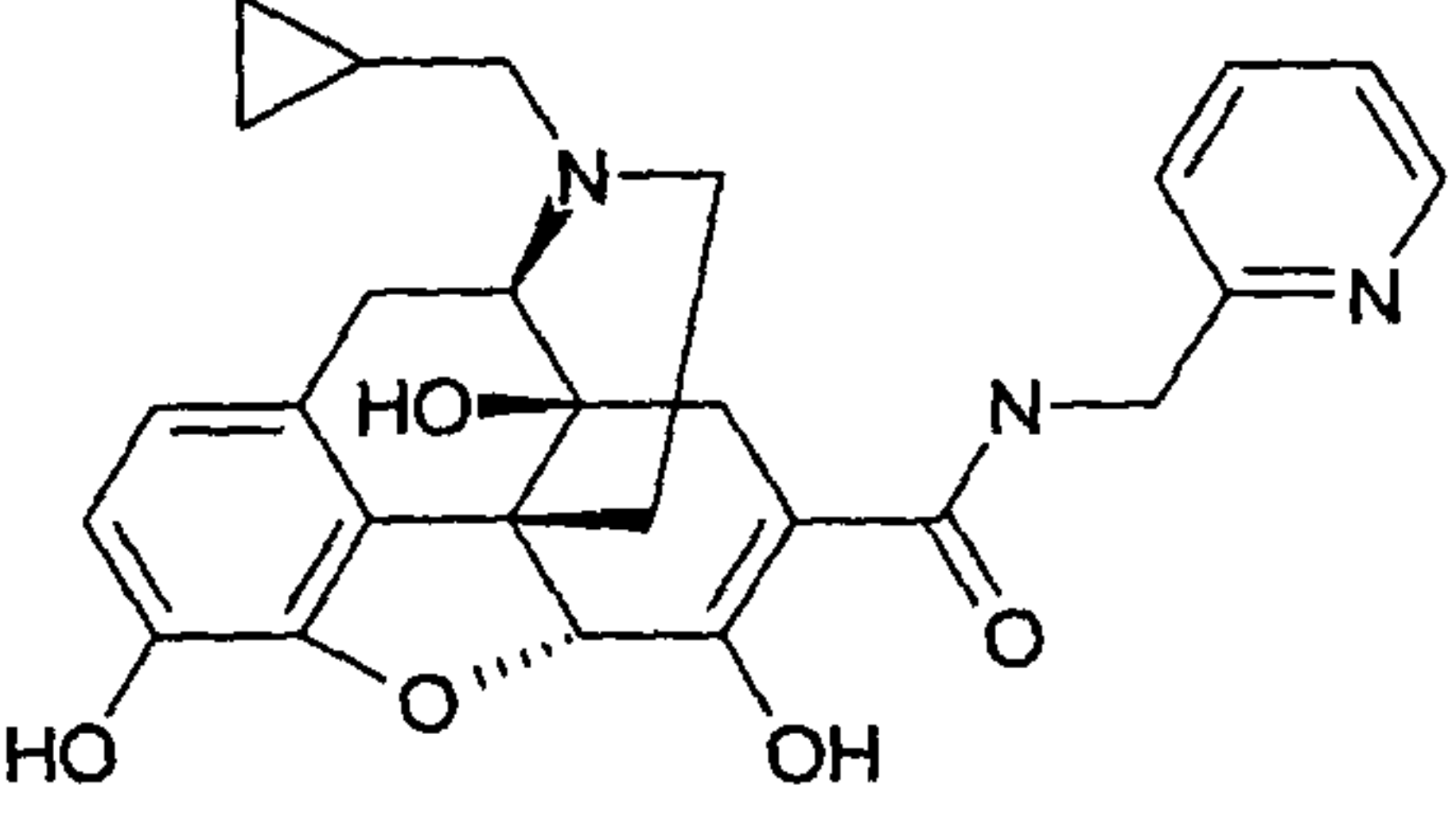
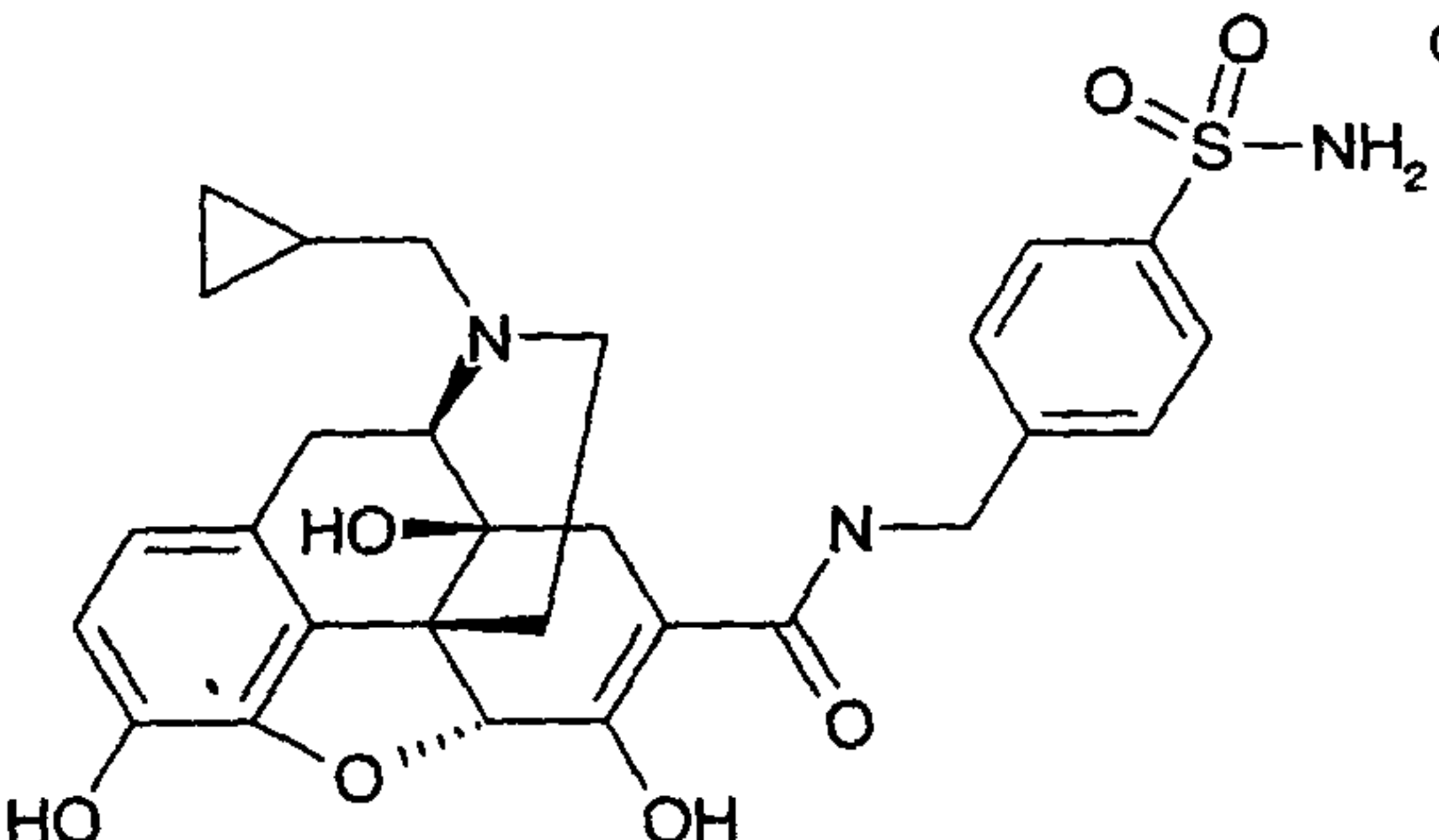
[0066]

[Table 21]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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).
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, 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)

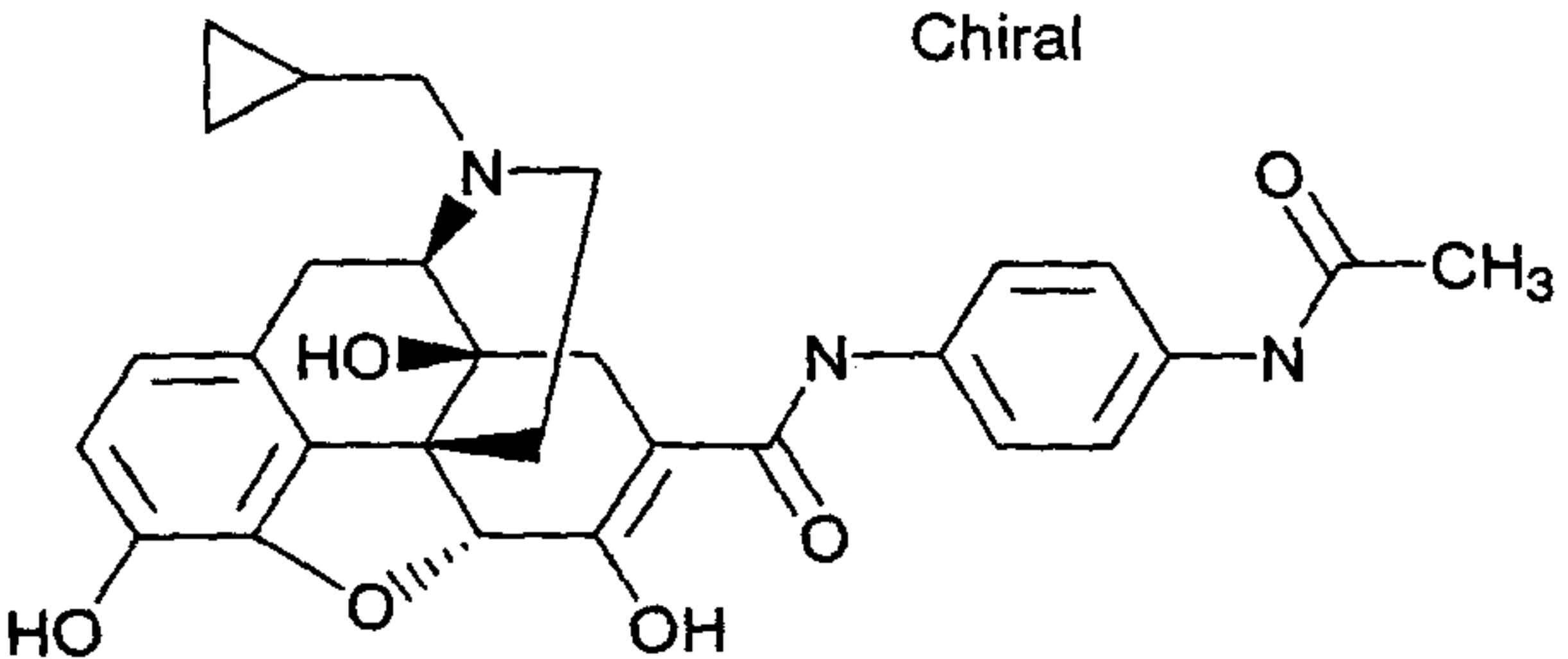
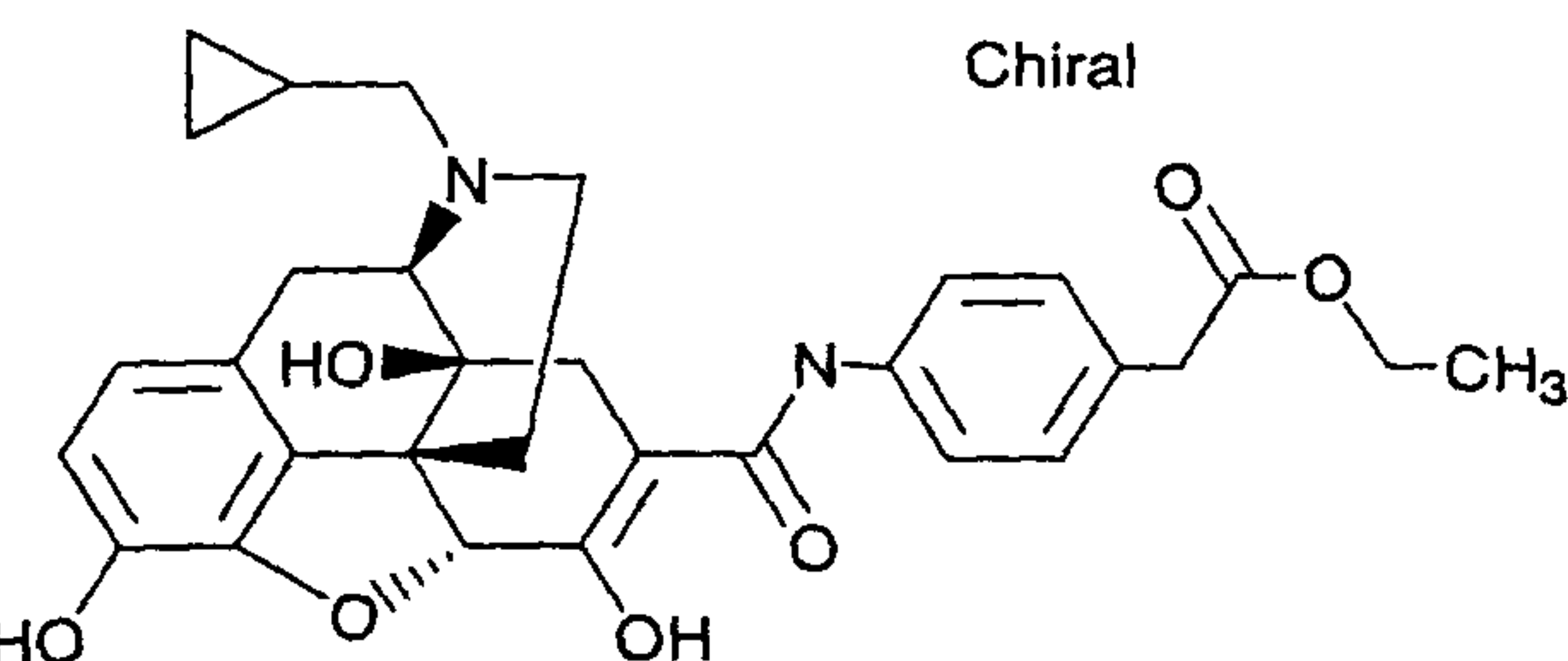
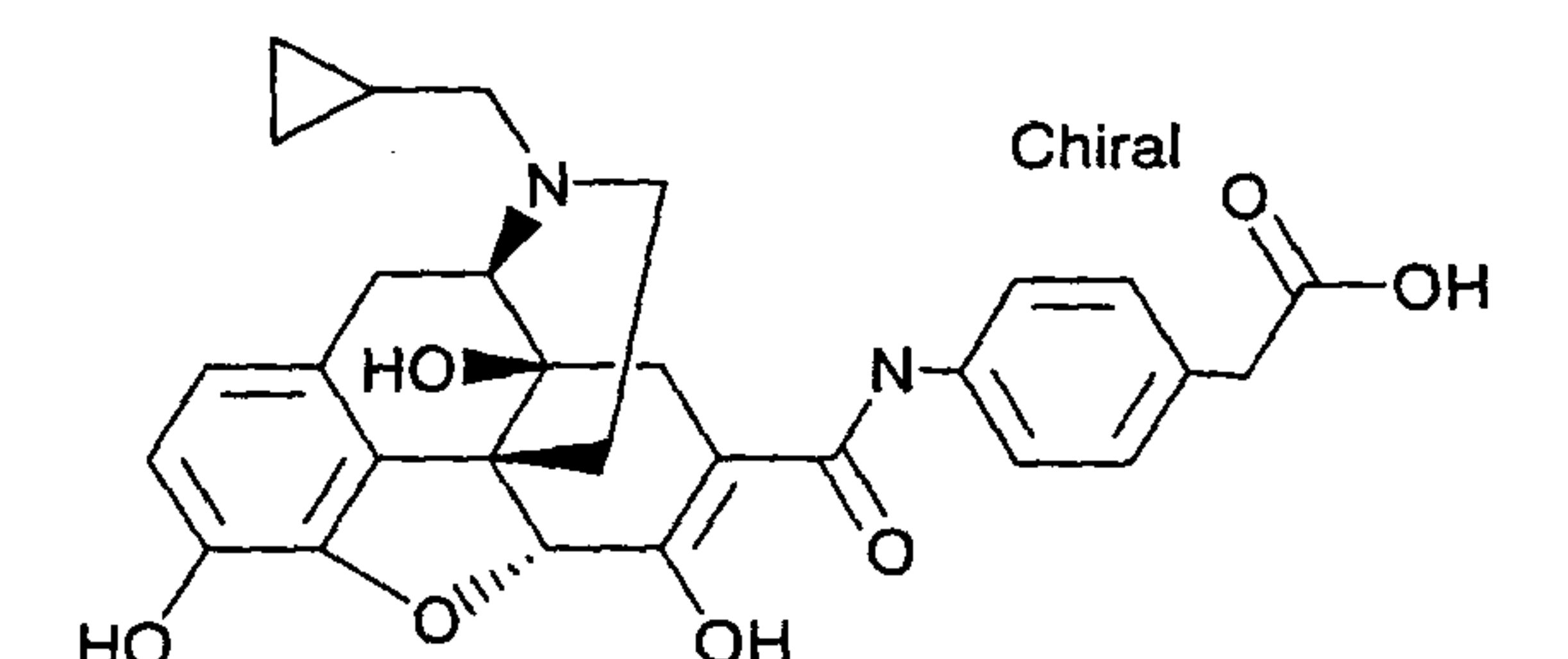
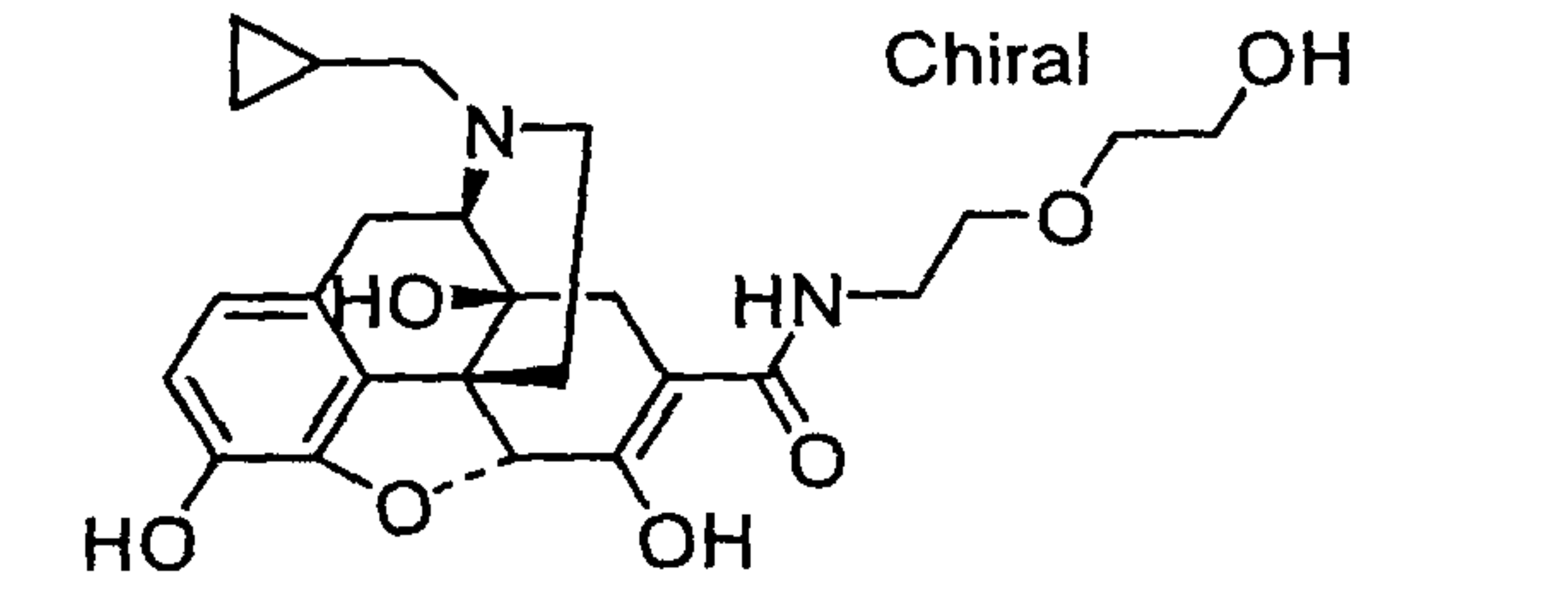
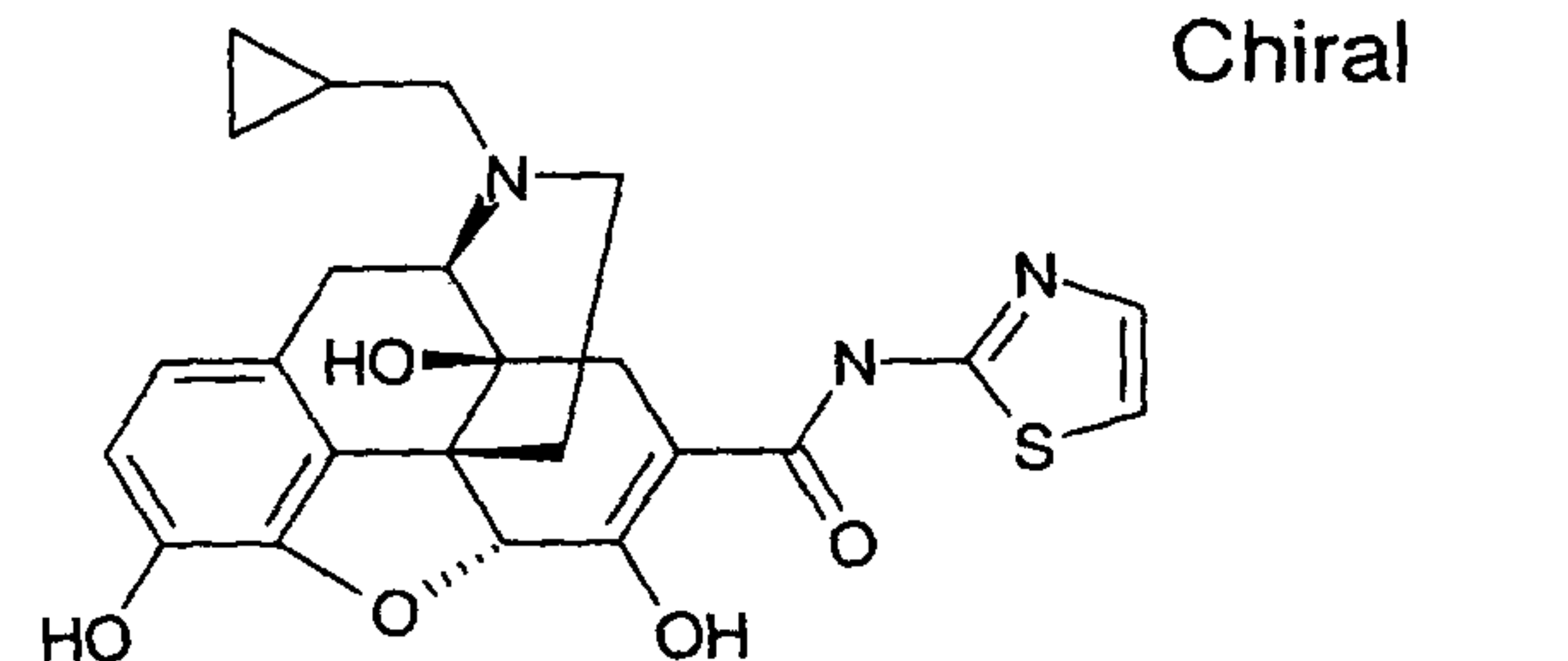
[0067]

[Table 22]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -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)
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	0.16-0.17 (m, 2H), 0.50-0.56 (m, 2H), 0.89 (m, 1H), 1.43 (br d, 1H), 1.97 (d, J = 15.6 Hz, 1H), 2.11-3.21 (m, 10H), 4.30-4.46 (m, 2H), 4.77 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 7.29 (s, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 8.42 (br, 1H), 9.17 (br, 1H), 14.19 (s, 1H).

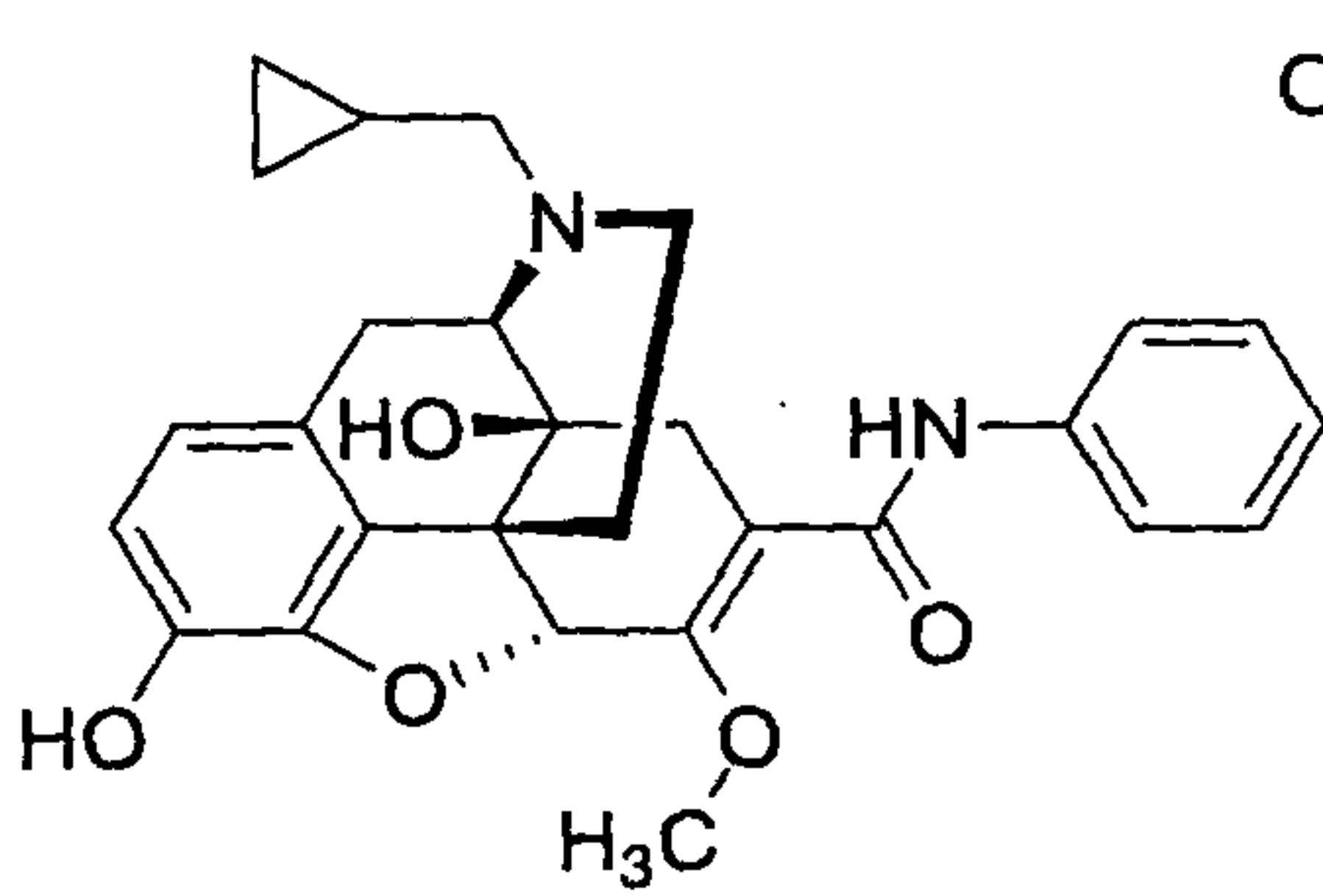
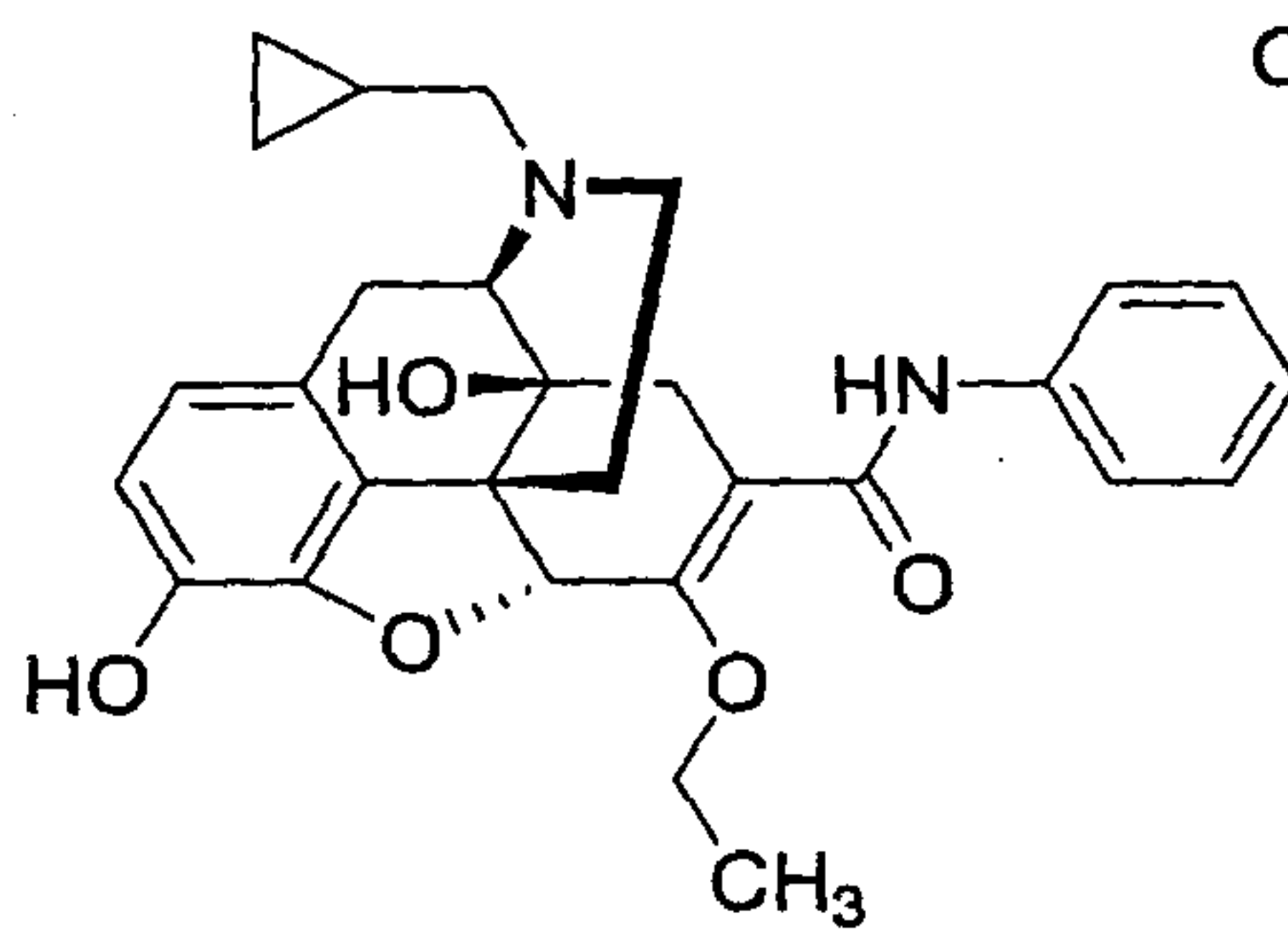
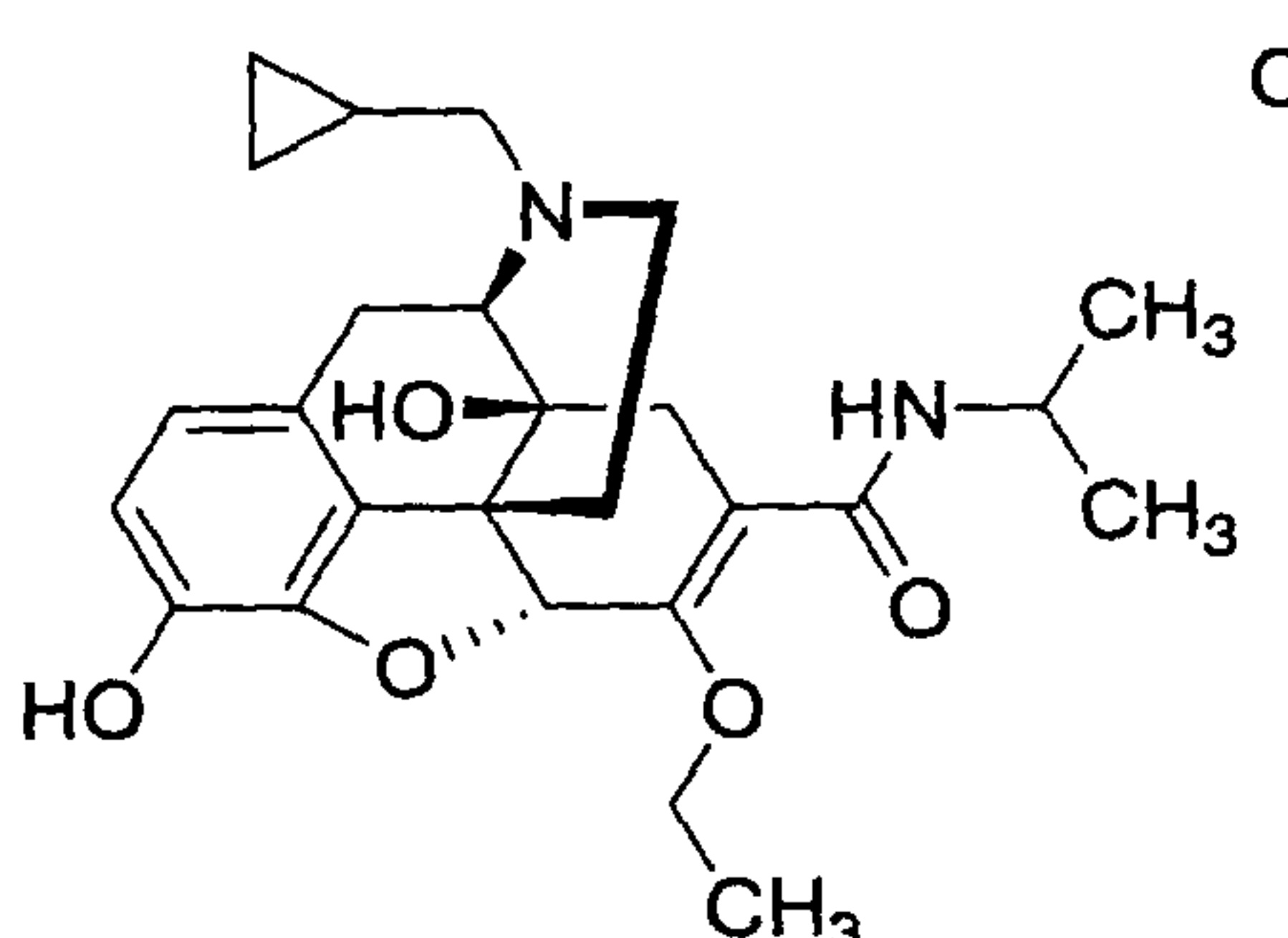
[0068]

[Table 23]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-77	Chiral 	0.10–0.25 (m, 2H), 0.44–0.60 (m, 2H), 0.88 (m, 1H), 1.45 (d, J = 11.1 Hz, 1H), 1.70–3.40 (m, 13H), 4.78 (s, 1H), 4.81 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 9.0 Hz, 2H), 9.15 (s, 1H), 9.25 (s, 1H), 9.88 (s, 1H), 14.00 (br s, 1H)
I-78	Chiral 	0.10–0.25 (m, 2H), 0.44–0.60 (m, 2H), 0.89 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.45 (d, J = 11.4 Hz, 1H), 1.70–3.40 (m, 10H), 3.60 (s, 2H), 4.06 (q, J = 7.2 Hz, 2H), 4.78 (s, 1H), 4.83 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 9.16 (s, 1H), 9.26 (s, 1H), 13.95 (br s, 1H)
I-79	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)

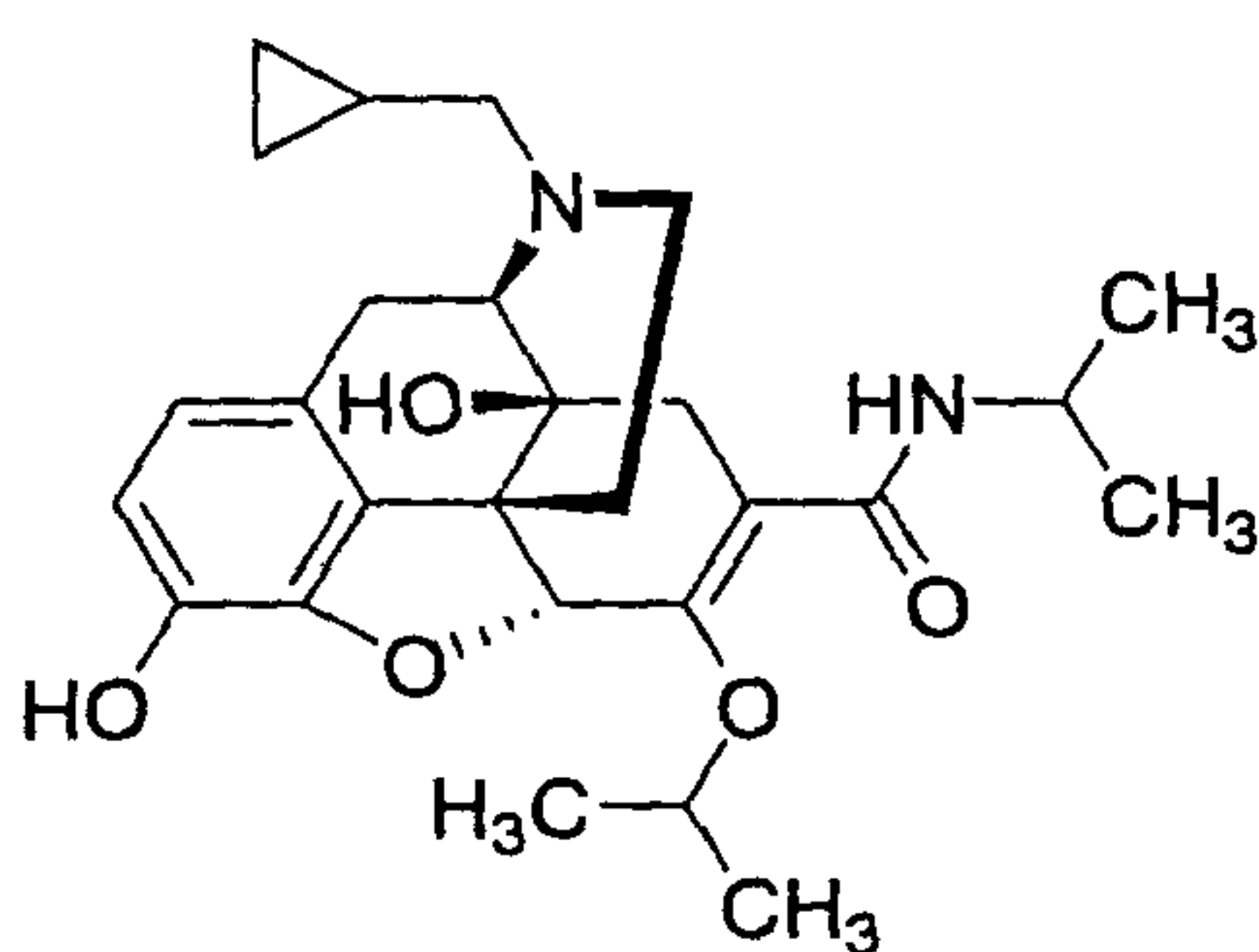
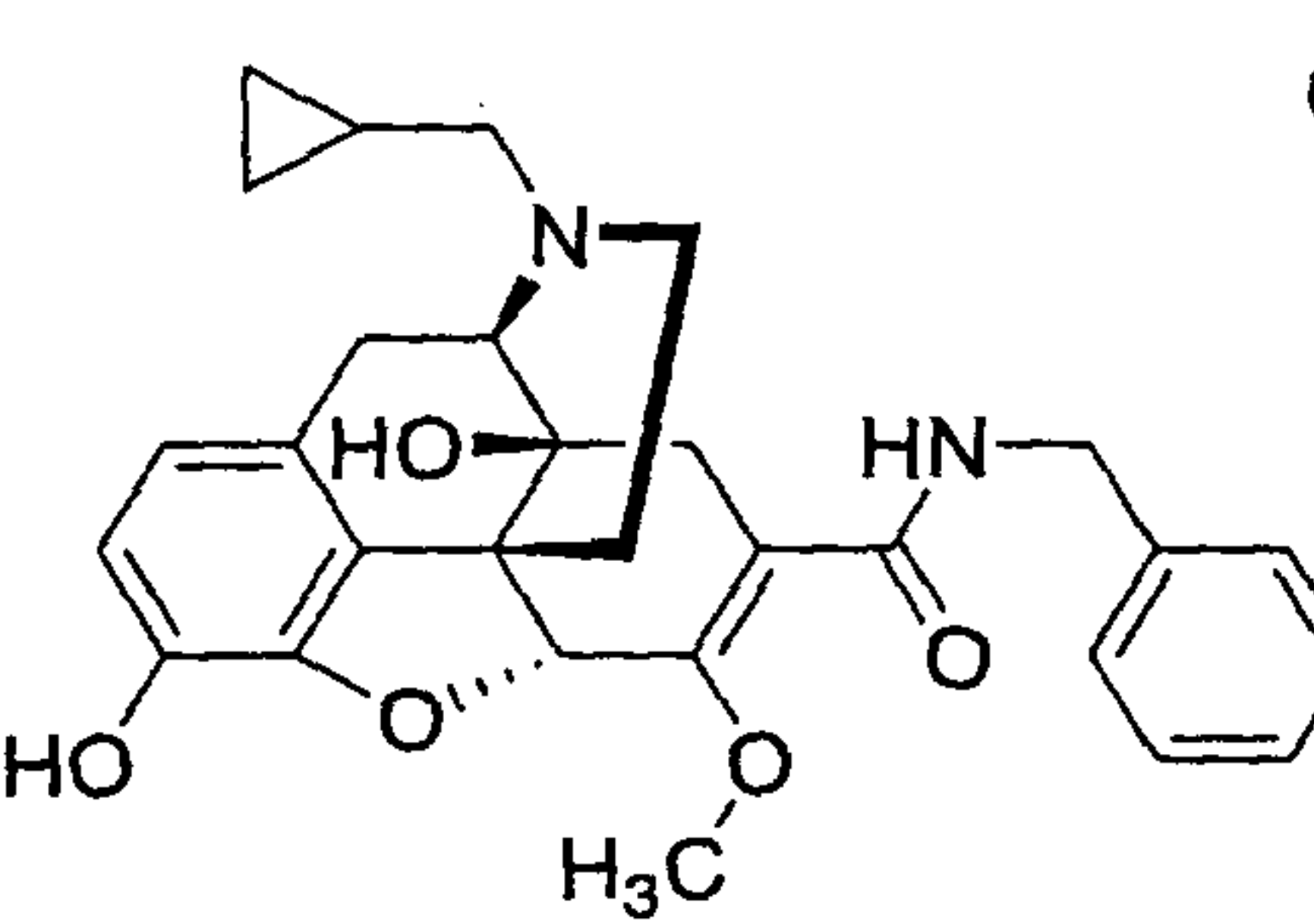
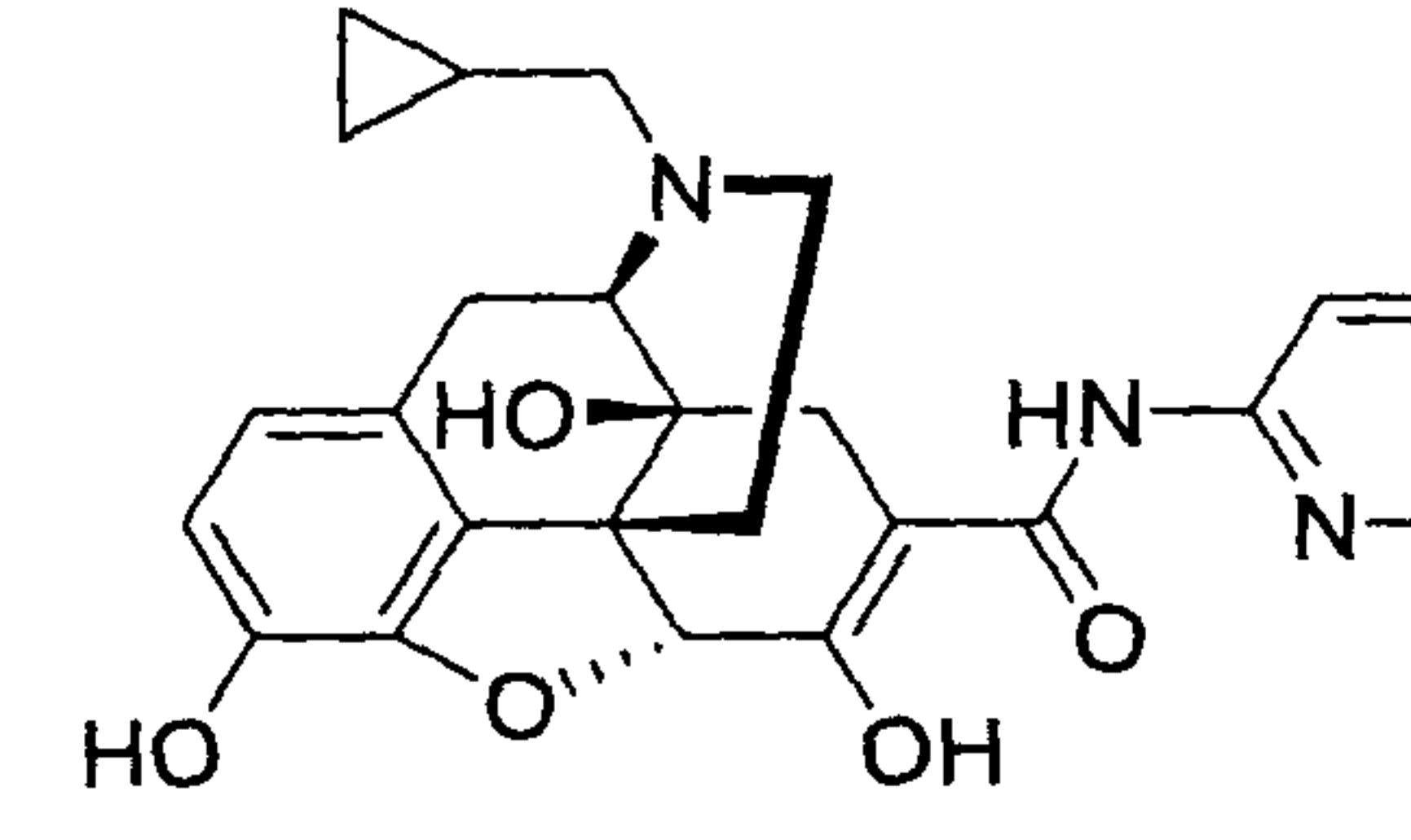
[0069]

[Table 24]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-82	 Chiral	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 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, 1H), 6.67 (d, J = 8.4 Hz, 1H), 7.02–7.10 (m, 1H), 7.26–7.32 (m, 2H), 7.39 (d.d, J = 8.4 & 0.9 Hz, 2H), 9.61 (s, 1H).
I-83	 Chiral	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 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	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 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).

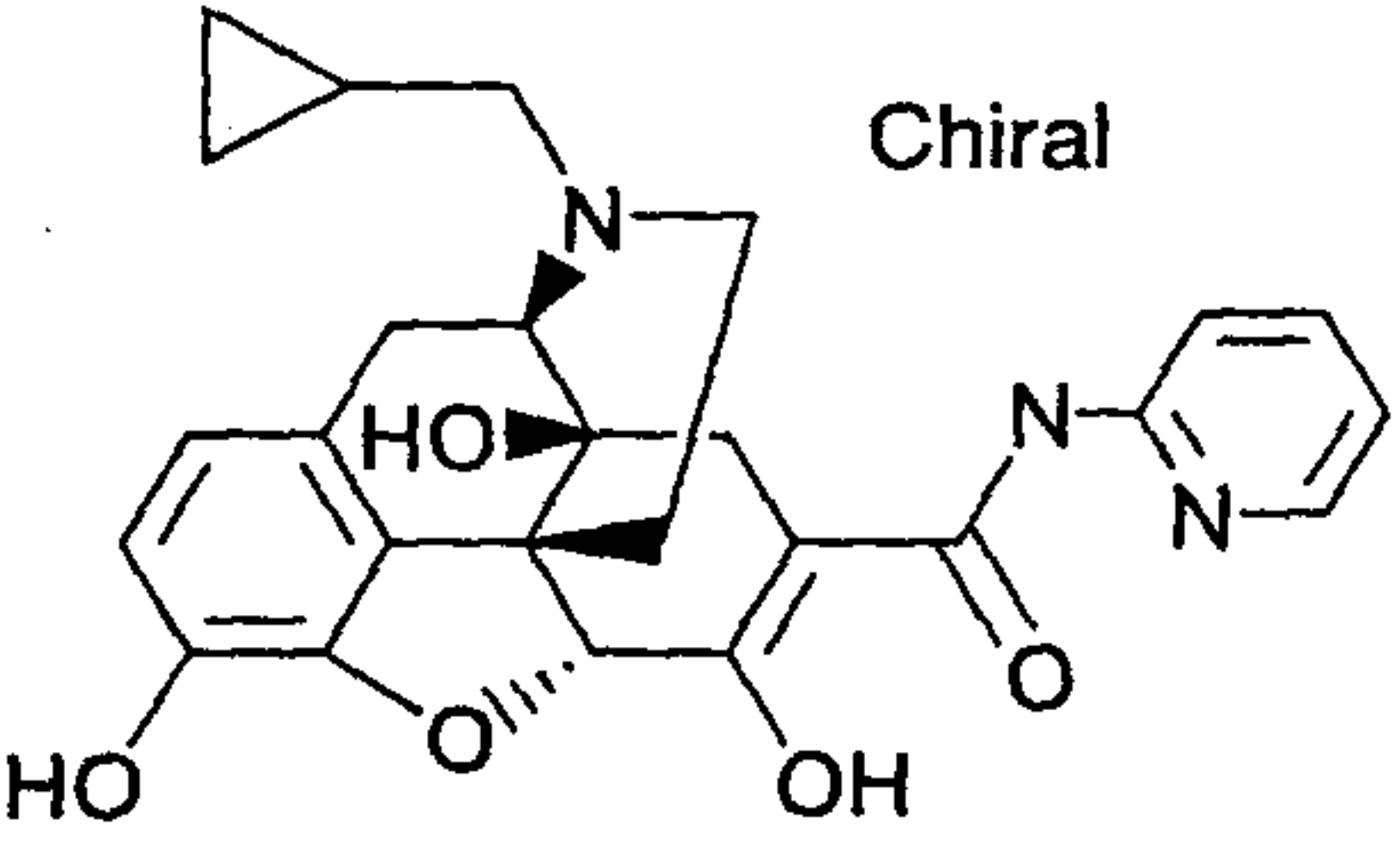
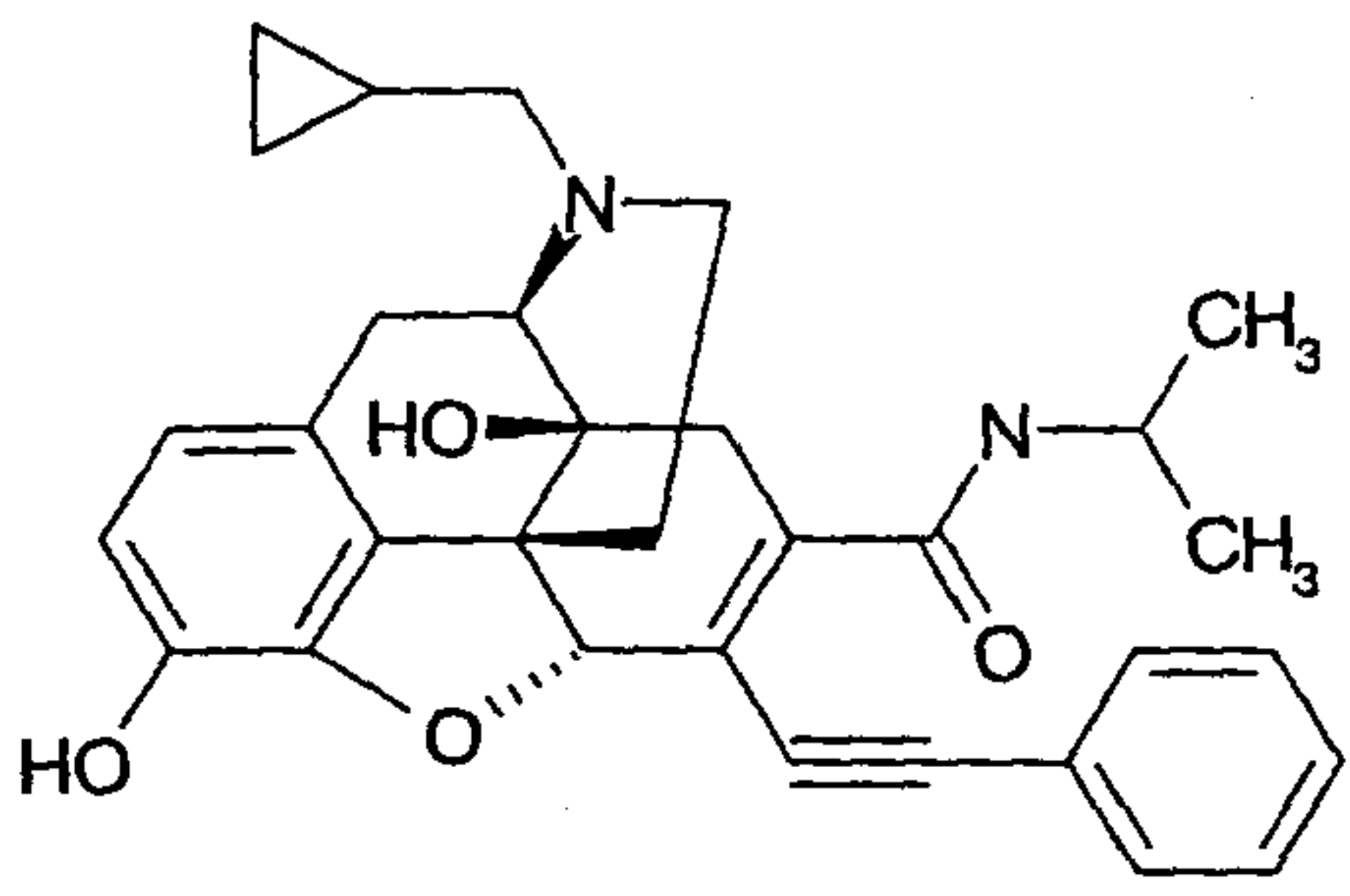
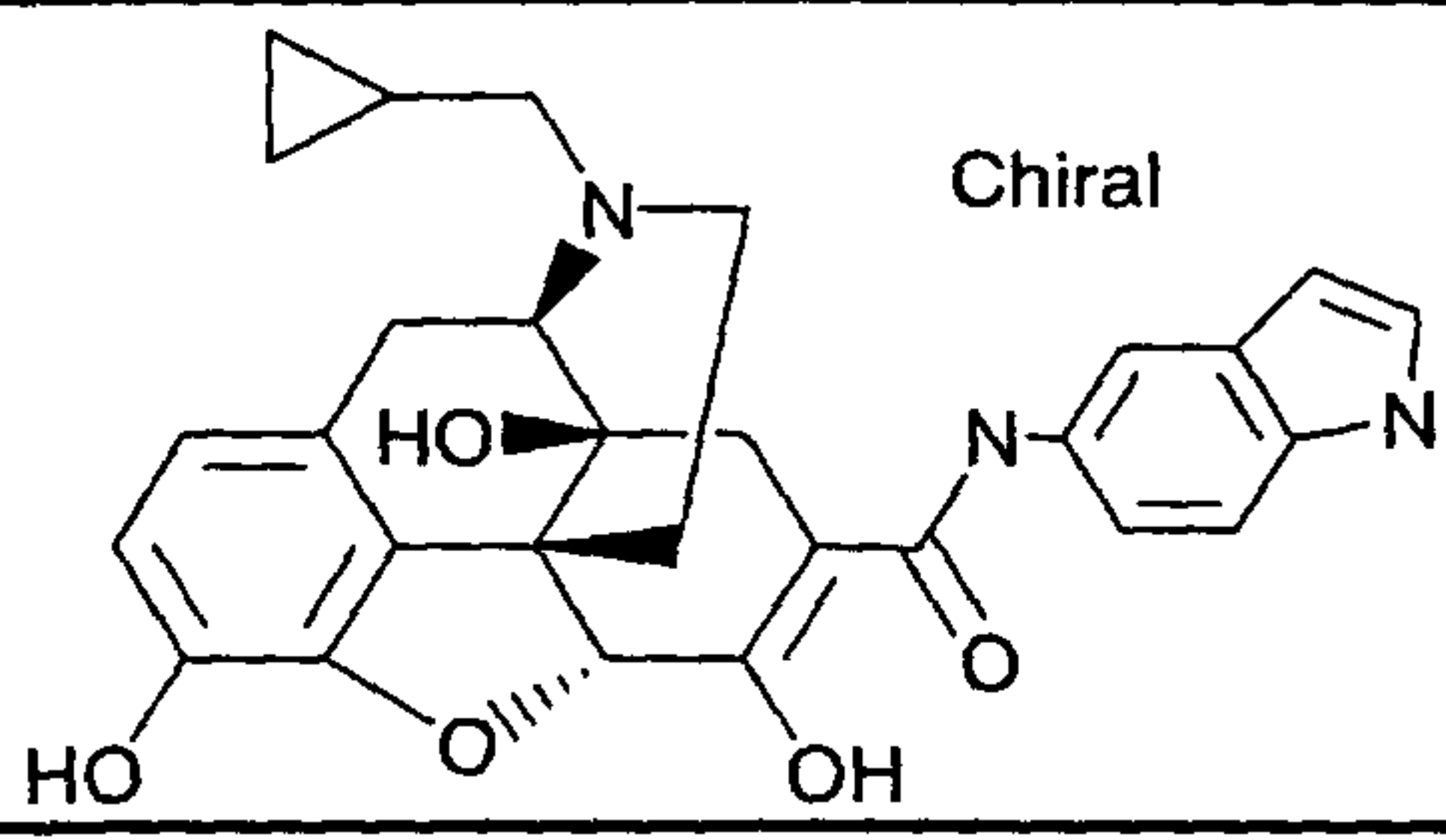
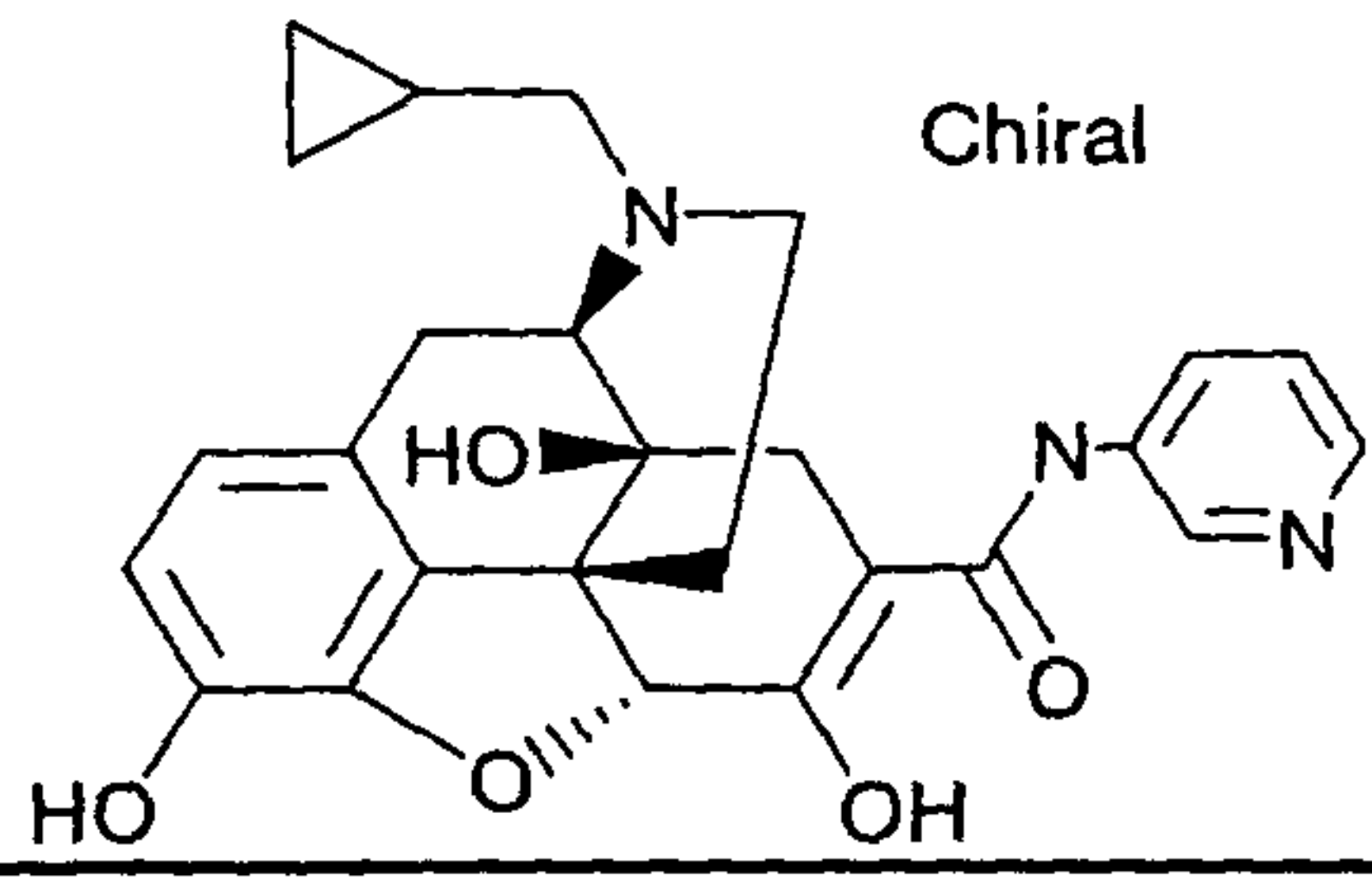
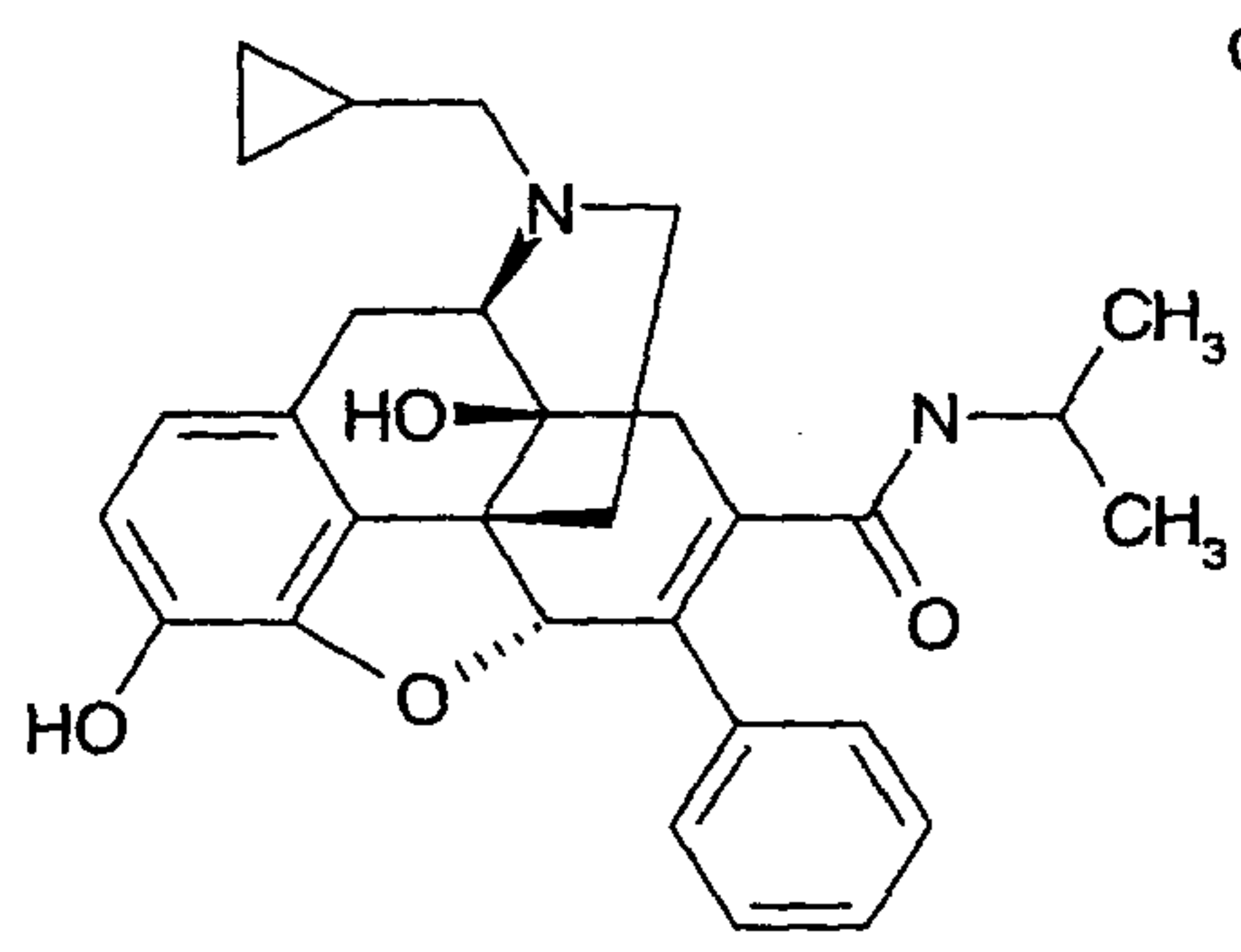
[0070]

[Table 25]

Compound No.	Chemical structure	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-85	 Chiral	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 0.14 (brs, 2H), 0.56 (brs, 2H), 0.86 (brs, 1H), 1.14 (d, J = 6.6 Hz, 3H), 1.15 (d, J=6.6 Hz, 3H), 1.32 (d, J =4.8 Hz, 1H), 1.34 (d, J=4.8 Hz, 3H), 1.64 (d, J=9.9 Hz, 1H), 2.10 (d.d, J=17.1 & 1.5 Hz, 1H), 2.27 (brs, 2H), 2.39 (brs, 2H), 2.55-2.77 (m, 3H), 3.04 (d, J = 18.3 Hz, 1H), 3.22 (brs, 1H), 4.03 (quint, J=6.6 Hz, 1H), 4.81 (quint., J=6.0 Hz, 1H), 5.10 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.67 (d, J =8.4 Hz, 1H), 7.76 (d, J =6.9 Hz, 1H).
I-86	 Chiral	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 0.16 (brs, 2H), 0.568 (brs, 2H), 0.87 (brs, 1H), 1.67 (d, J=9.9 Hz, 1H), 2.14 (d.d, J=18.3 & 1.2 Hz, 1H), 2.27 (brs, 2H), 2.41 (brs, 2H), 3.05 (d, J = 18.6 Hz, 1H), 3.25 (brd, J=4.5 Hz, 1H), 3.92 (s, 1H), 4.46 (d, J=5.7 Hz, 2H), 5.23 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.64 (d, J =8.1 Hz, 1H), 7.20-7.36 (m, 5H), 8.03 (brt, J =5.7 Hz, 1H).
I-87	 Chiral	¹ H-NMR (CDCl ₃ +CD ₃ OD) δ : 0.26 (brs, 2H), 0.63 (brs, 2H), 0.94 (brs, 1H), 1.72 (brd, J = 9.0 Hz, 1H), 2.09-2.93 (m, 8H), 3.15 (d, J = 18.9 Hz, 1H), 4.97 (s, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.70 (d, J =8.1 Hz, 1H), 7.04-7.08 (m, 1H), 7.69-7.75 (m, 1H), 8.13 (d, J =14.0 Hz, 2H), 8.23 (d, J =3.9 Hz, 1H).

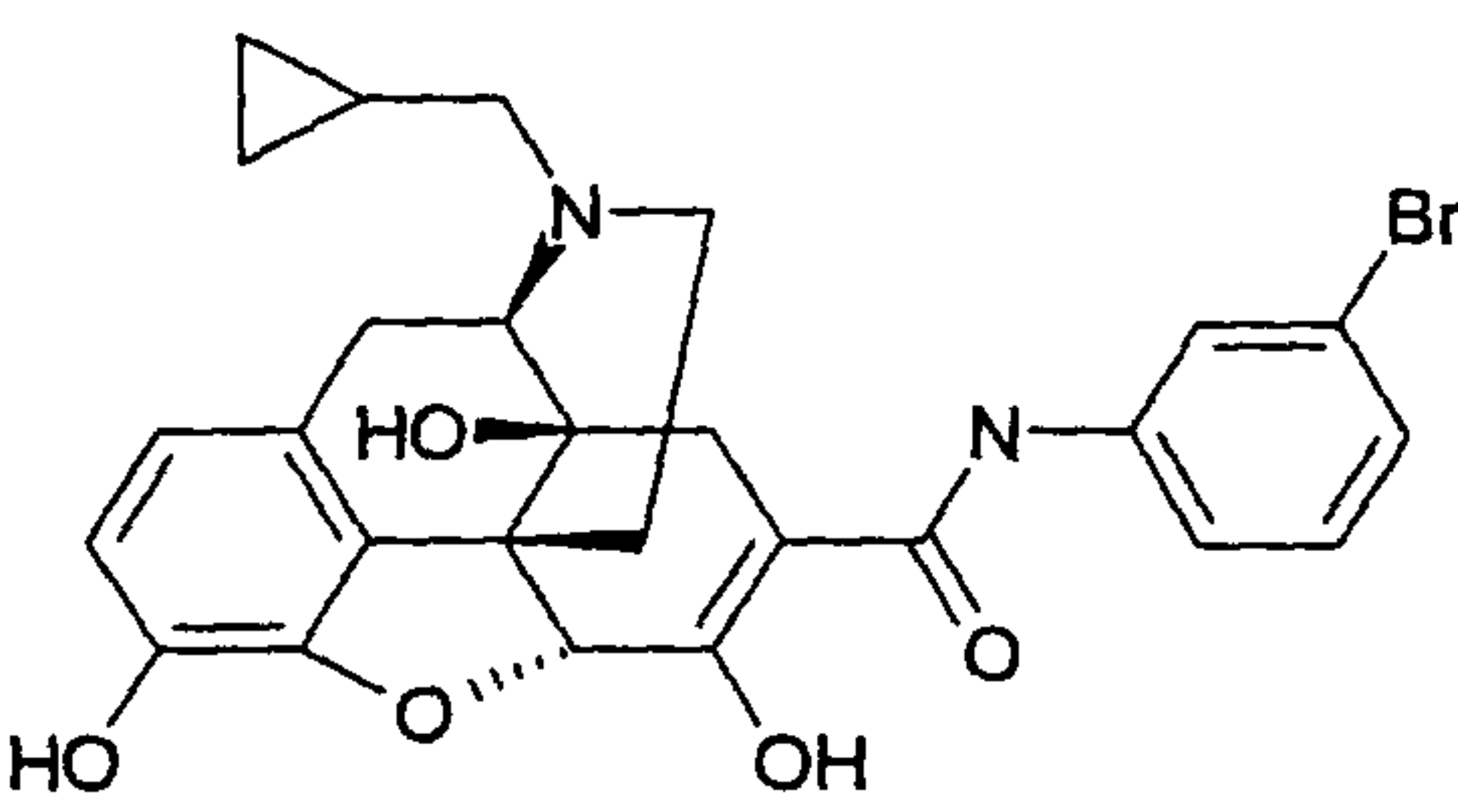
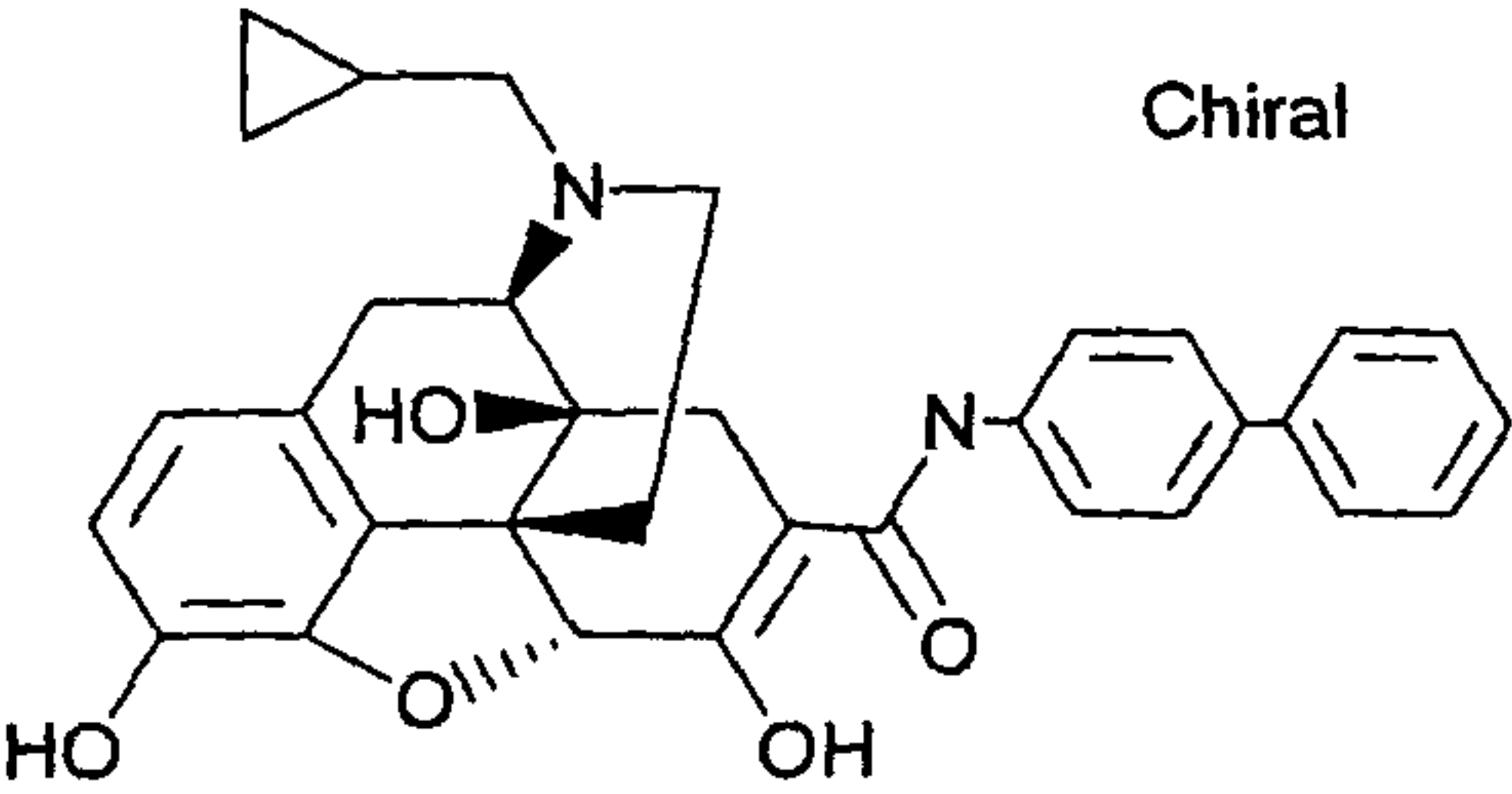
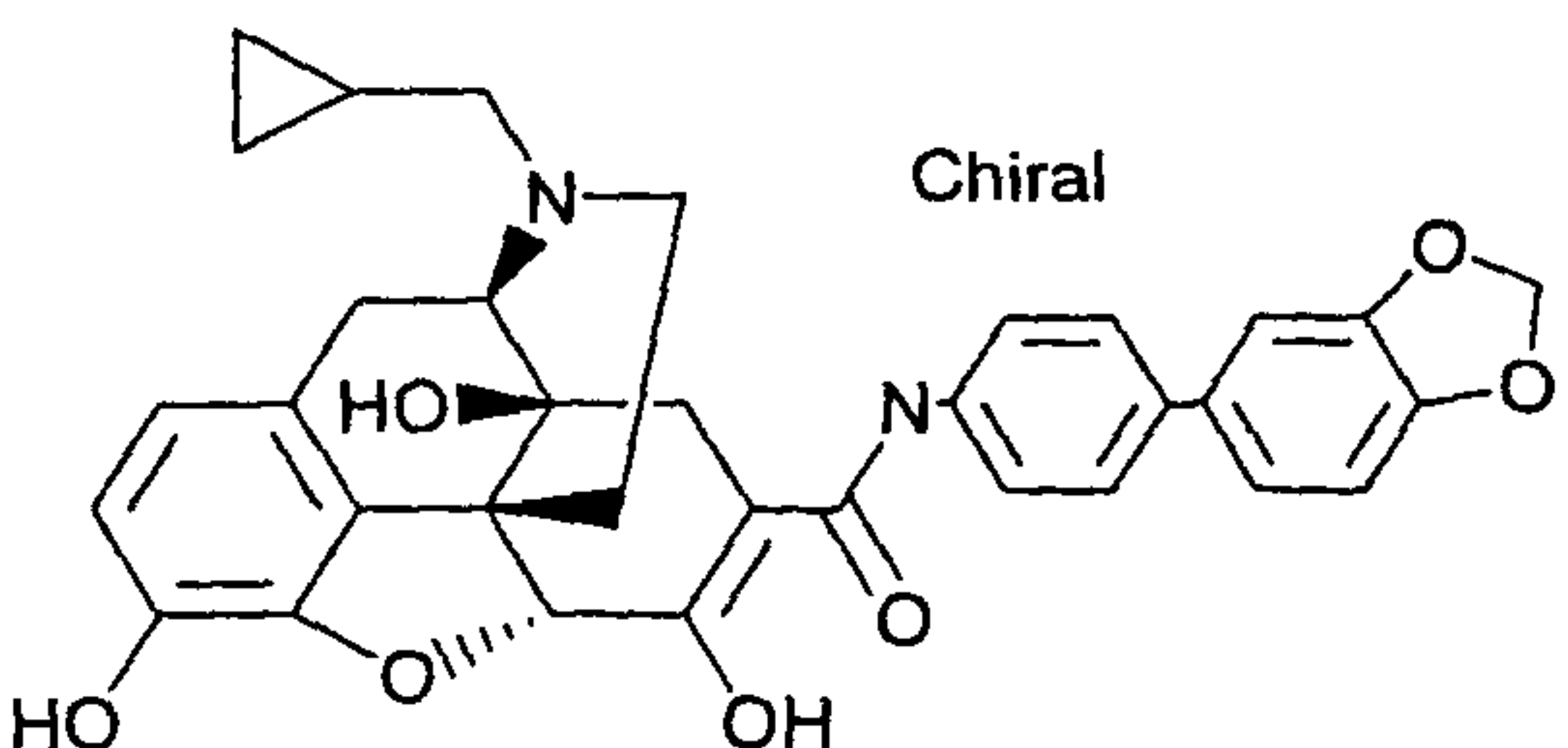
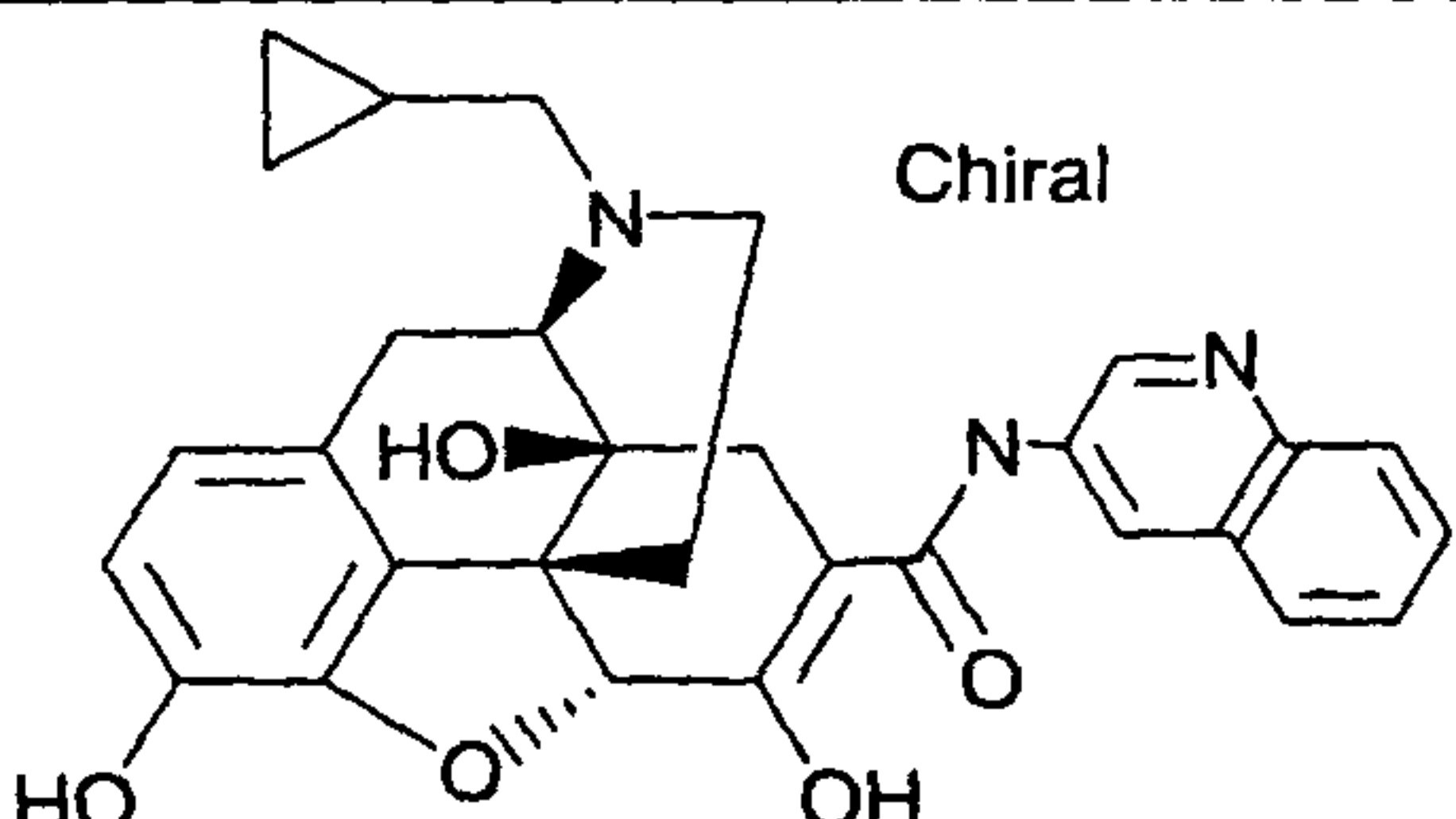
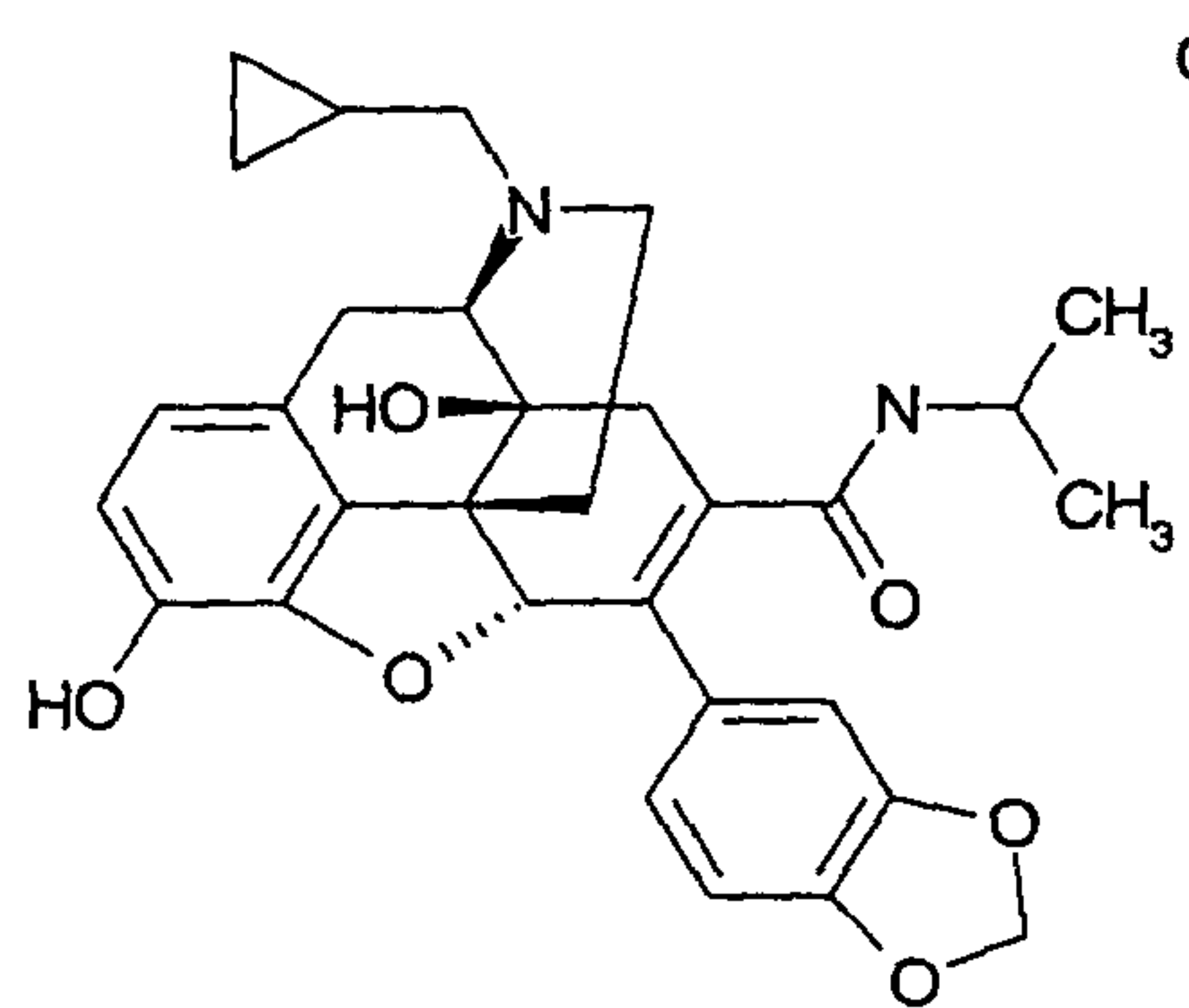
[0071]

[Table 26]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -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	
I-93	 Chiral	m/z 487 [M+H] ⁺ 0.50 min	

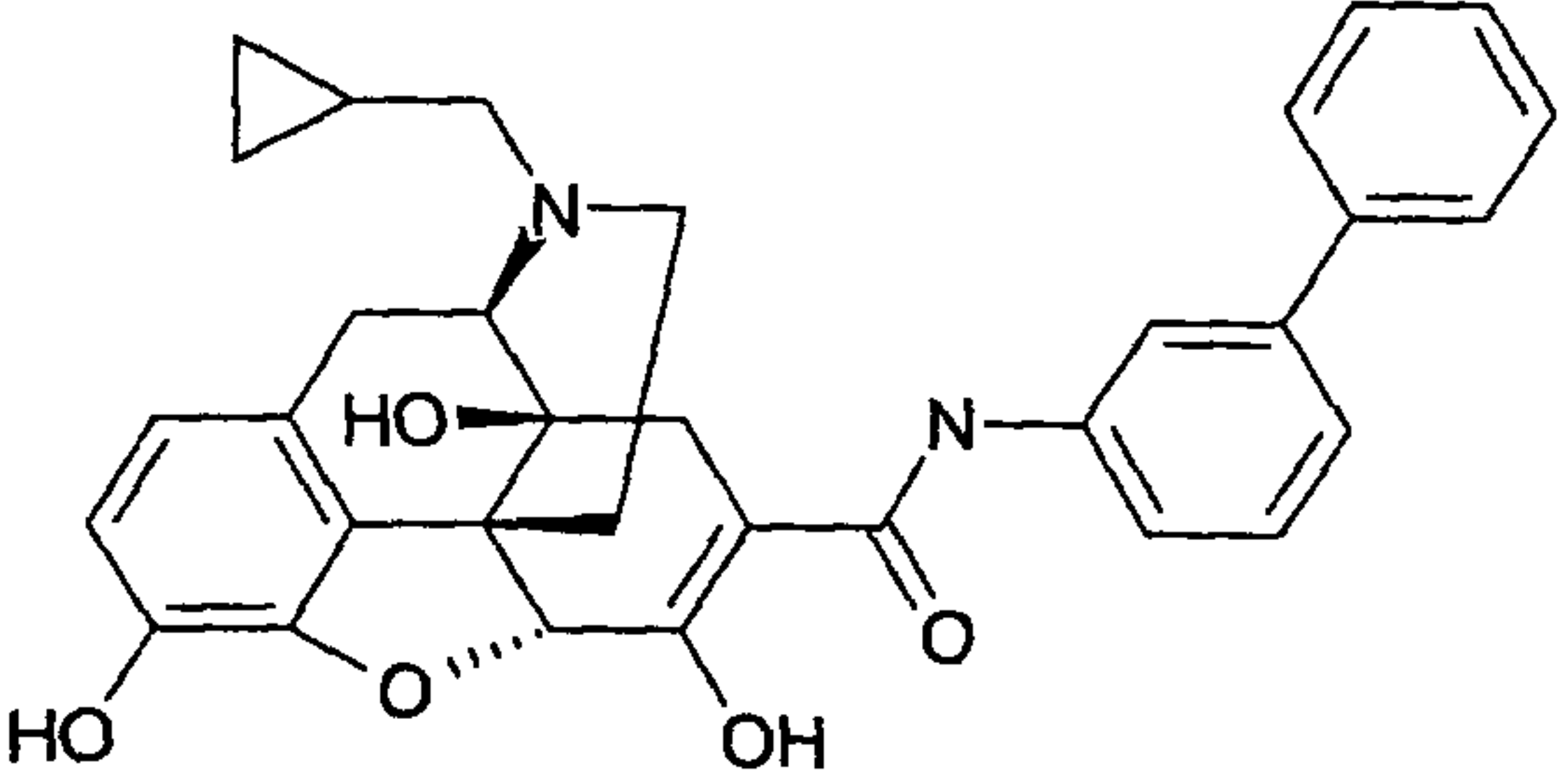
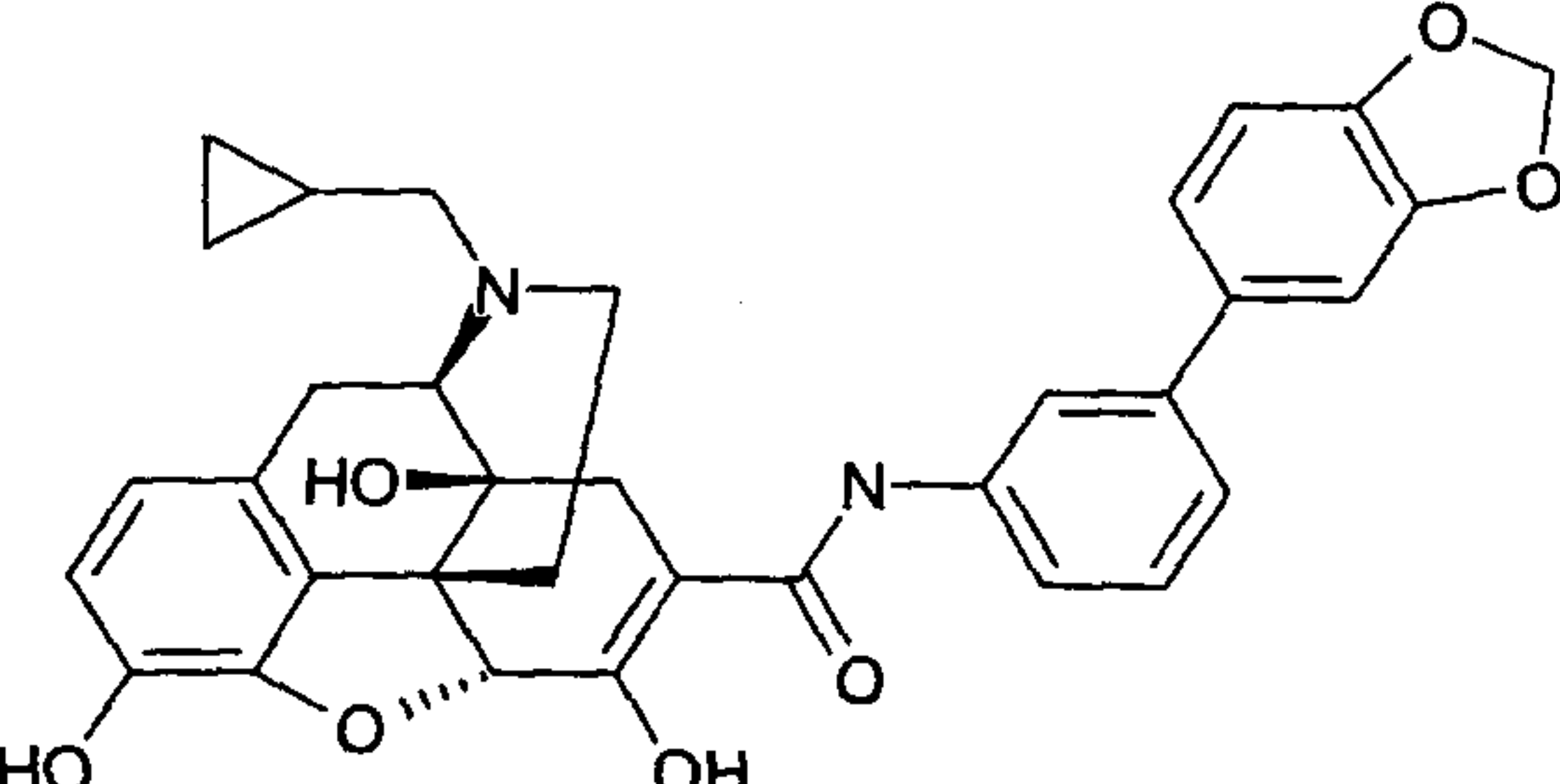
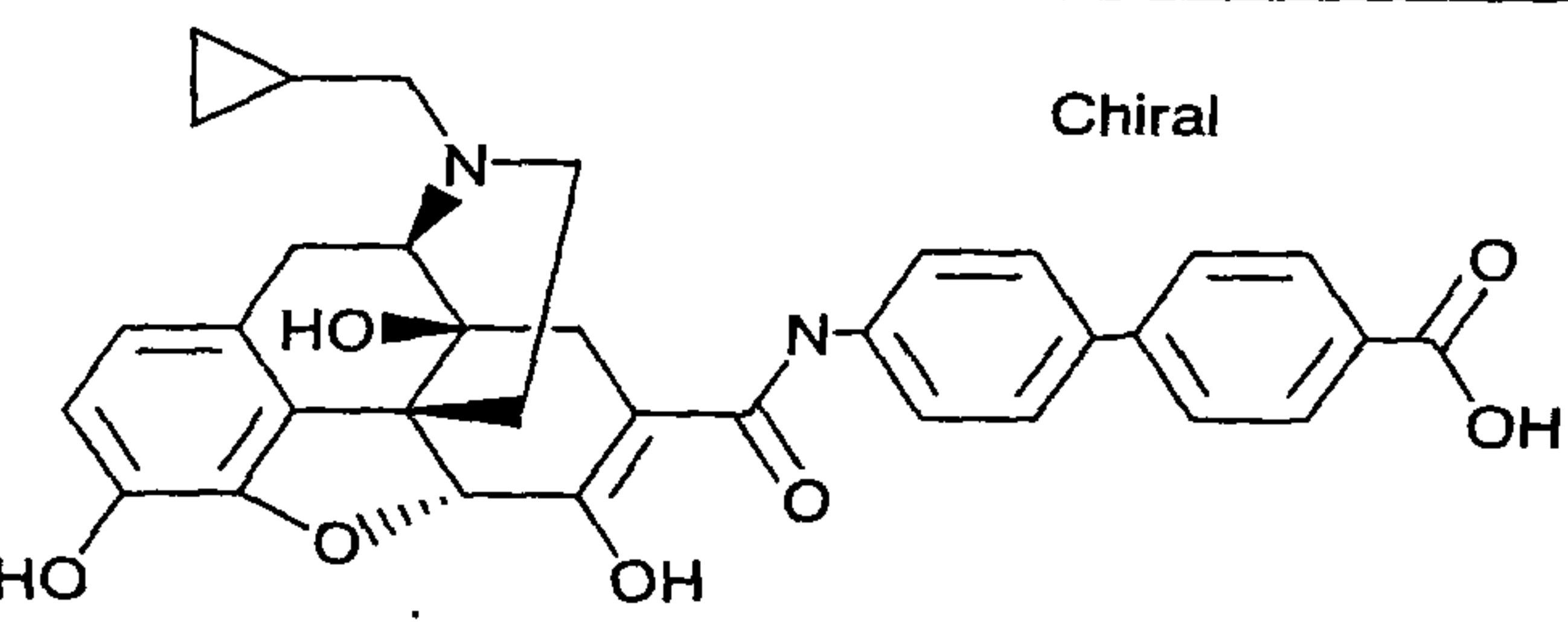
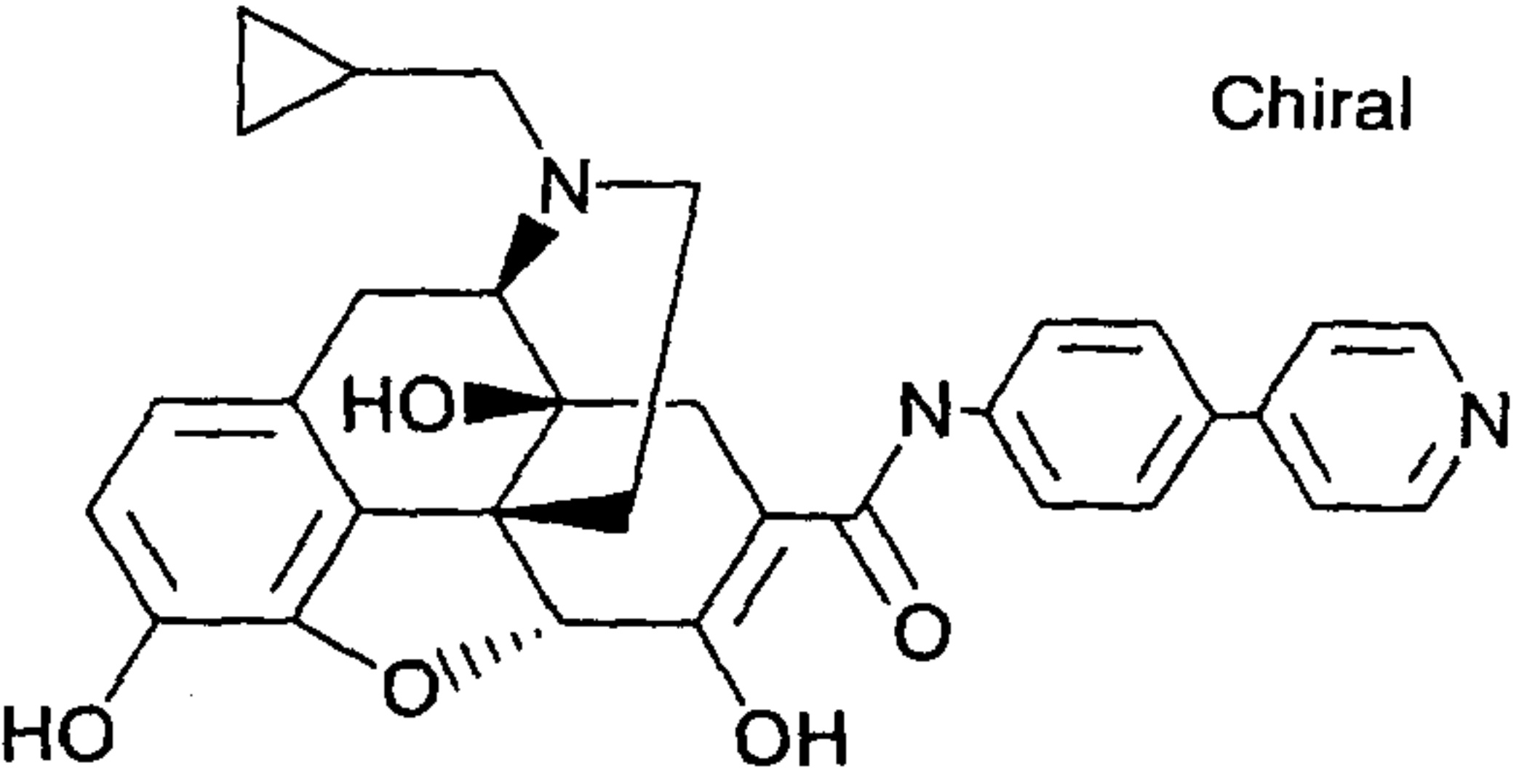
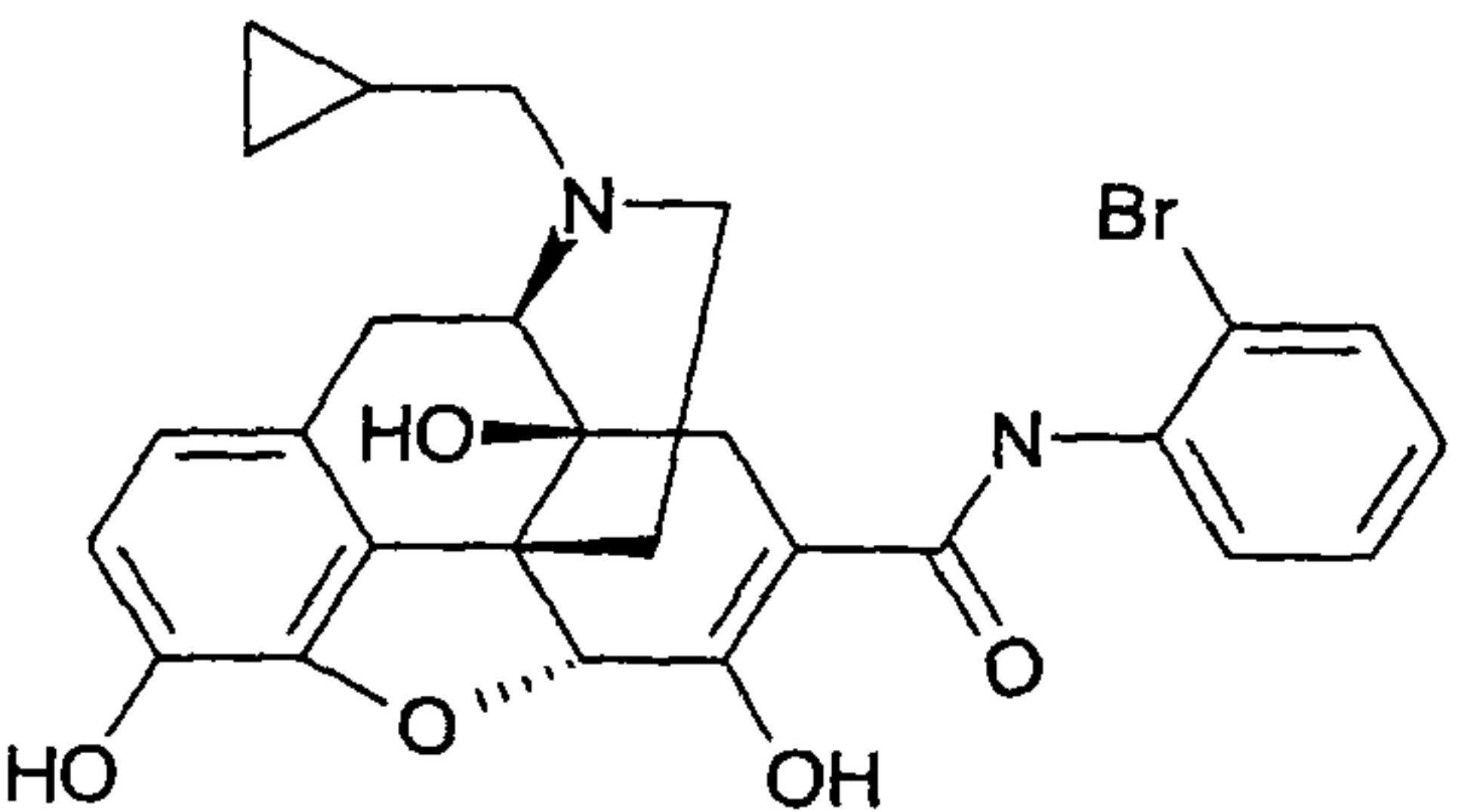
[0072]

[Table 27]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -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	
I-97	Chiral 	m/z 512 [M+H]⁺ 0.50 min	
I-98	Chiral 	m/z 531 [M+H]⁺ 0.50 min	

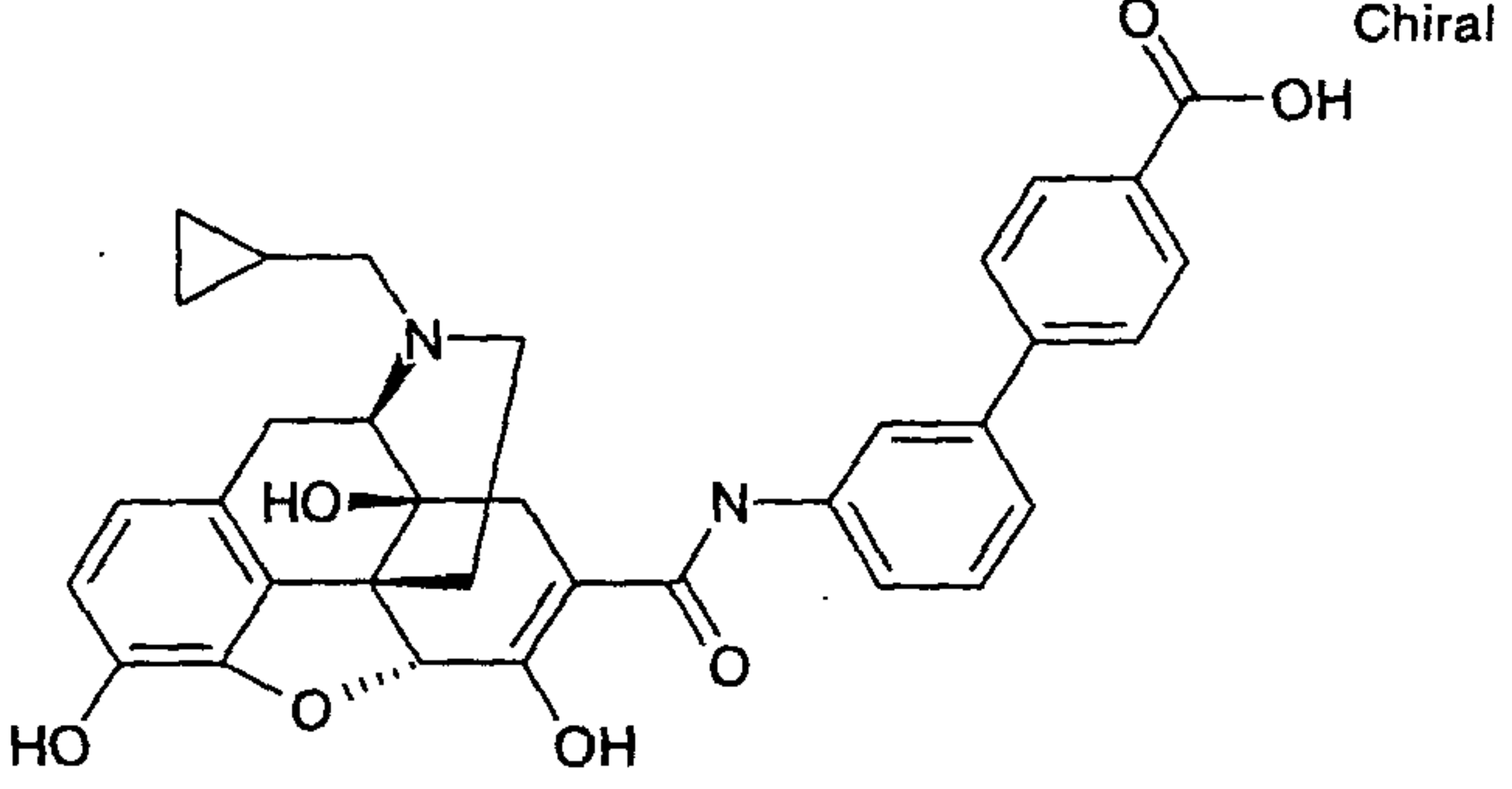
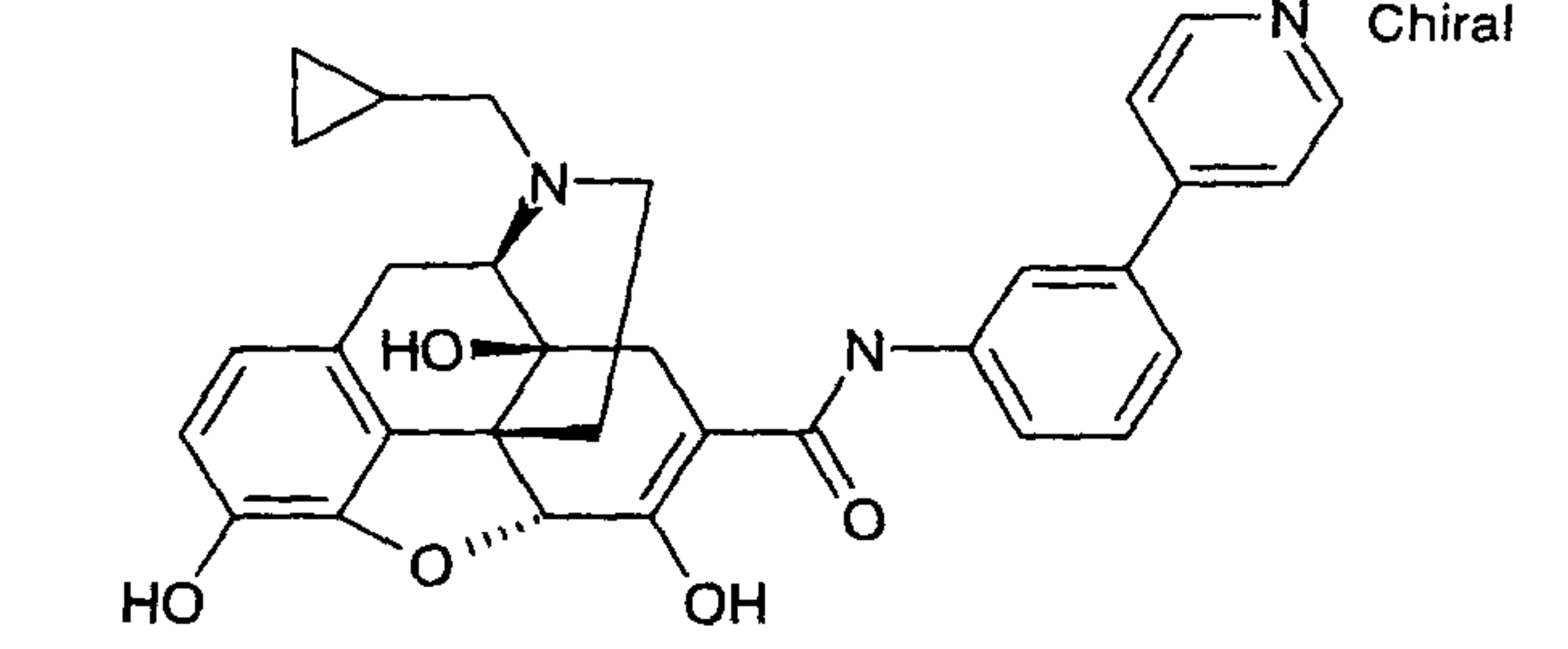
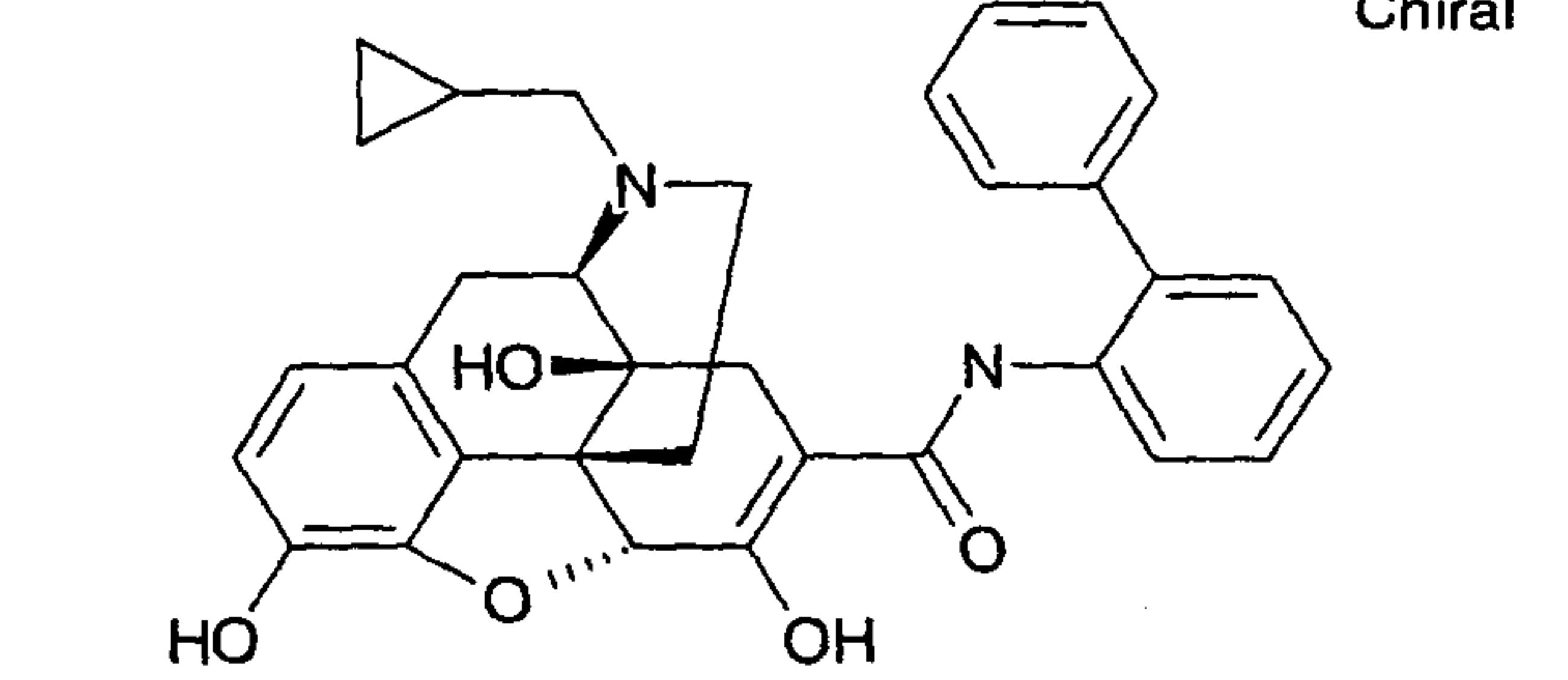
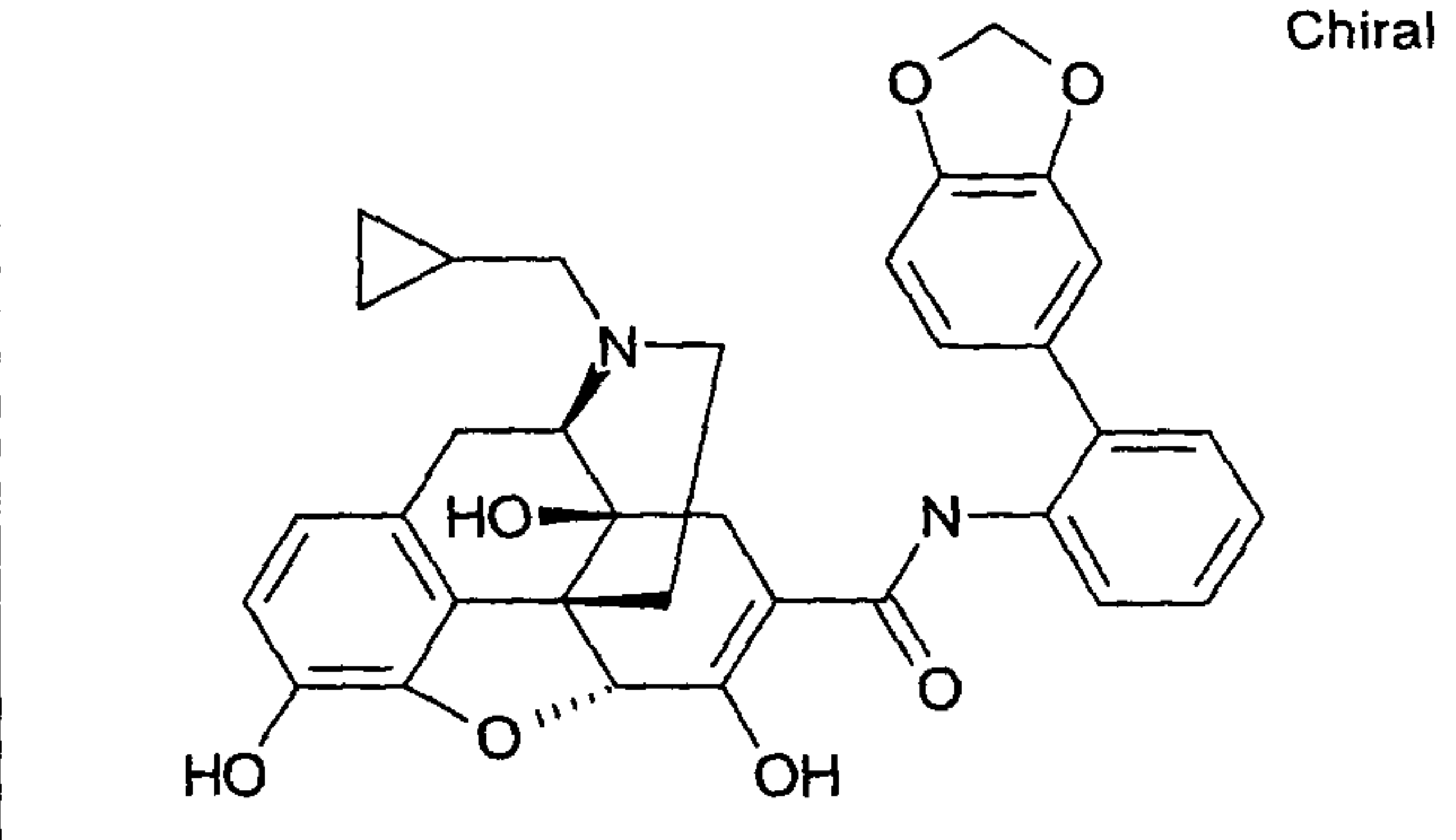
[0073]

[Table 28]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-99	 Chiral	m/z 537 [M+H] ⁺ 1.17 min	
I-100	 Chiral	m/z 581 [M+H] ⁺ 1.15 min	
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	

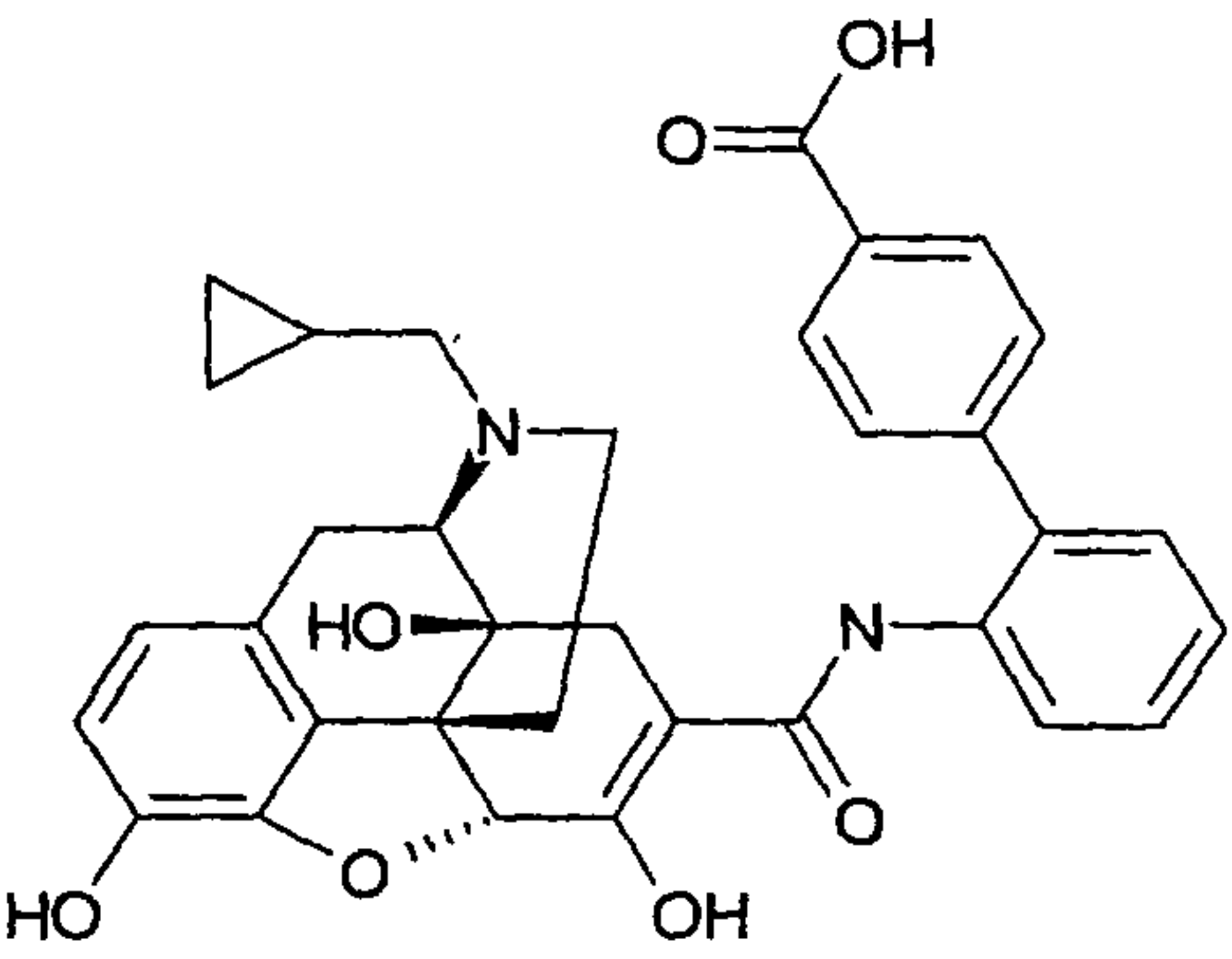
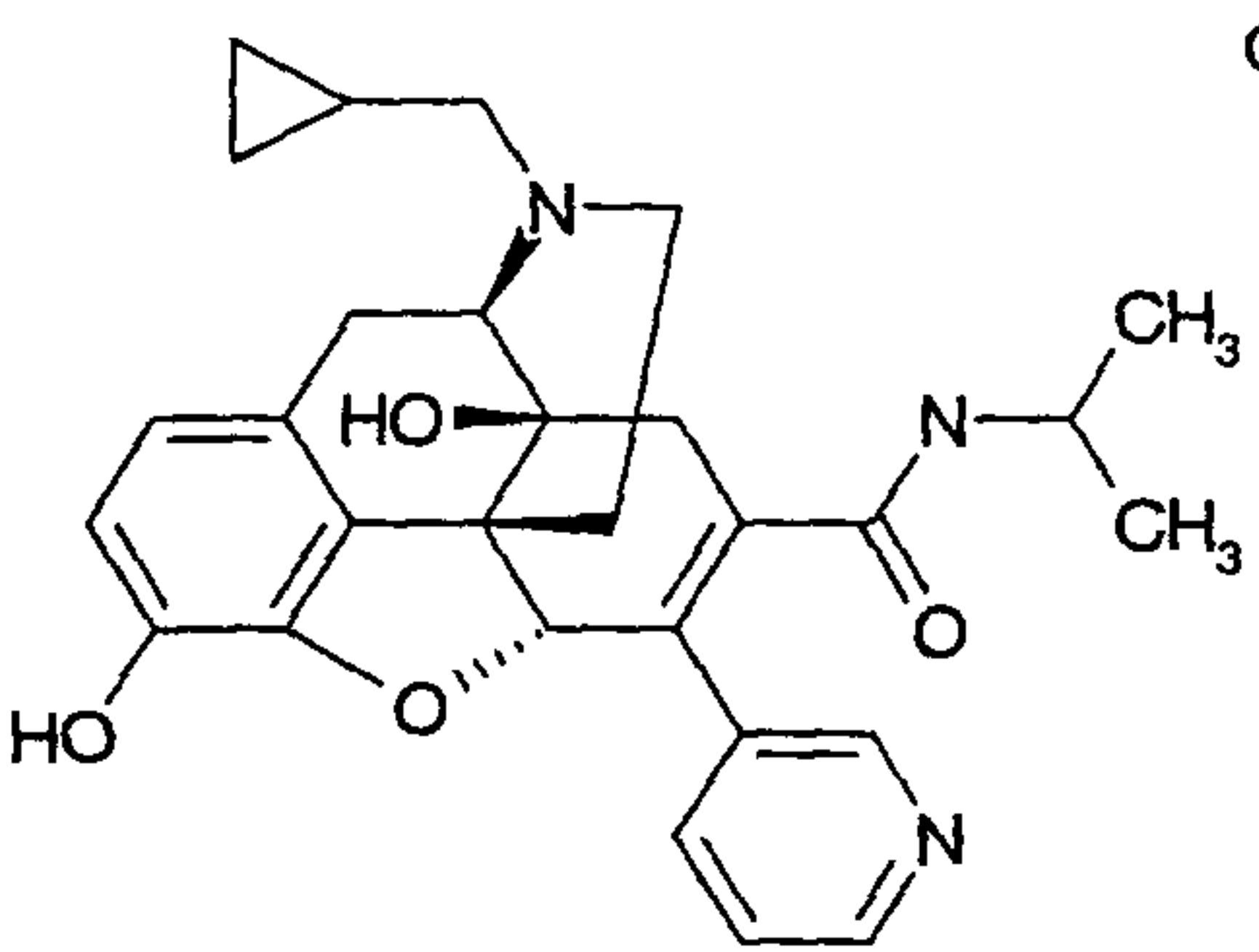
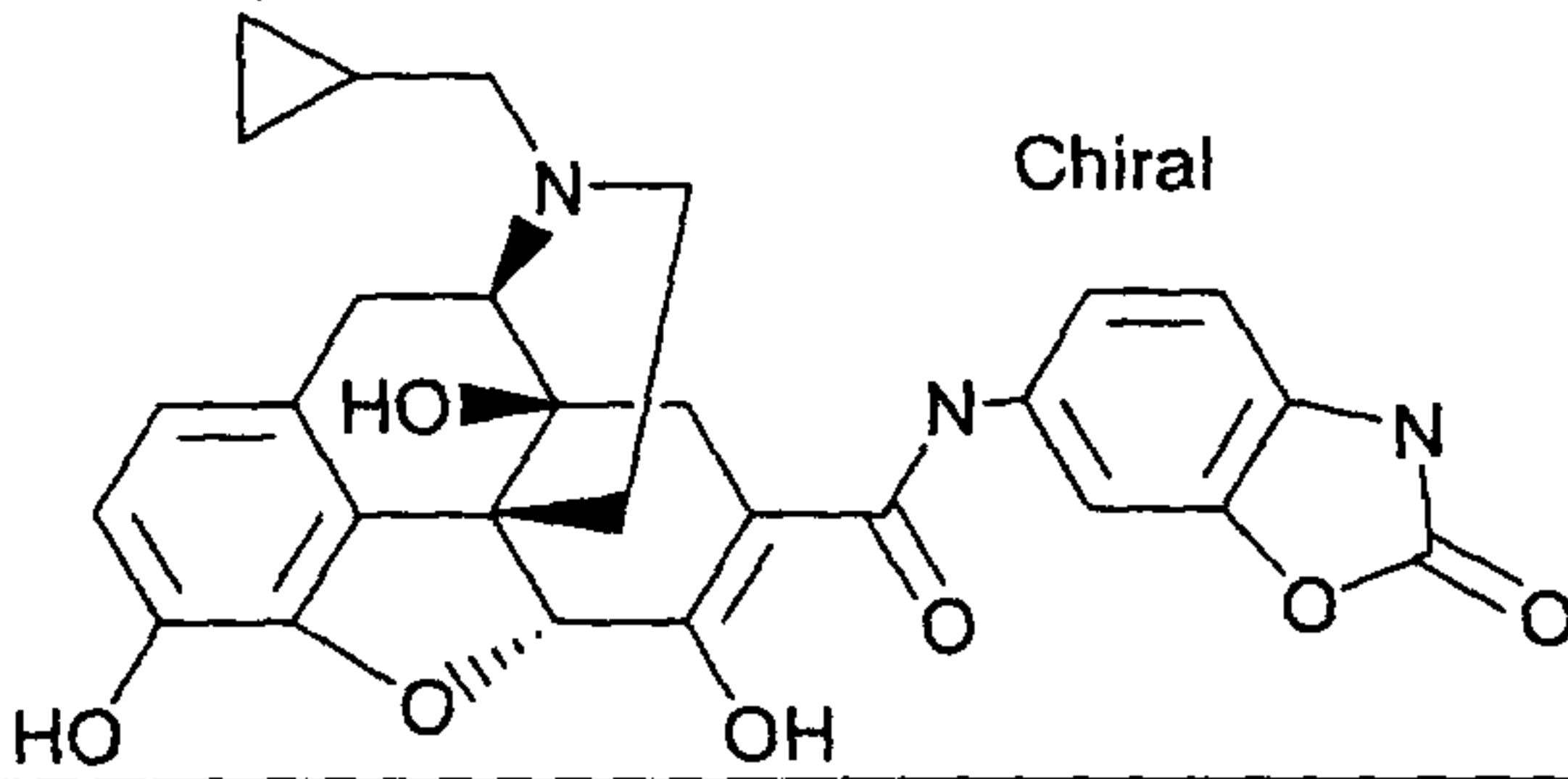
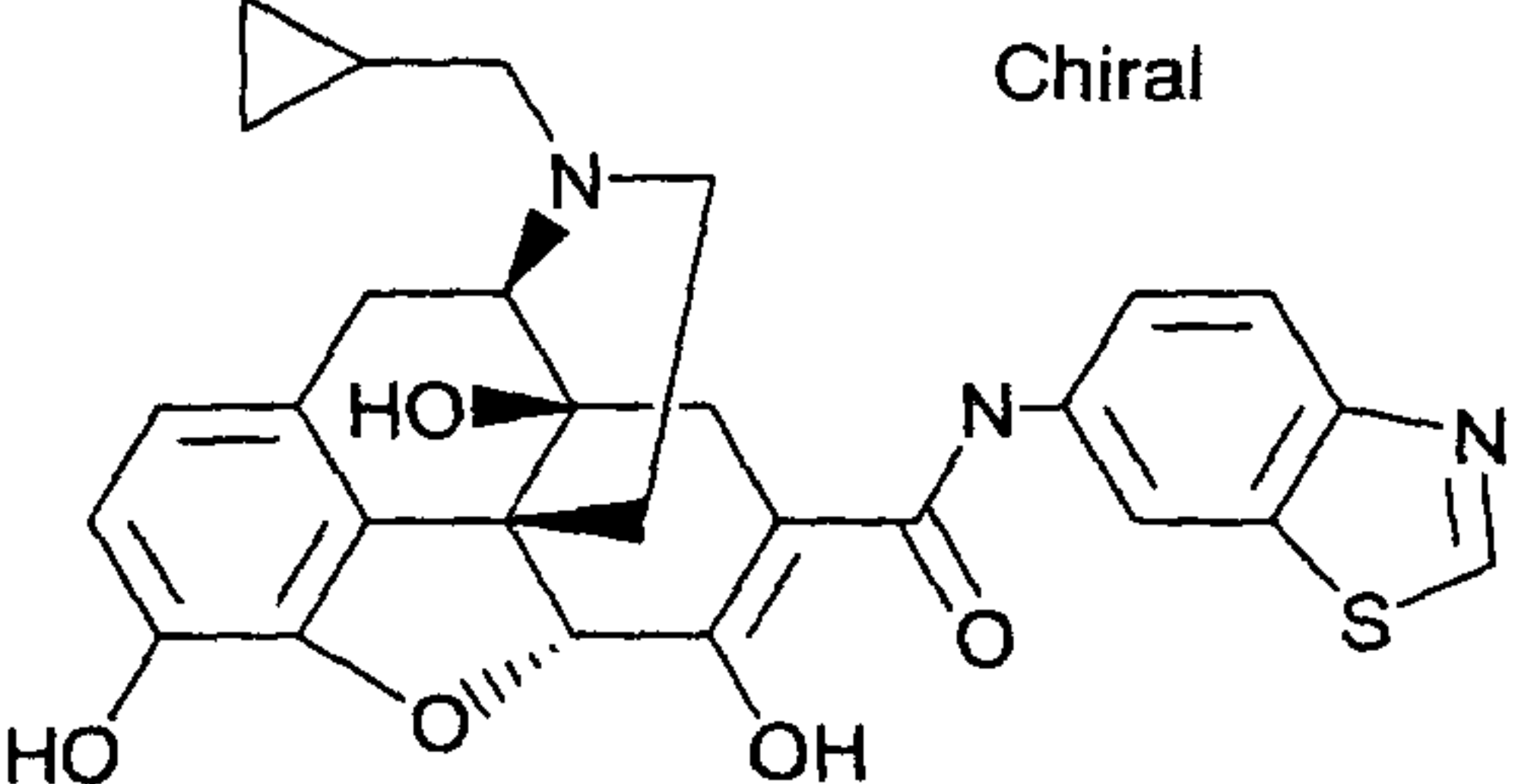
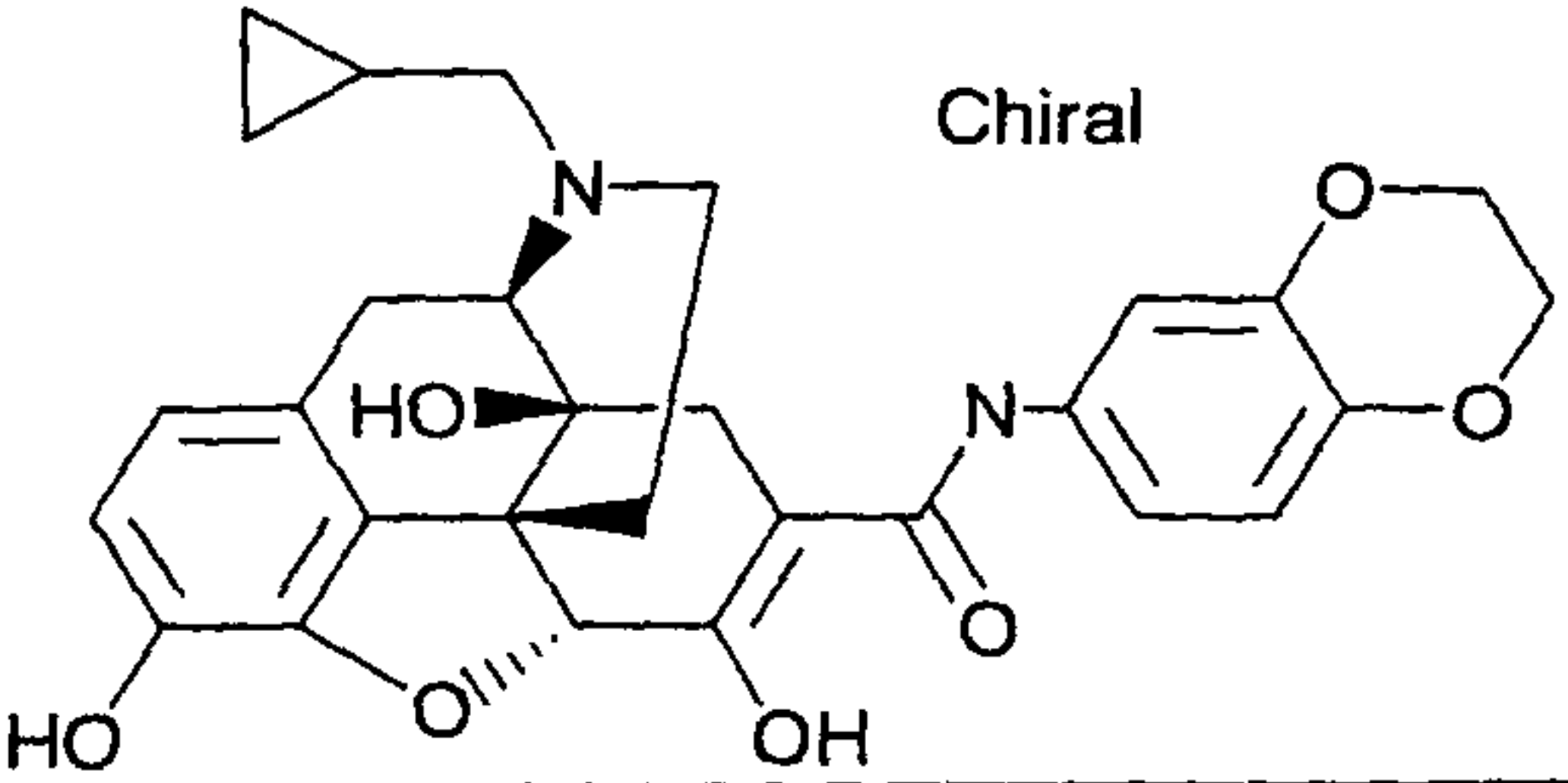
[0074]

[Table 29]

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

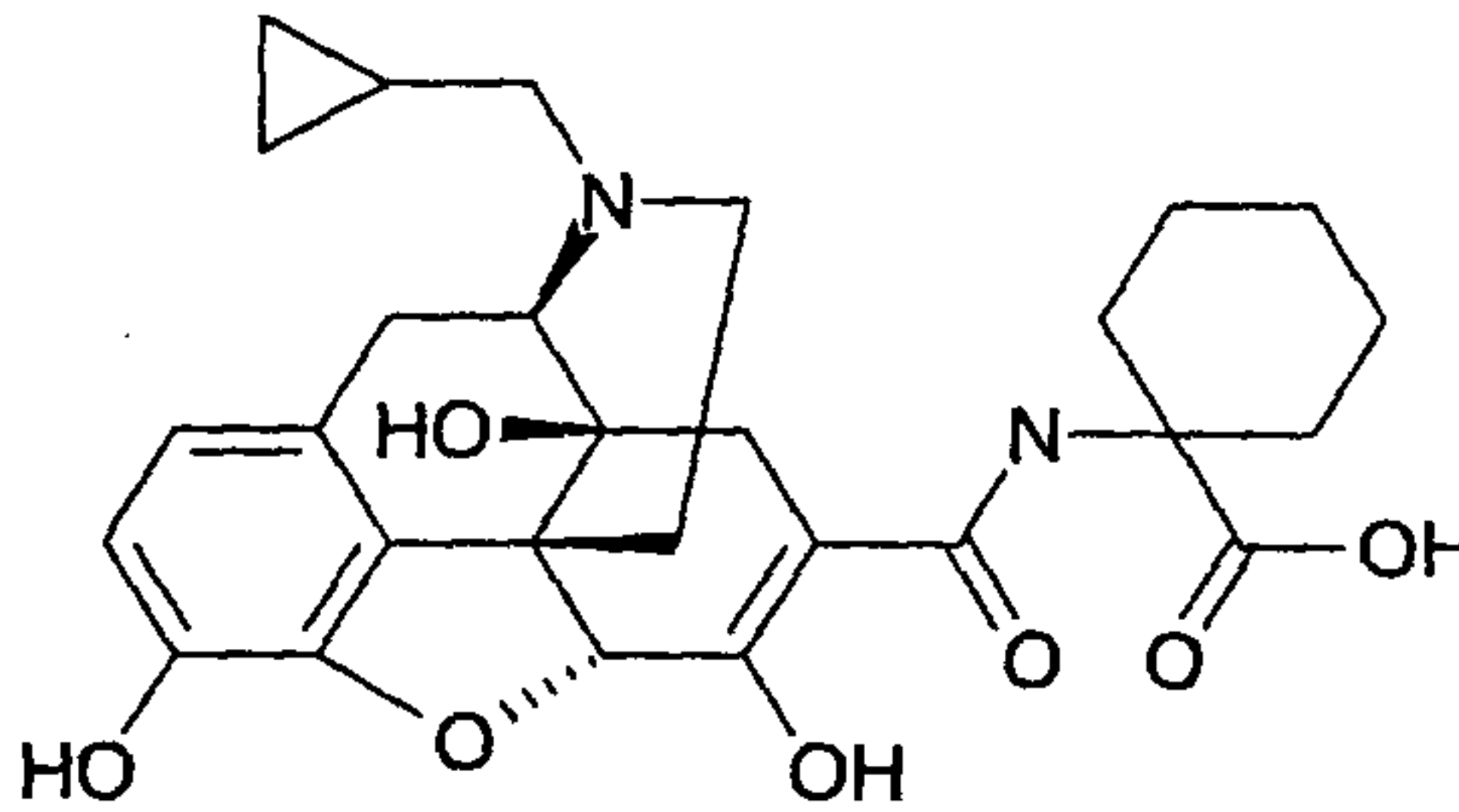
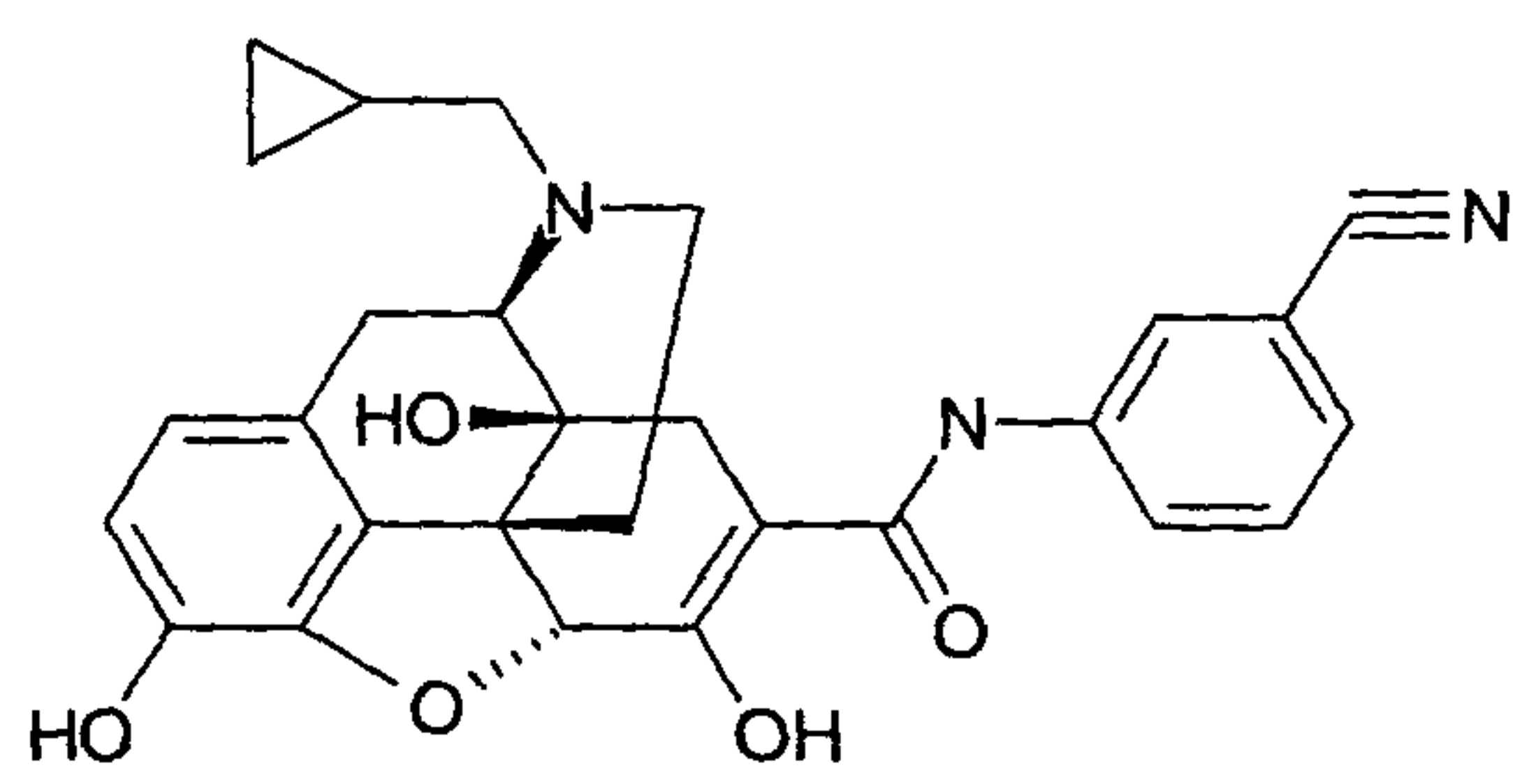
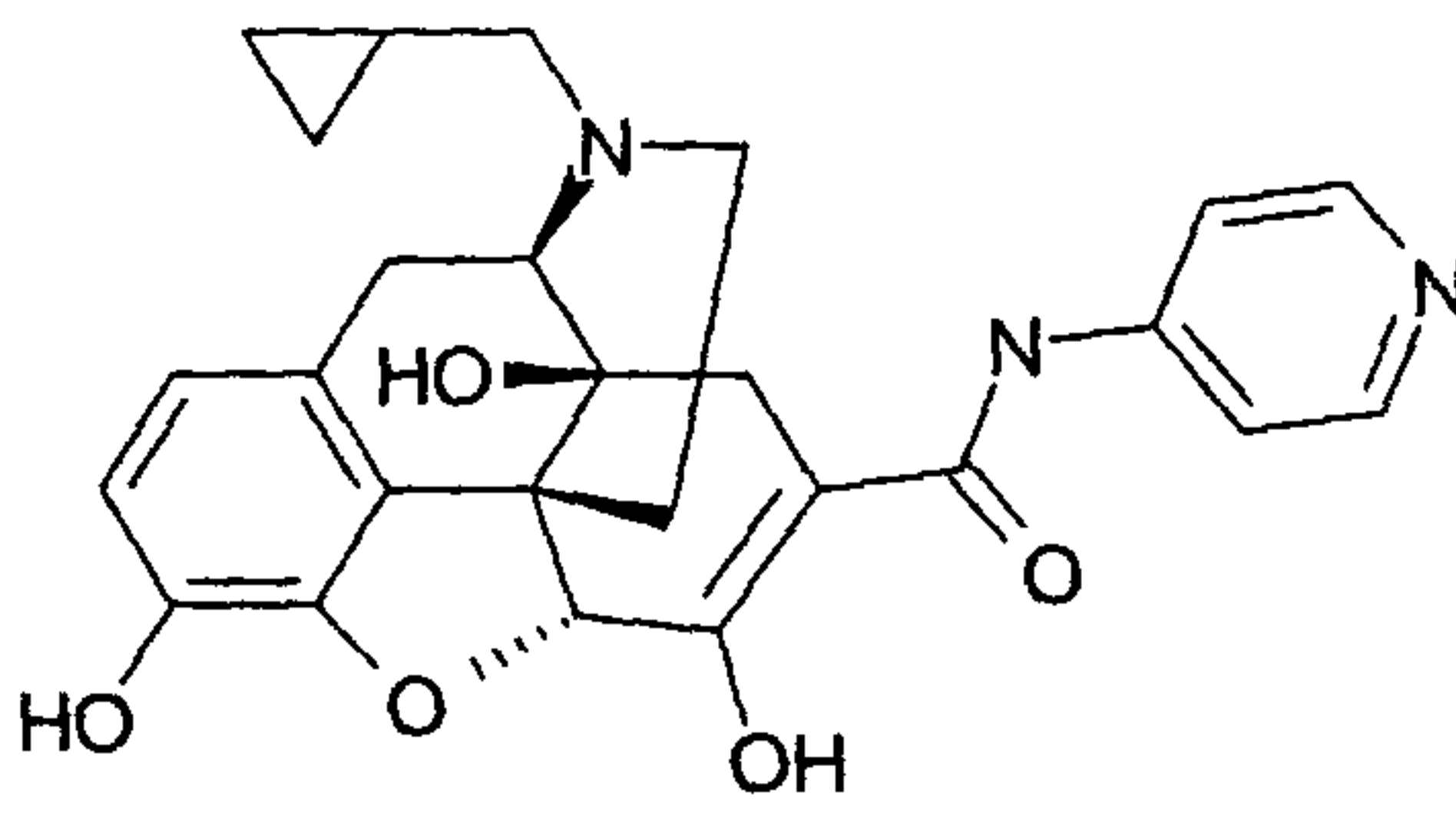
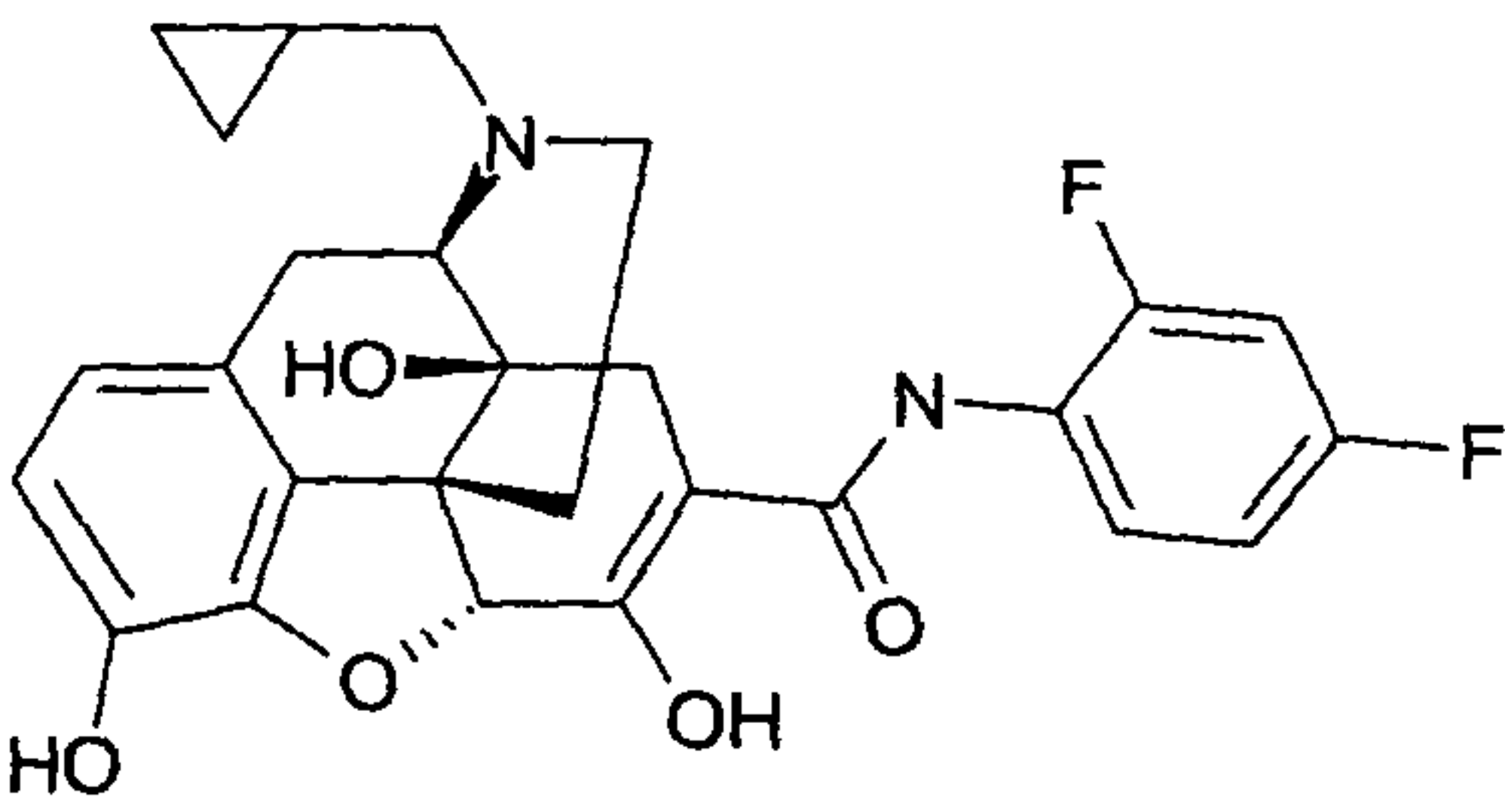
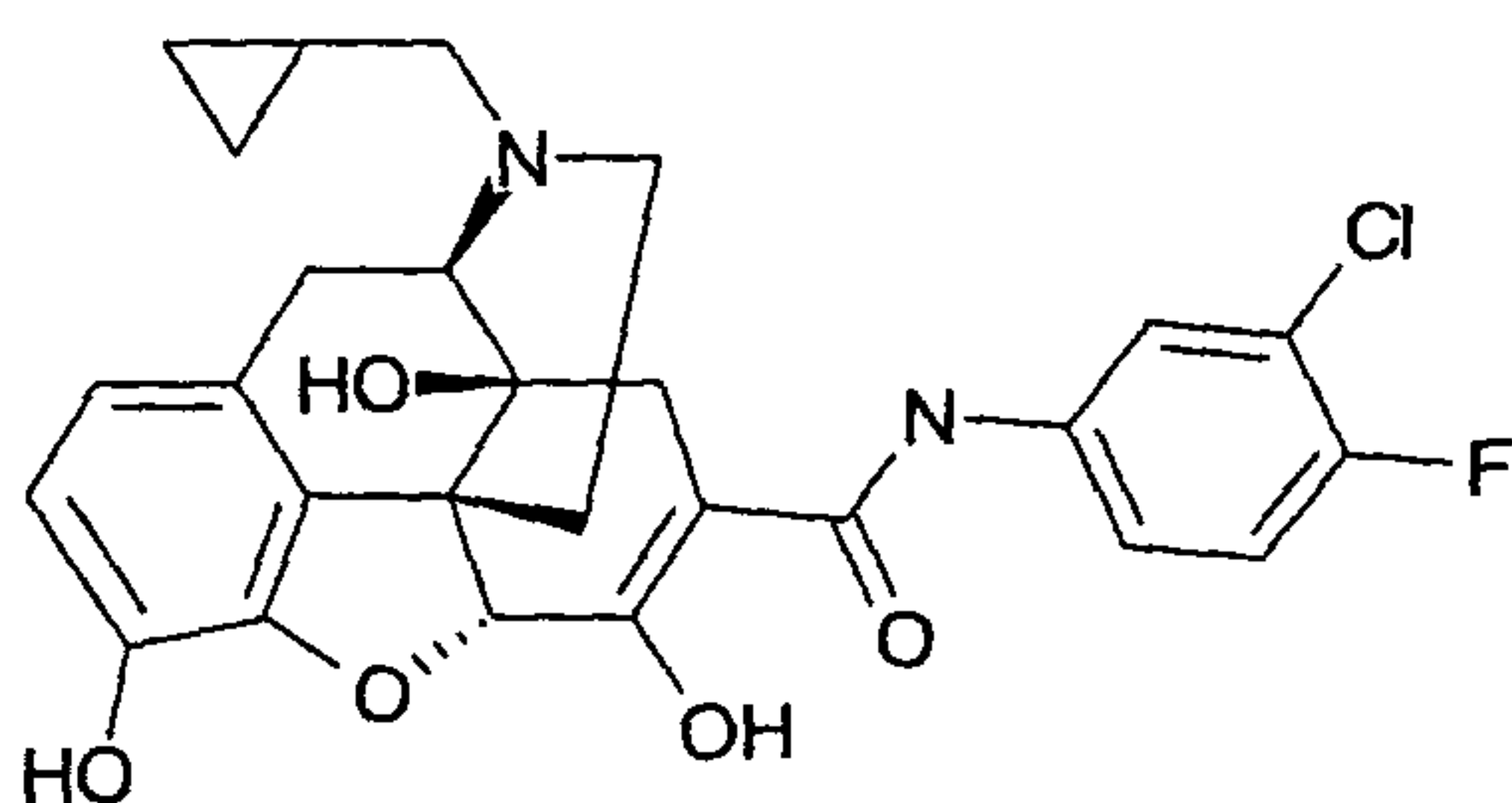
[0075]

[Table 30]

Compound No.	Chemical structure	LC/MS*1	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-108	Chiral 	m/z 581 [M+H] ⁺ 1.03 min	
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	

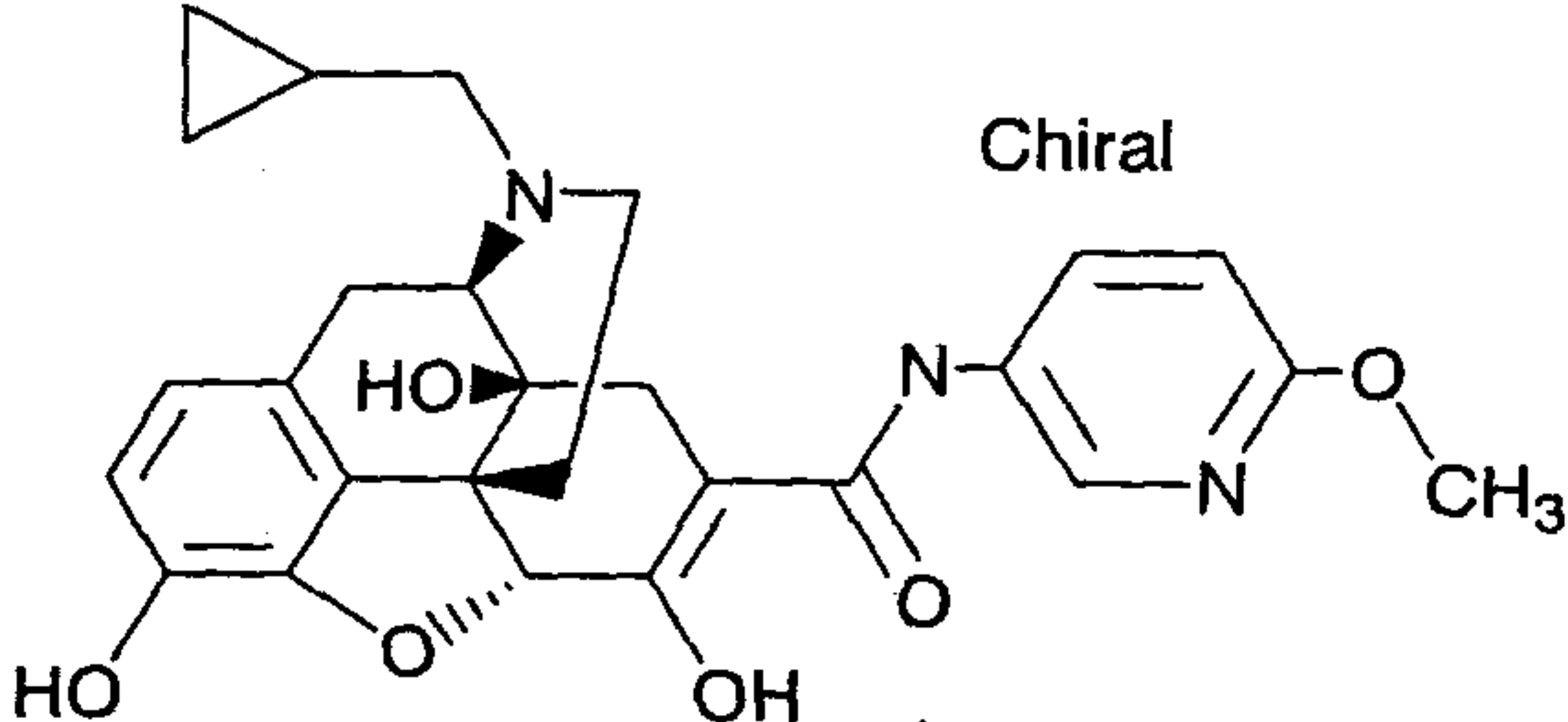
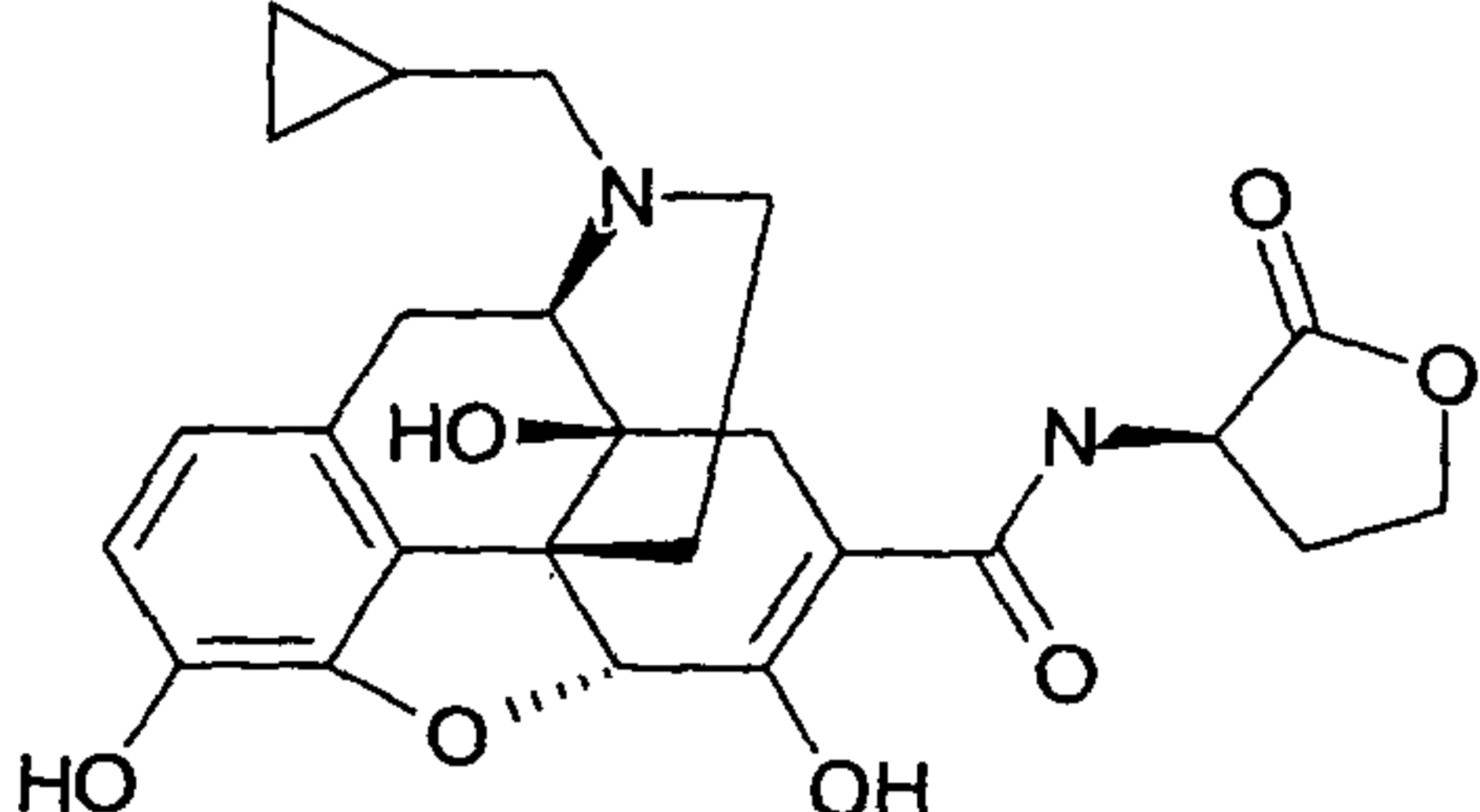
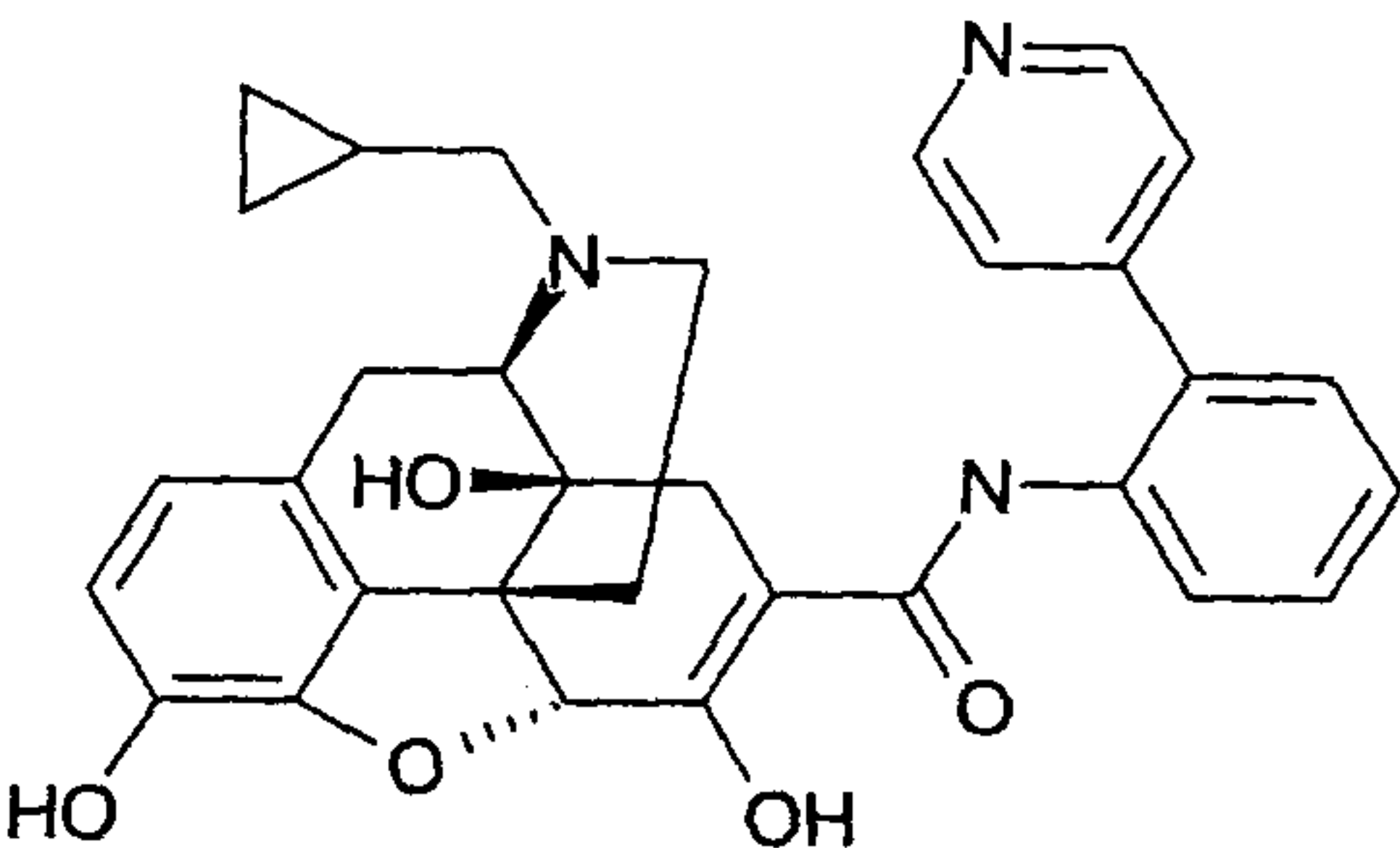
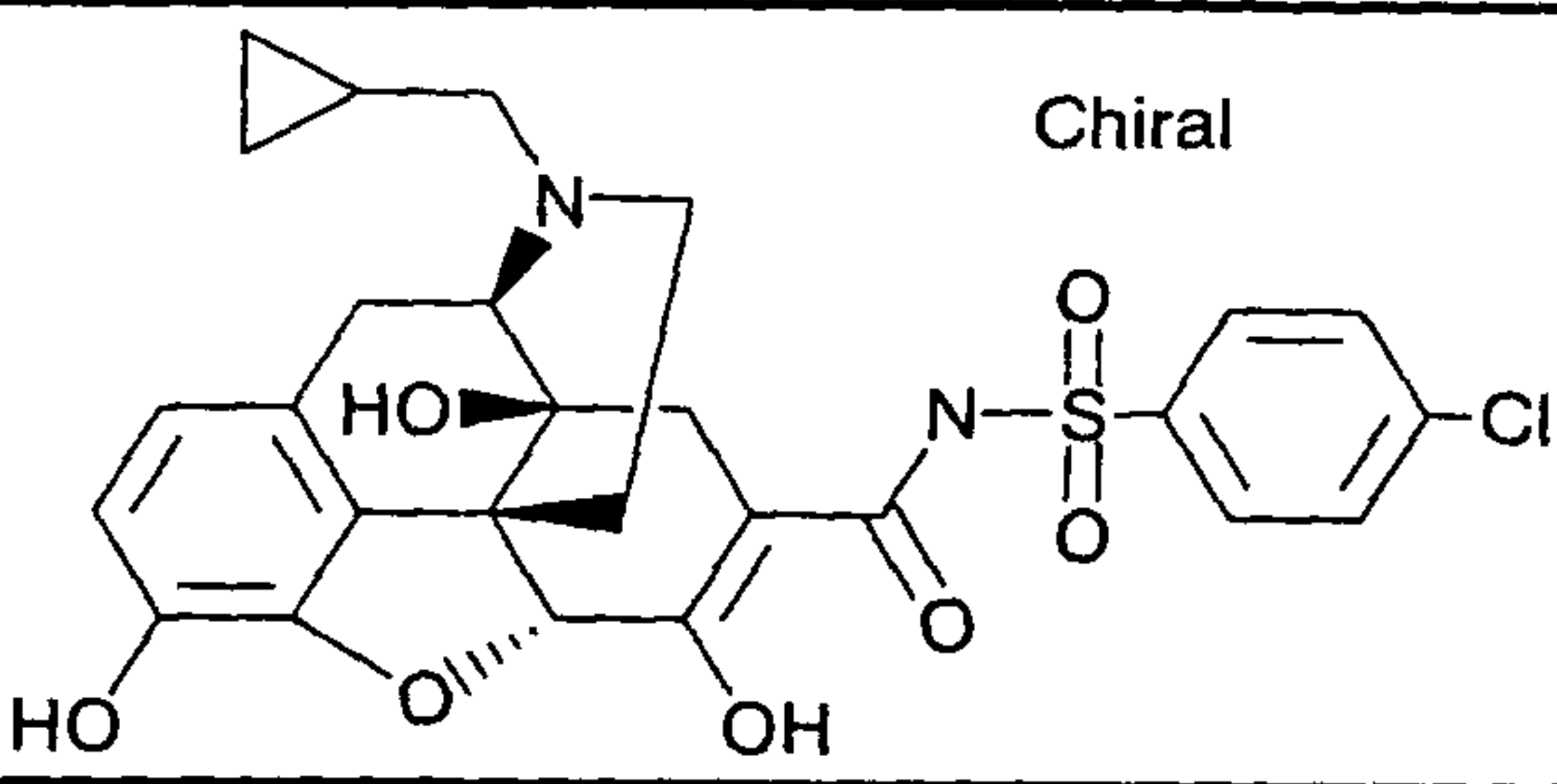
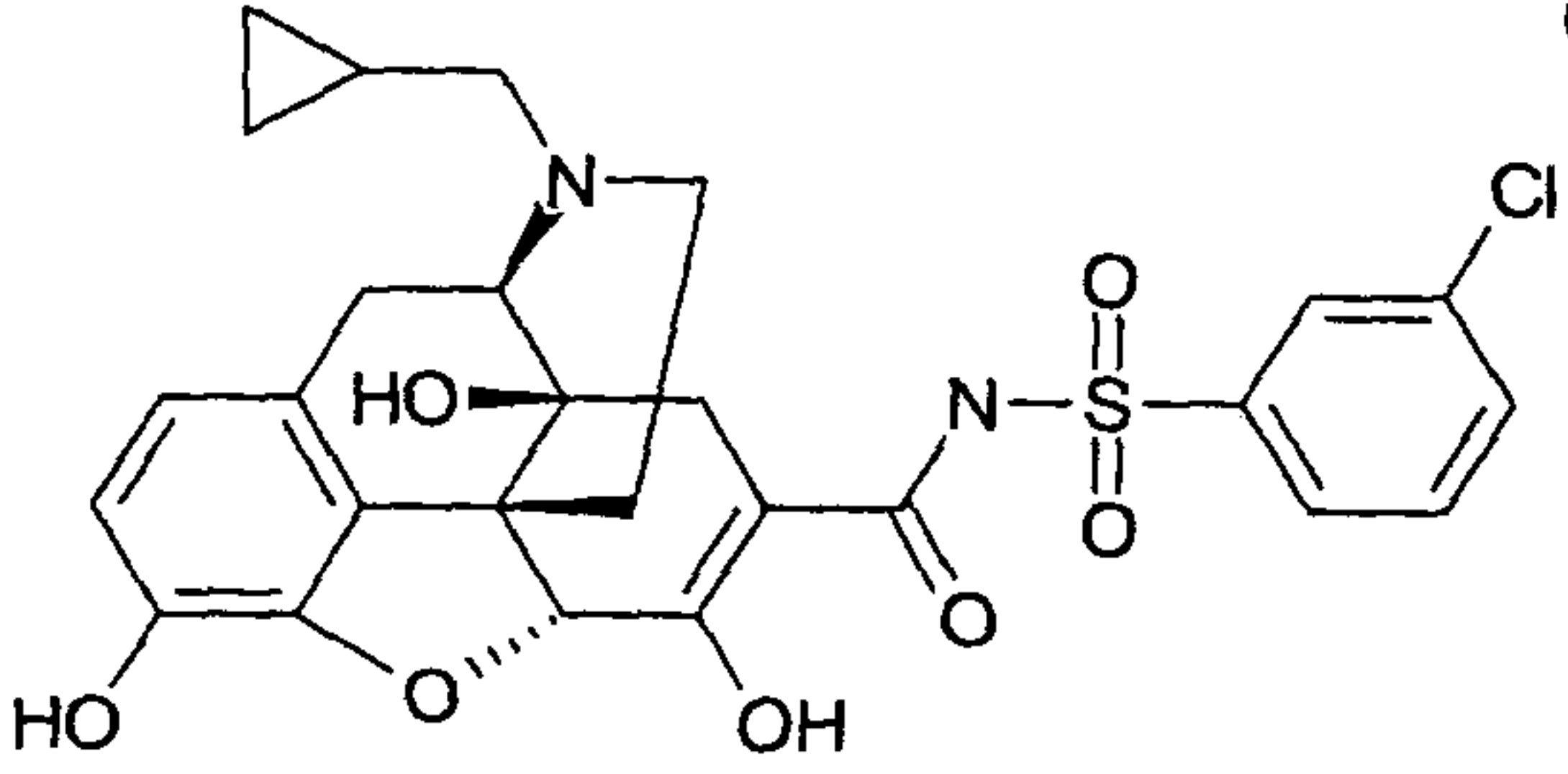
[0076]

[Table 31]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-113	Chiral 	m/z 511 [M+H] ⁺ 0.50 min	
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	

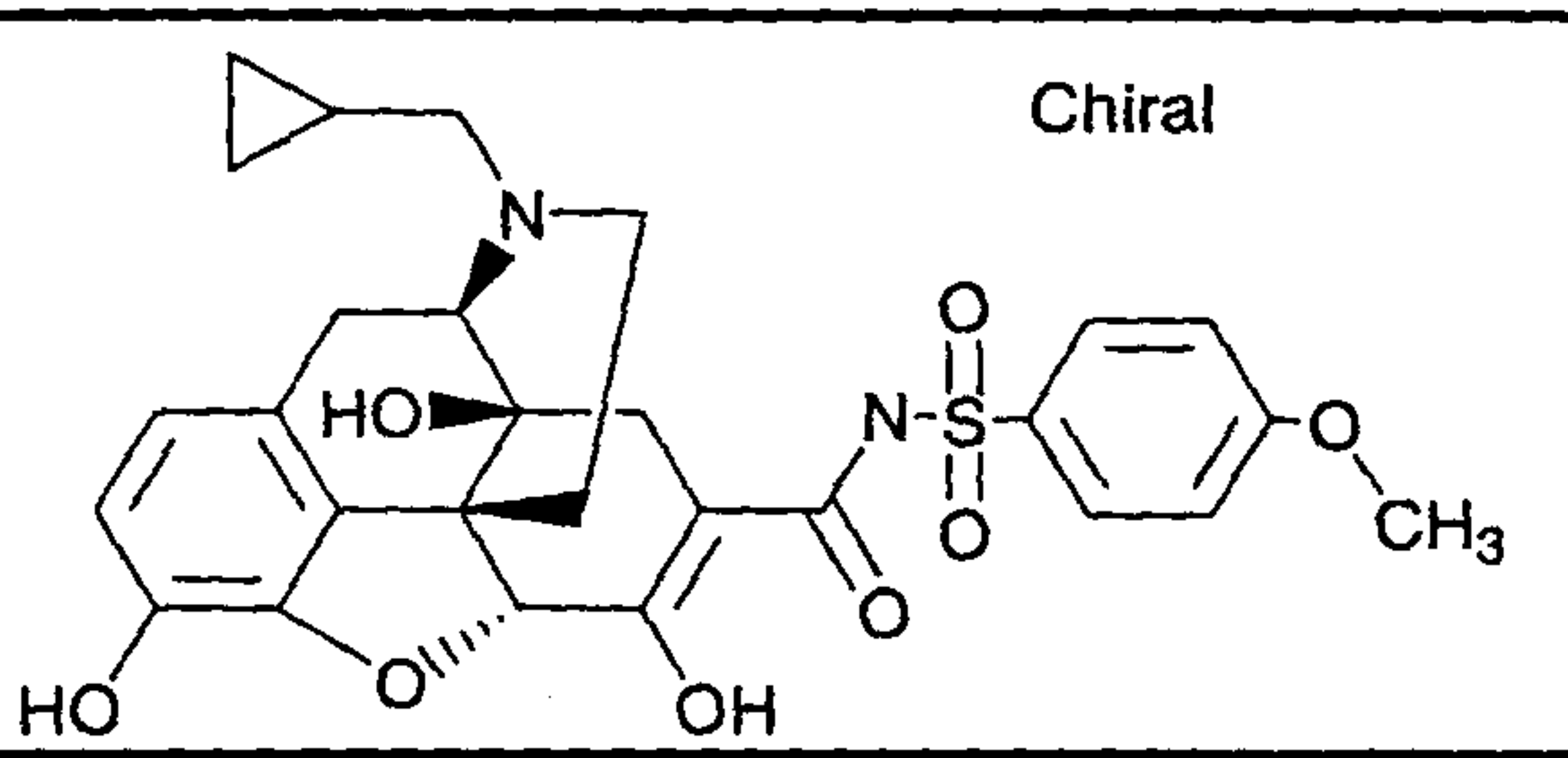
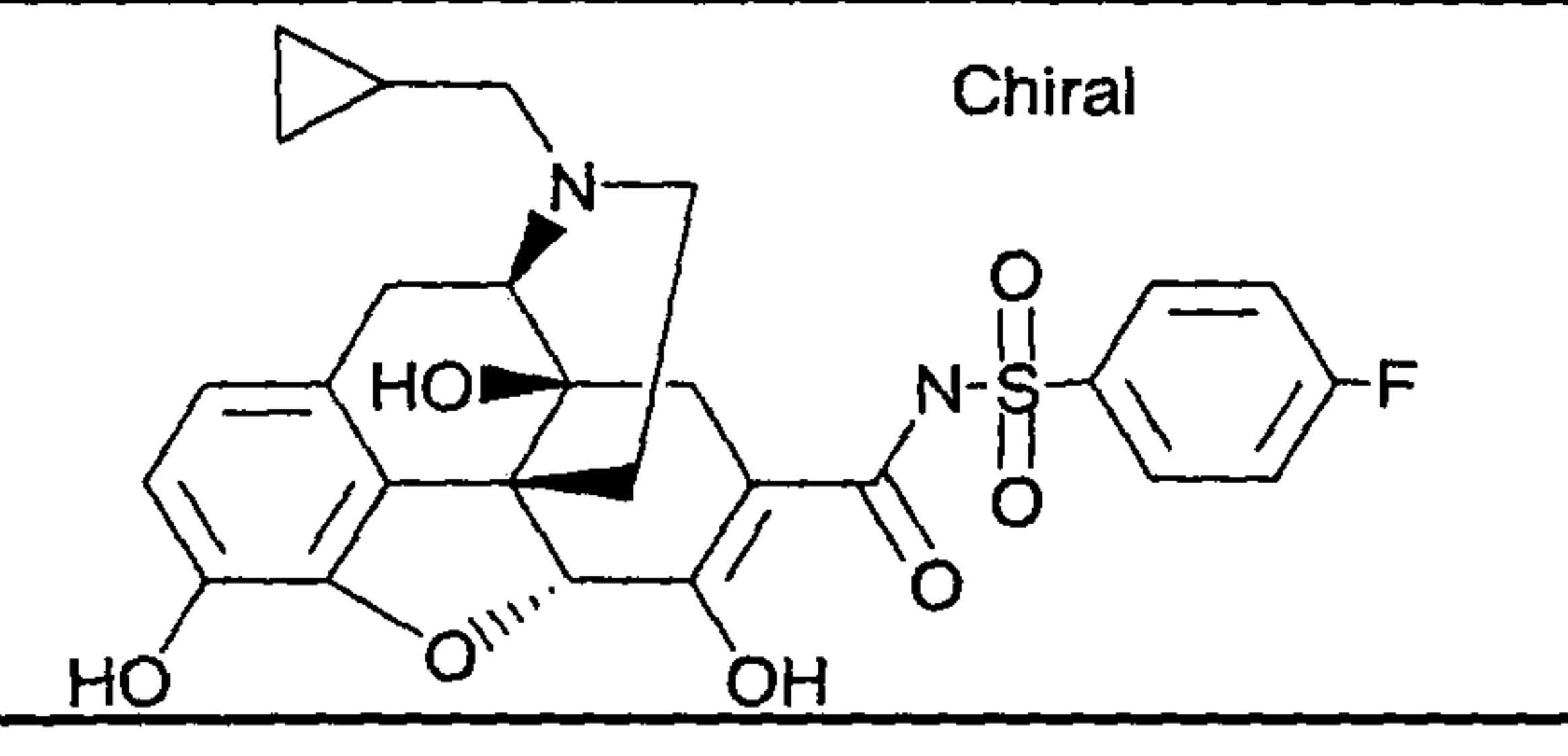
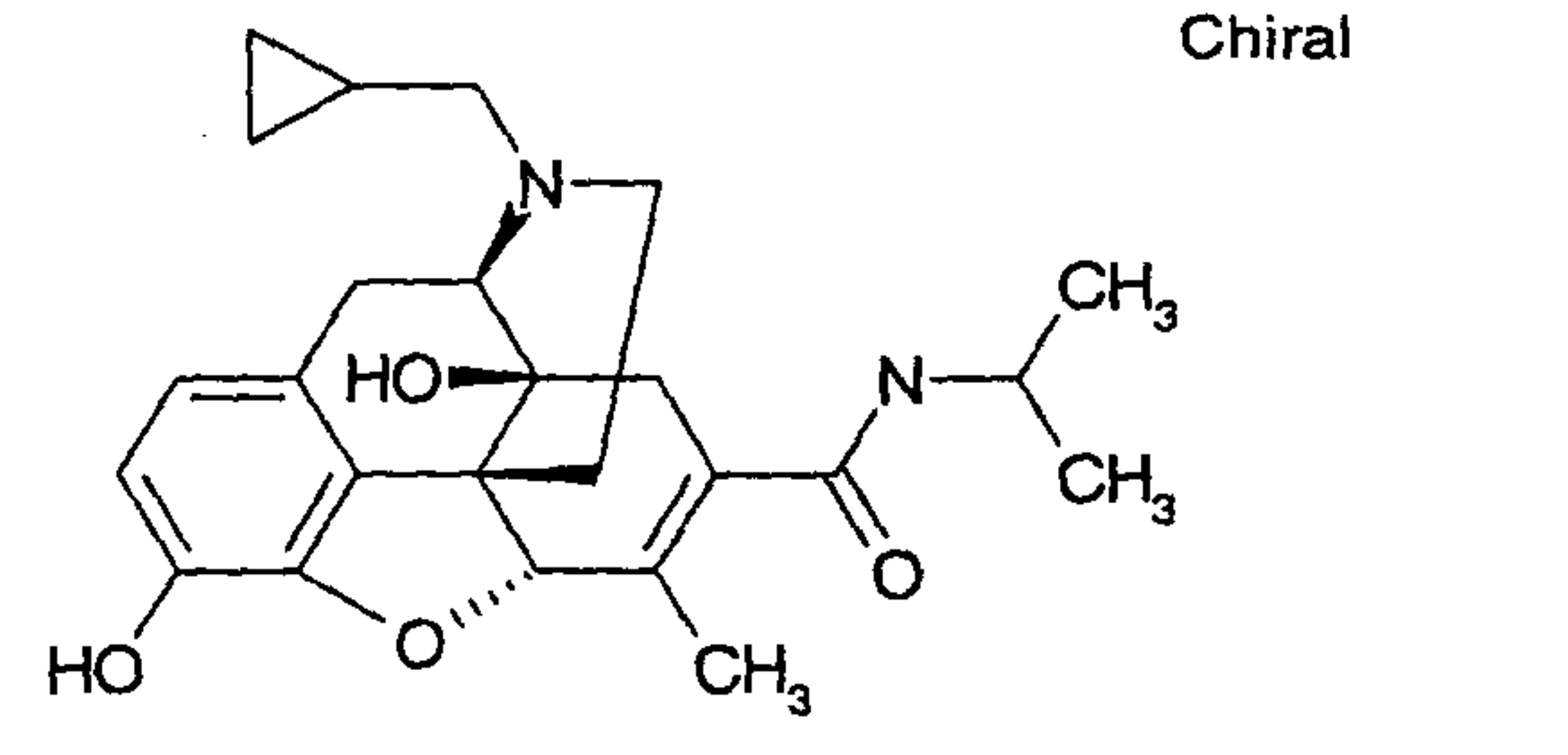
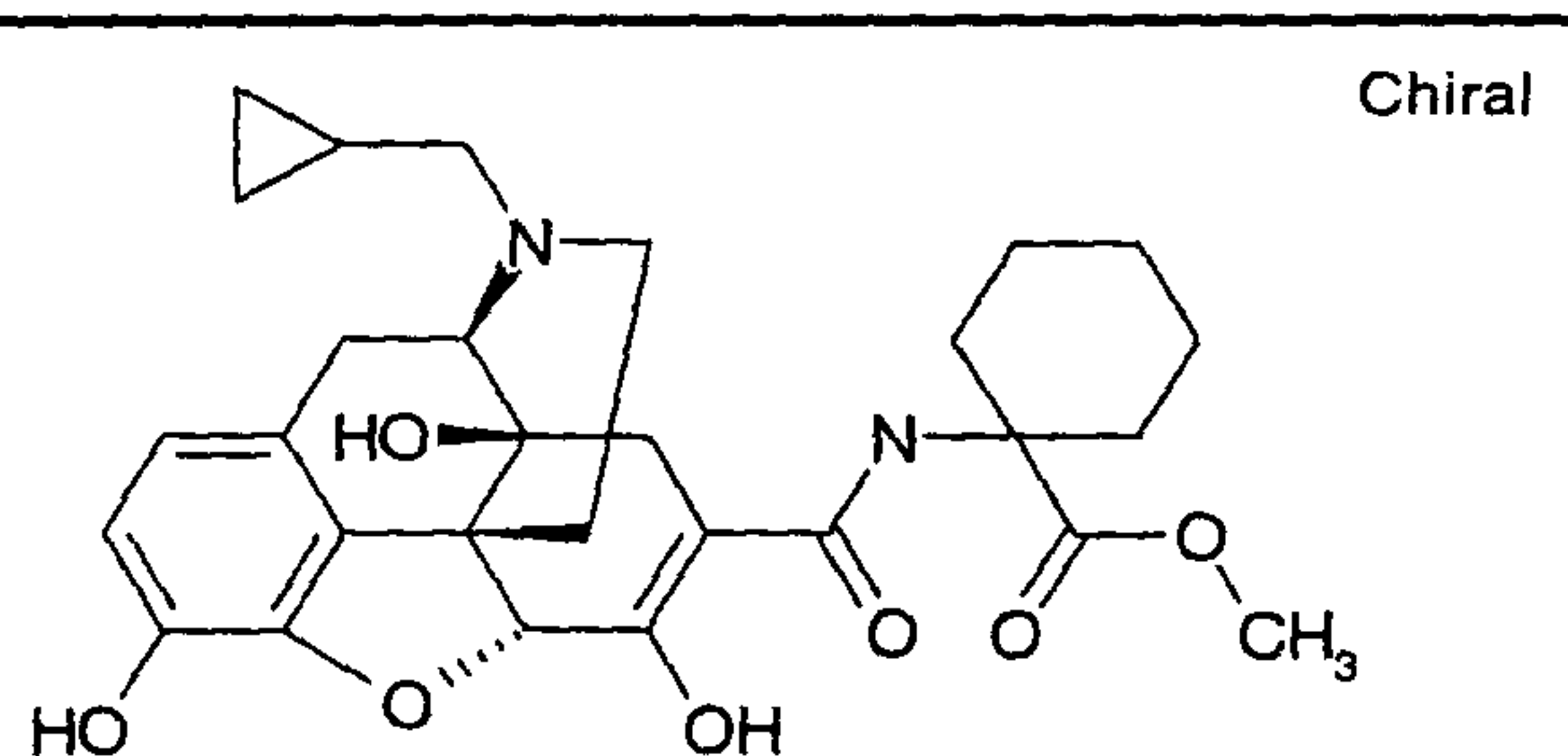
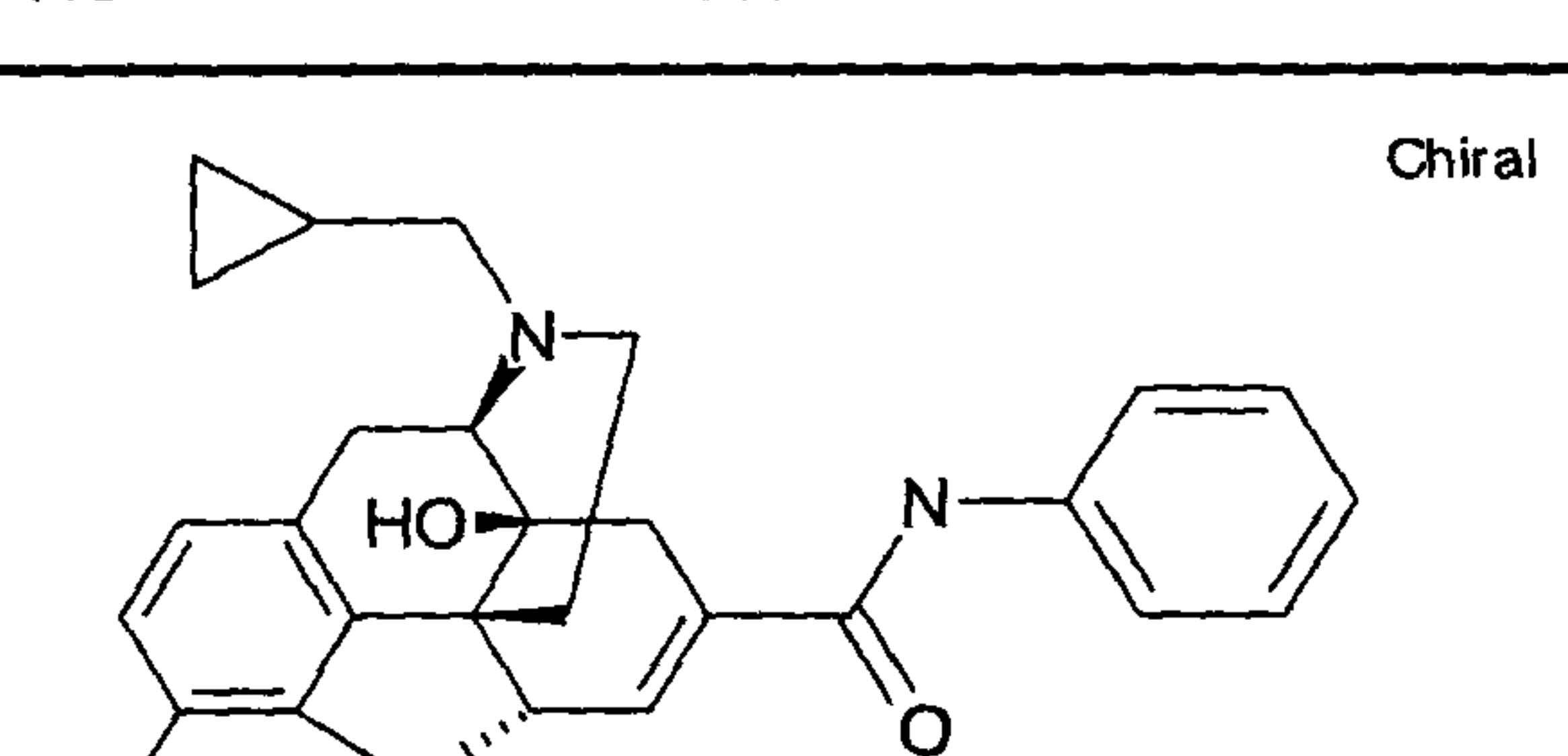
[0077]

[Table 32]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-118	 Chiral	m/z 493 [M+H] ⁺ 1.06 min	
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	

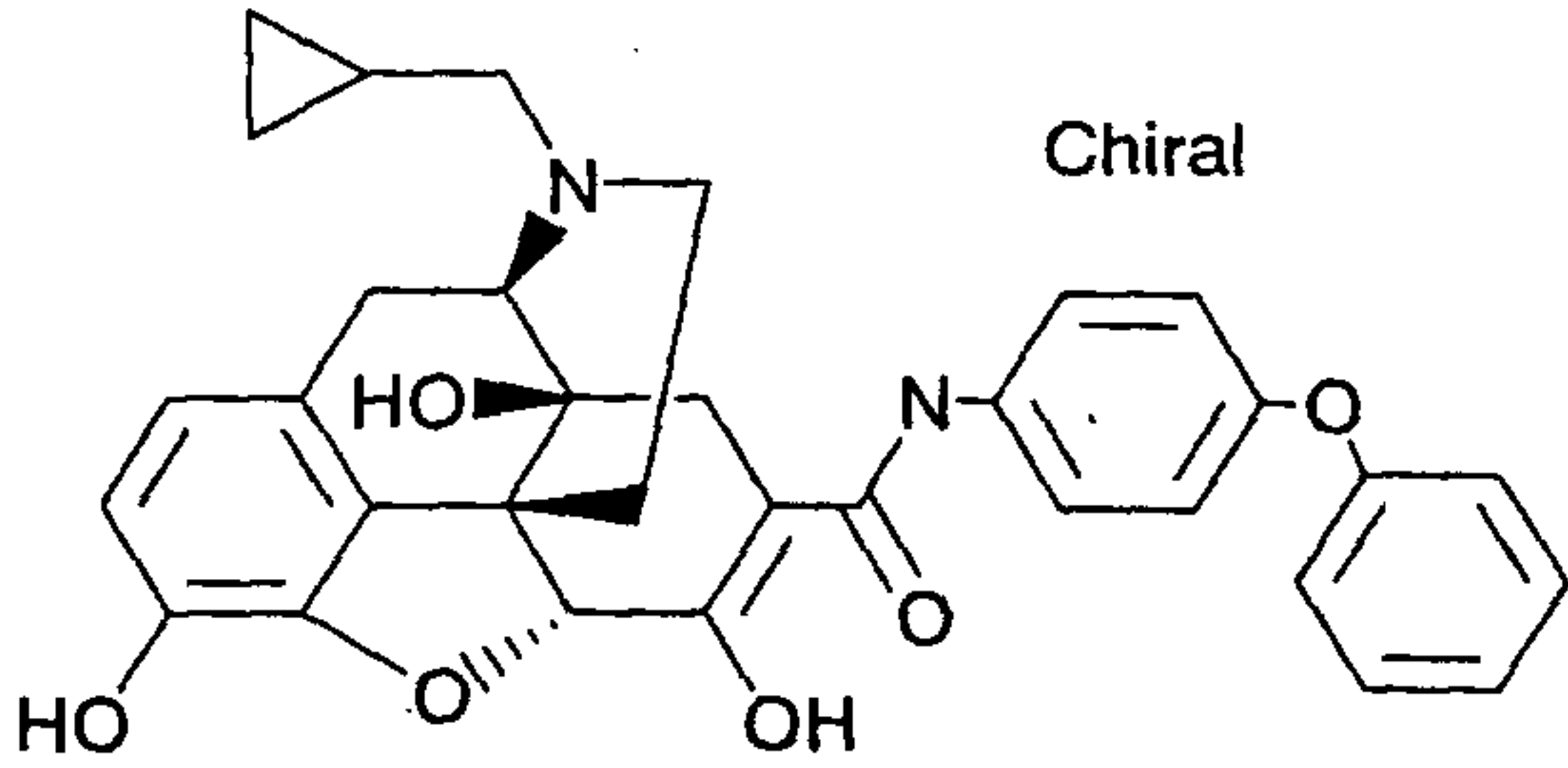
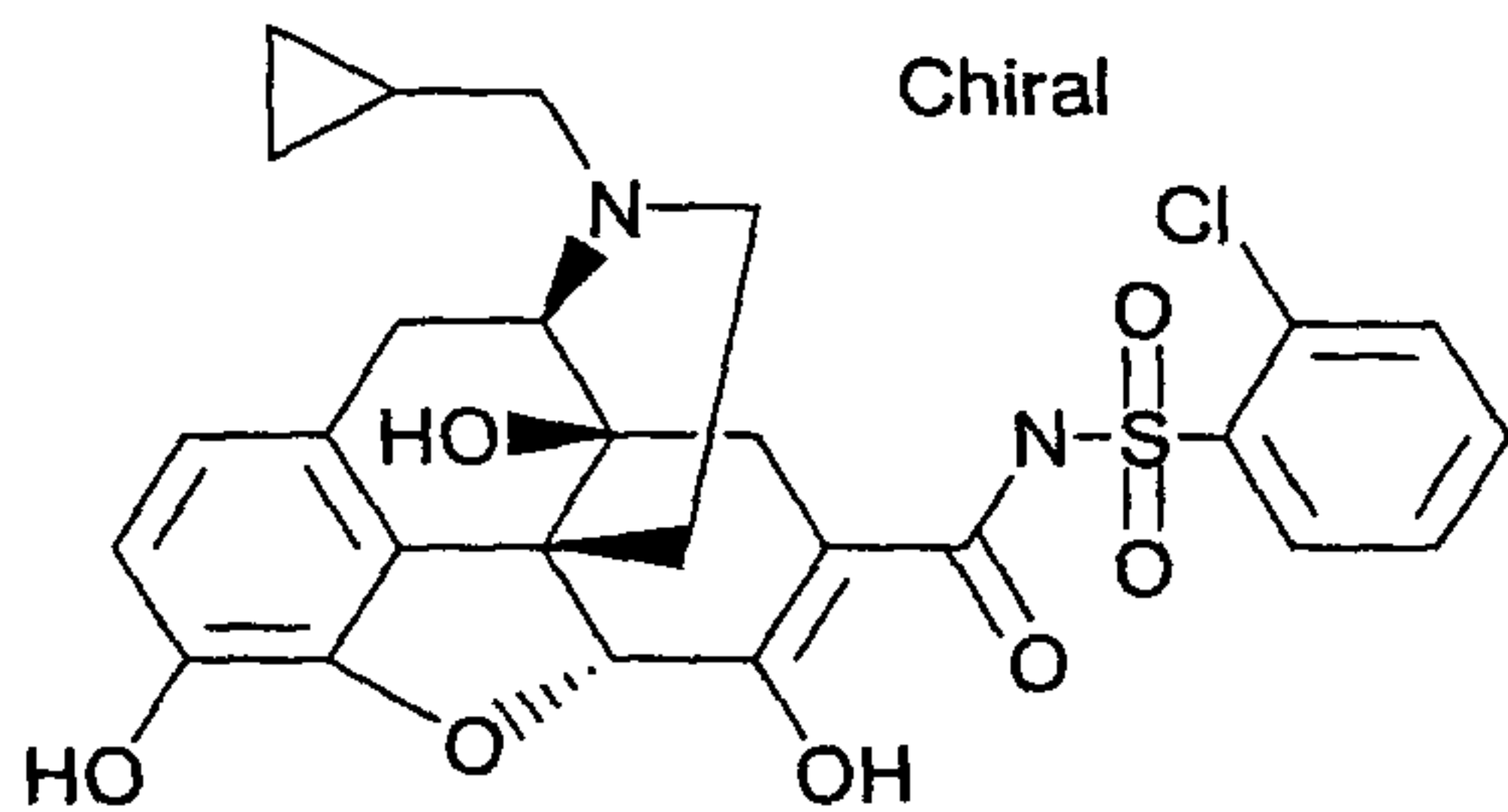
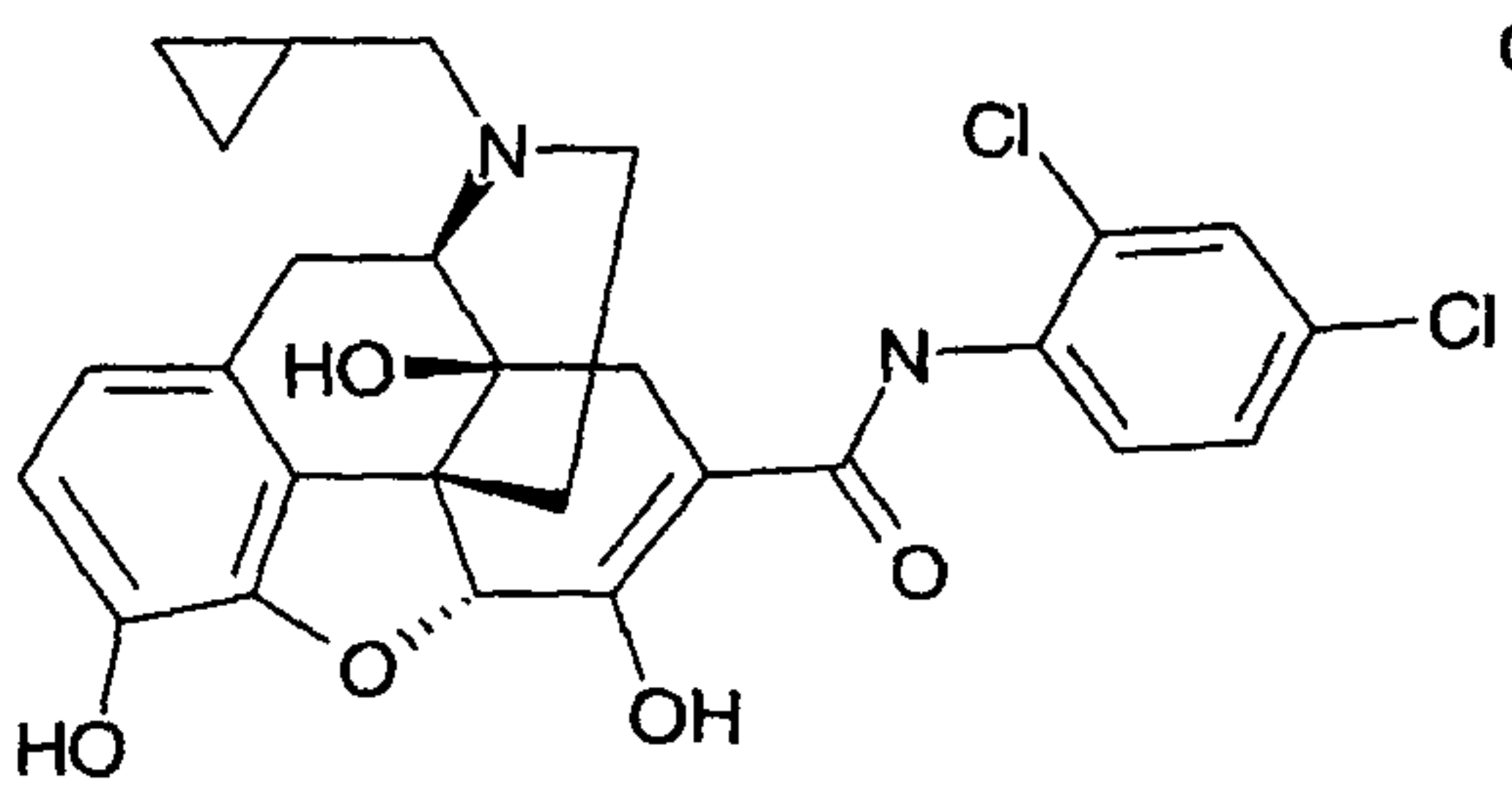
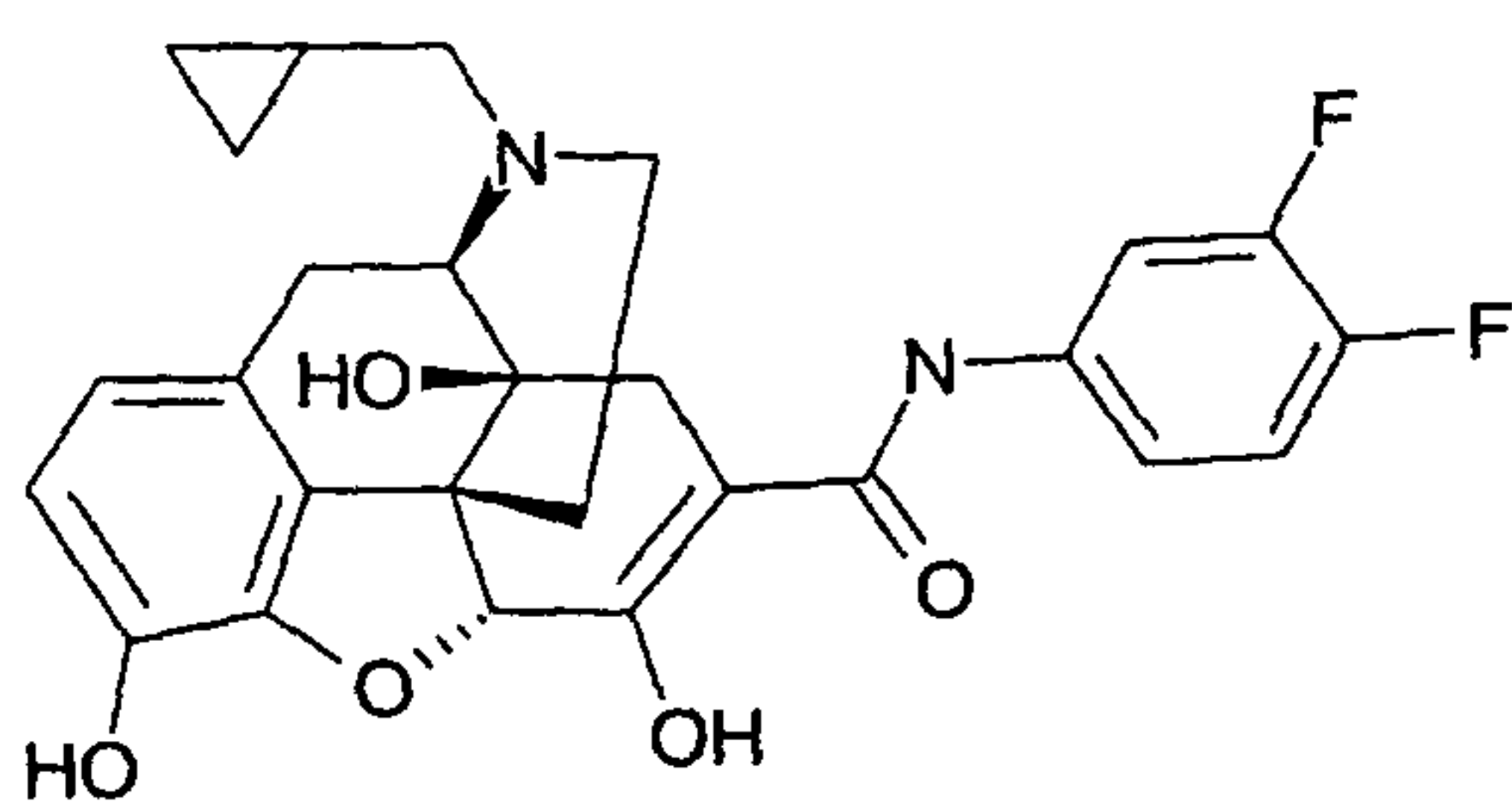
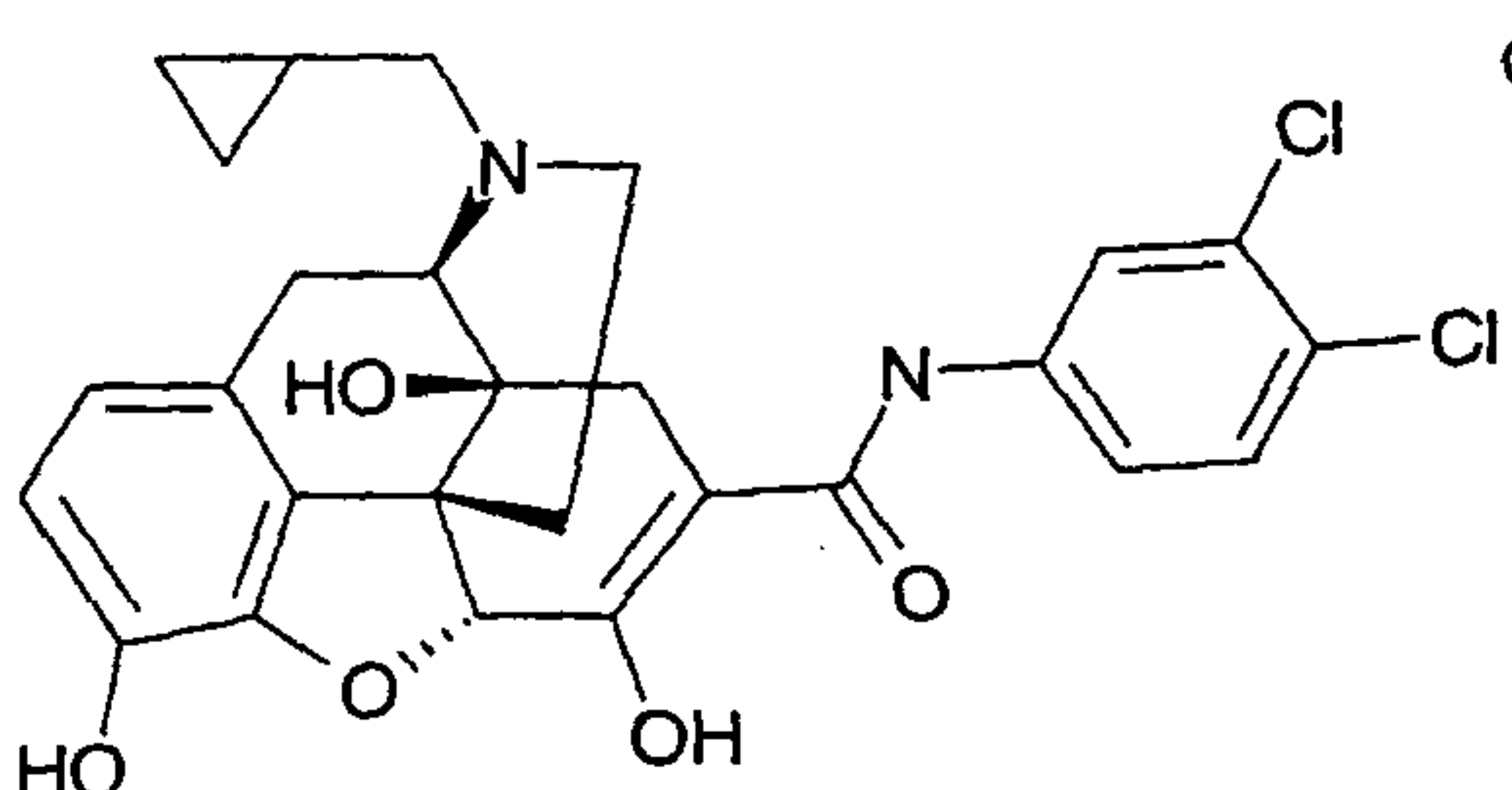
[0078]

[Table 33]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-123	Chiral 	m/z 555 [M+H] ⁺ 0.56 min	
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 		(CDCl ₃ +CD ₃ OD) δ : 0.10–0.21 (m, 2H), 0.48–0.63 (m, 2H), 0.78–0.94 (m, 1H), 1.67 (d, J = 9.6 Hz, 1H), 2.10–2.50 (m, 6H), 2.57–2.80 (m, 2H), 3.06 (d, J = 18.6 Hz, 1H), 3.27 (brs, 1H), 5.10 (d, J = 1.7 Hz, 1H), 6.31–6.40 (m, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 7.02–7.12 (m, 1H), 7.22–7.34 (m, 2H), 7.44–7.56 (m, 2H).

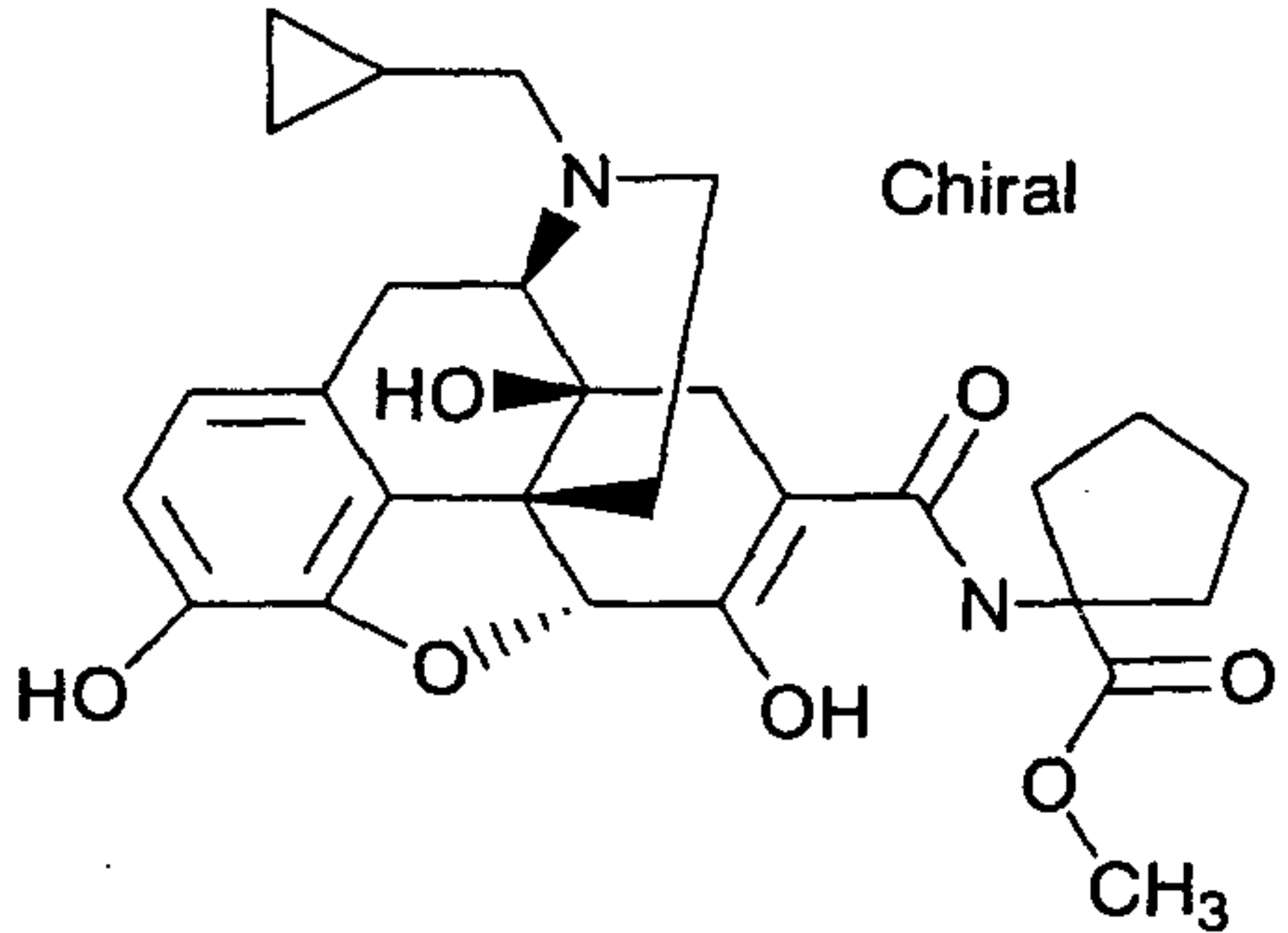
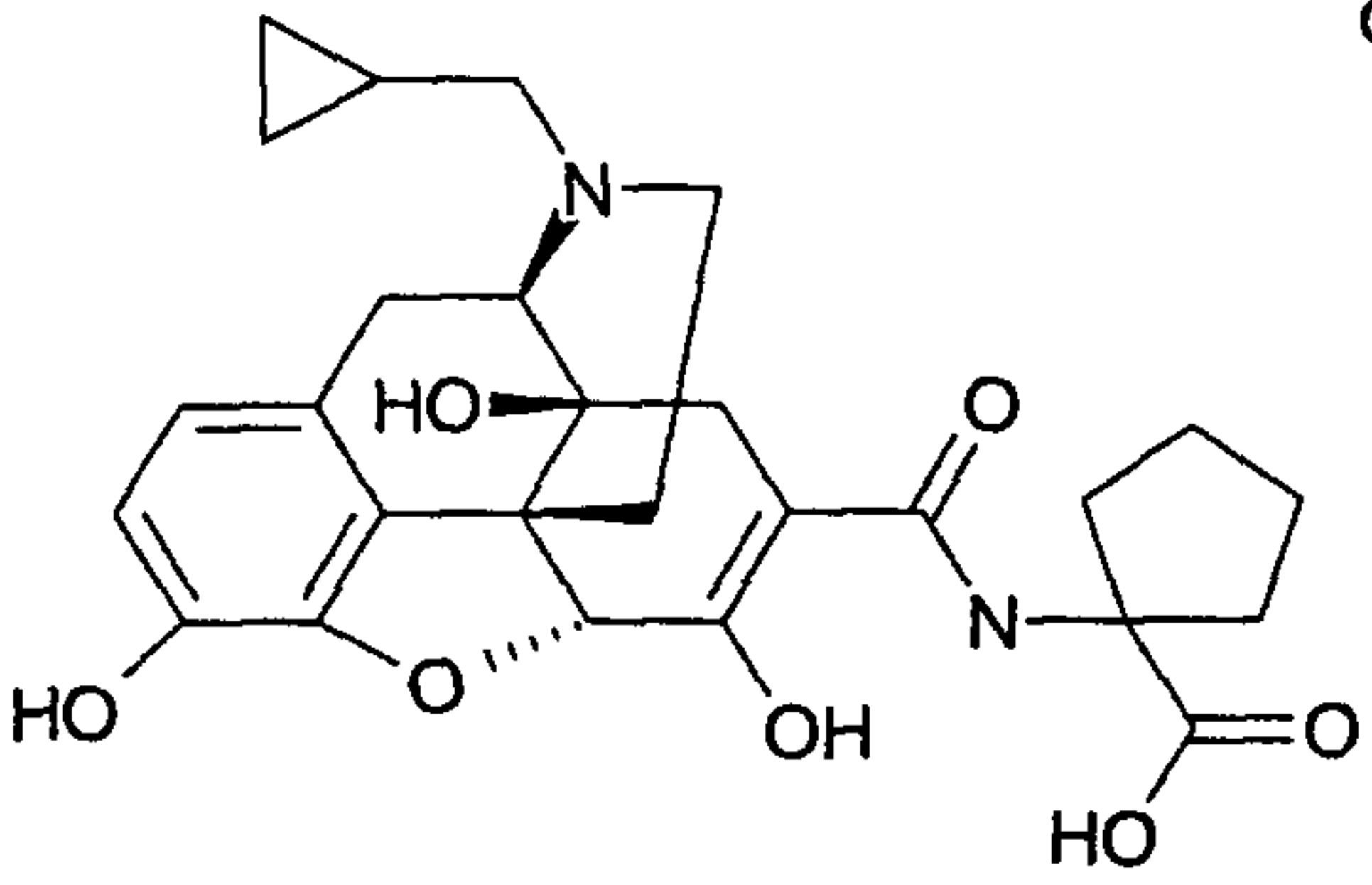
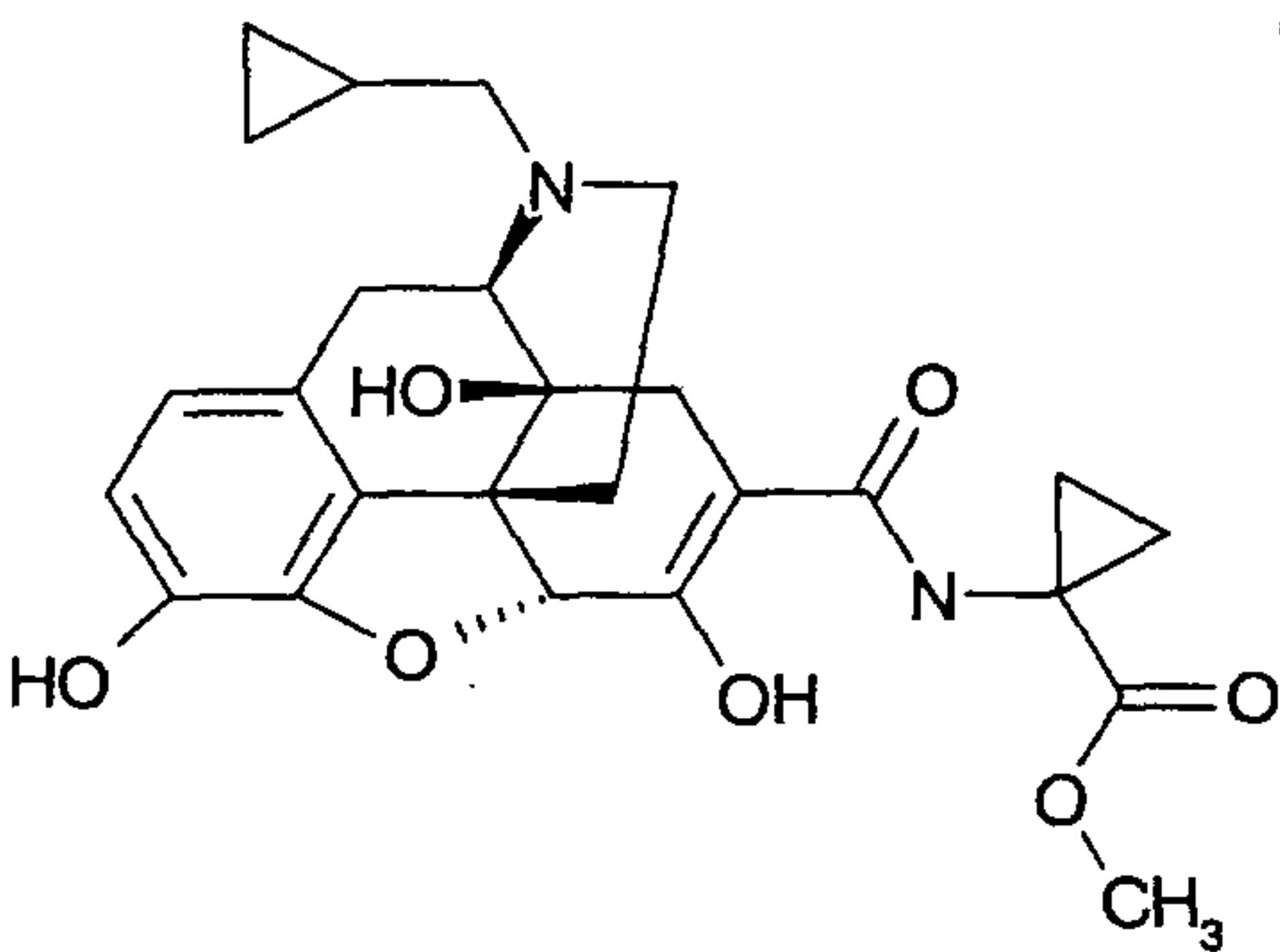
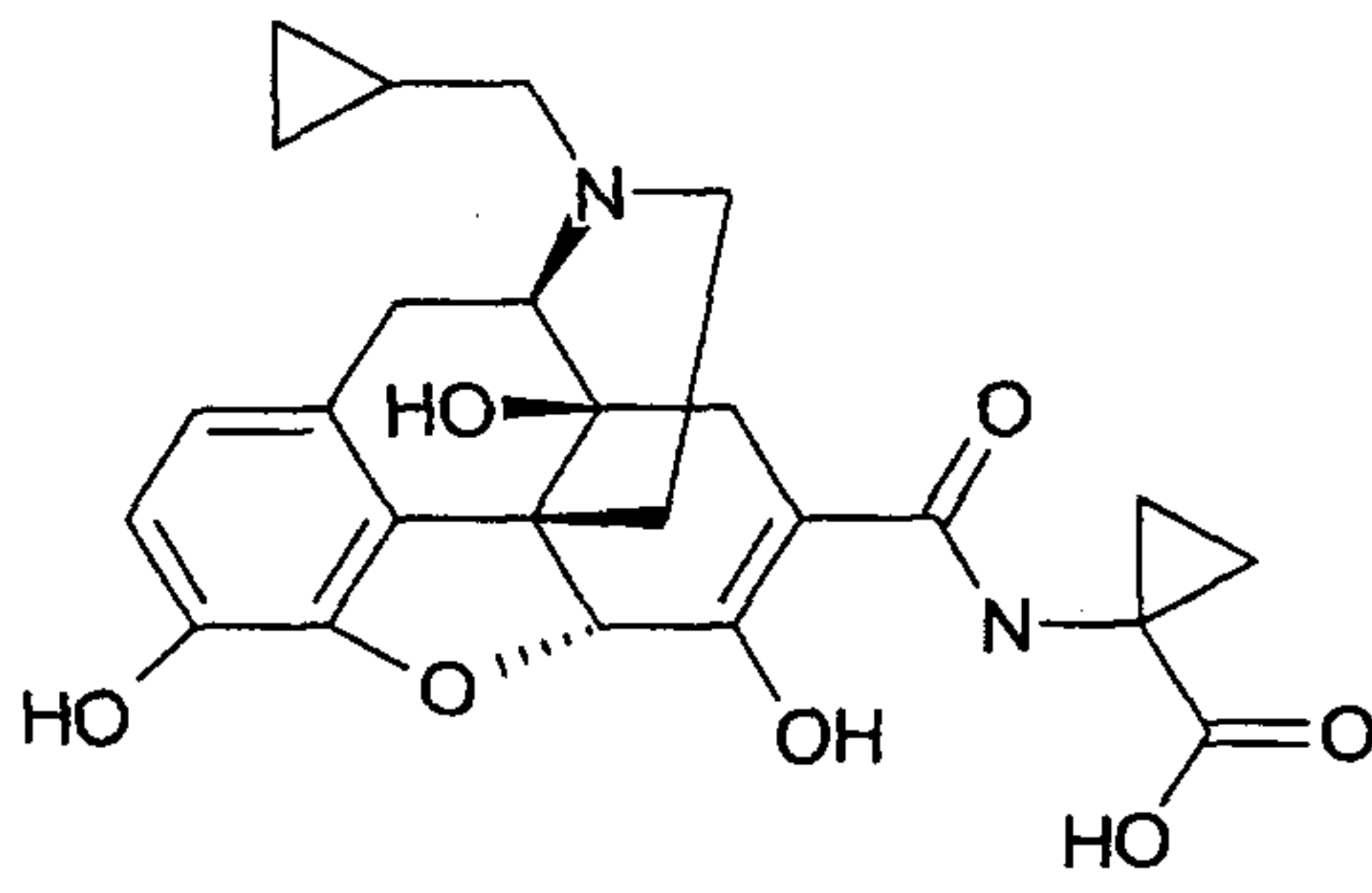
[0079]

[Table 34]

Compound No.	Chemical structure	LC/MS [†]	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-128	 Chiral	m/z 553 [M+H] ⁺ 0.94 min	
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	

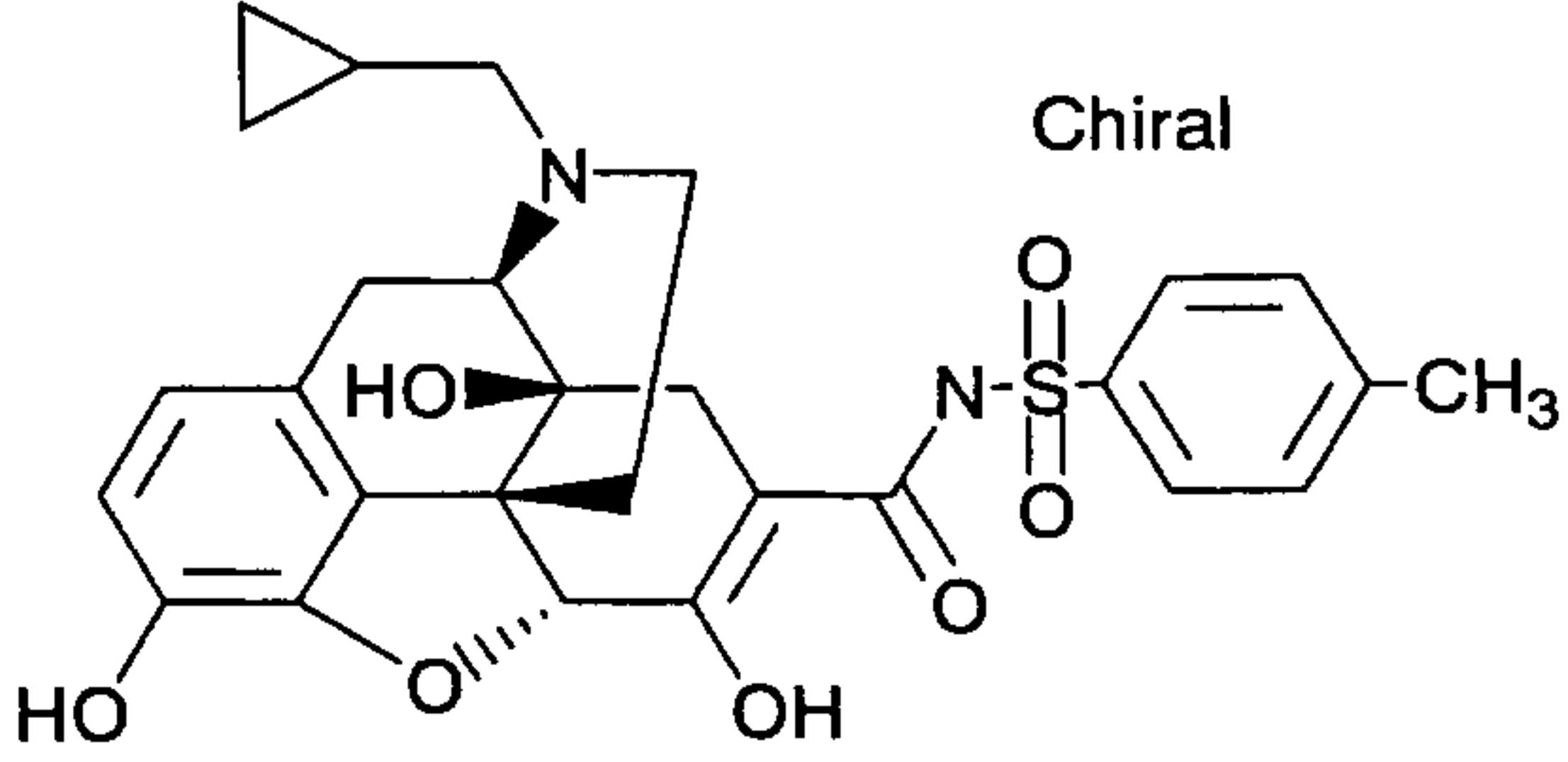
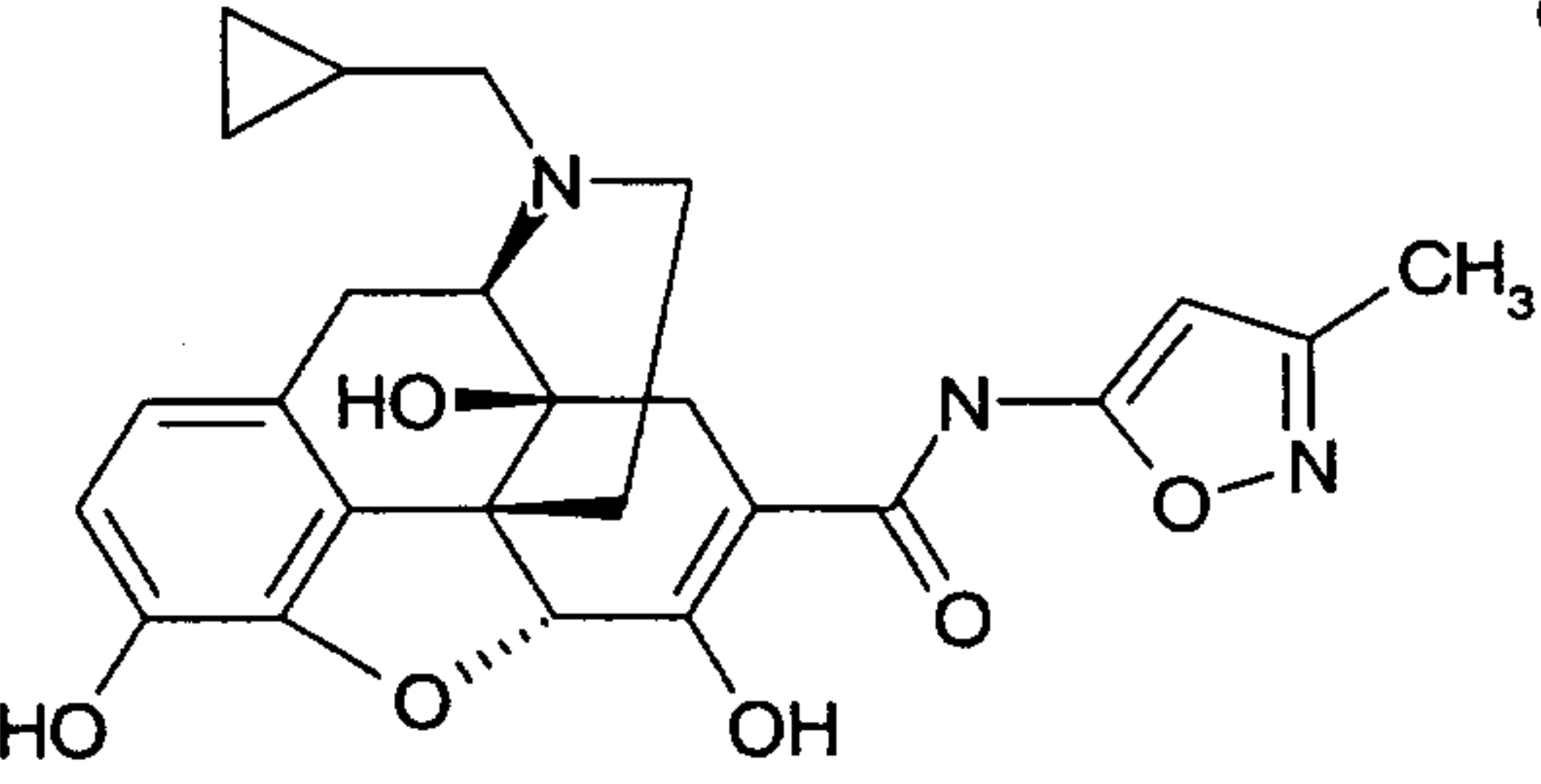
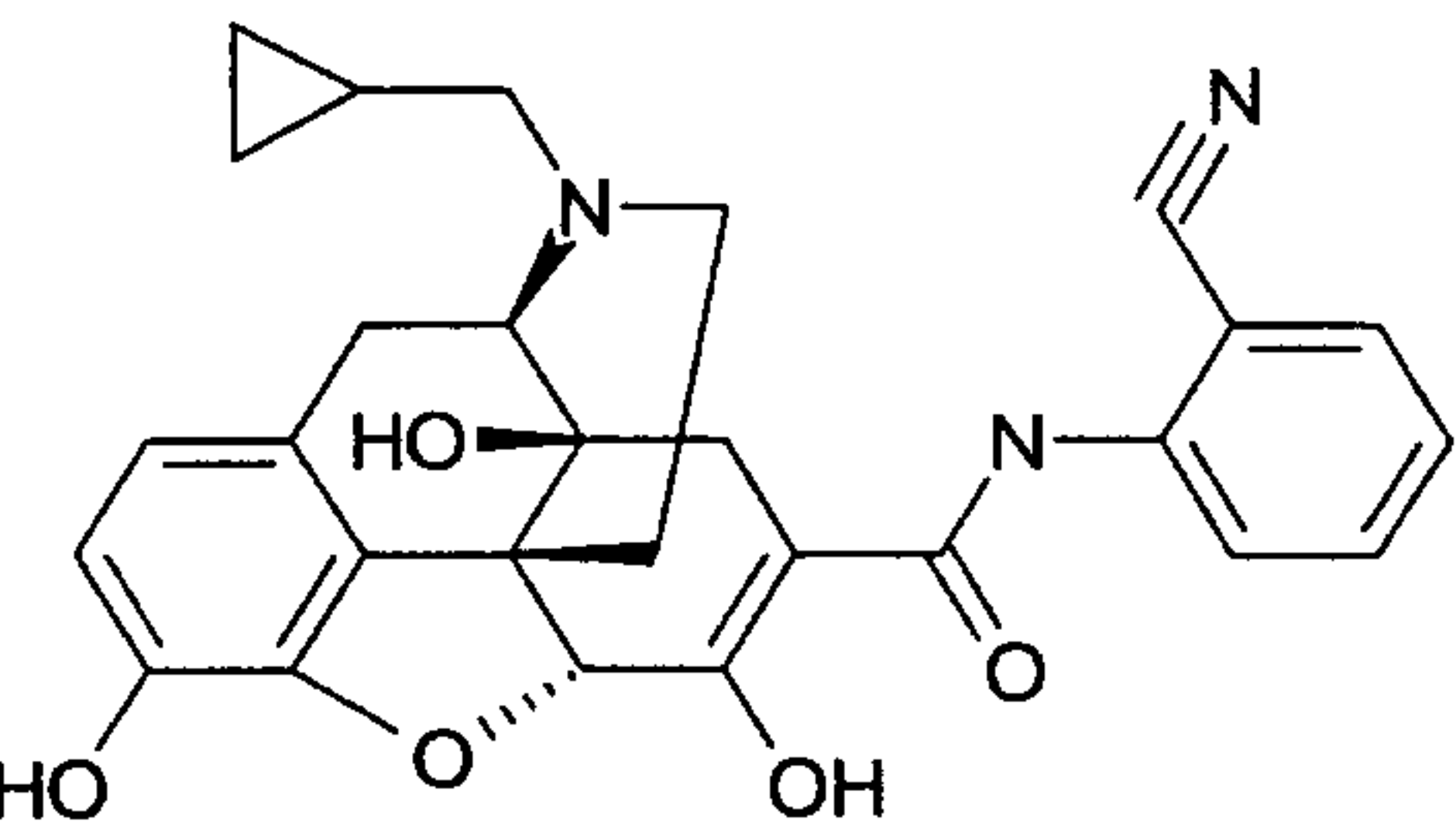
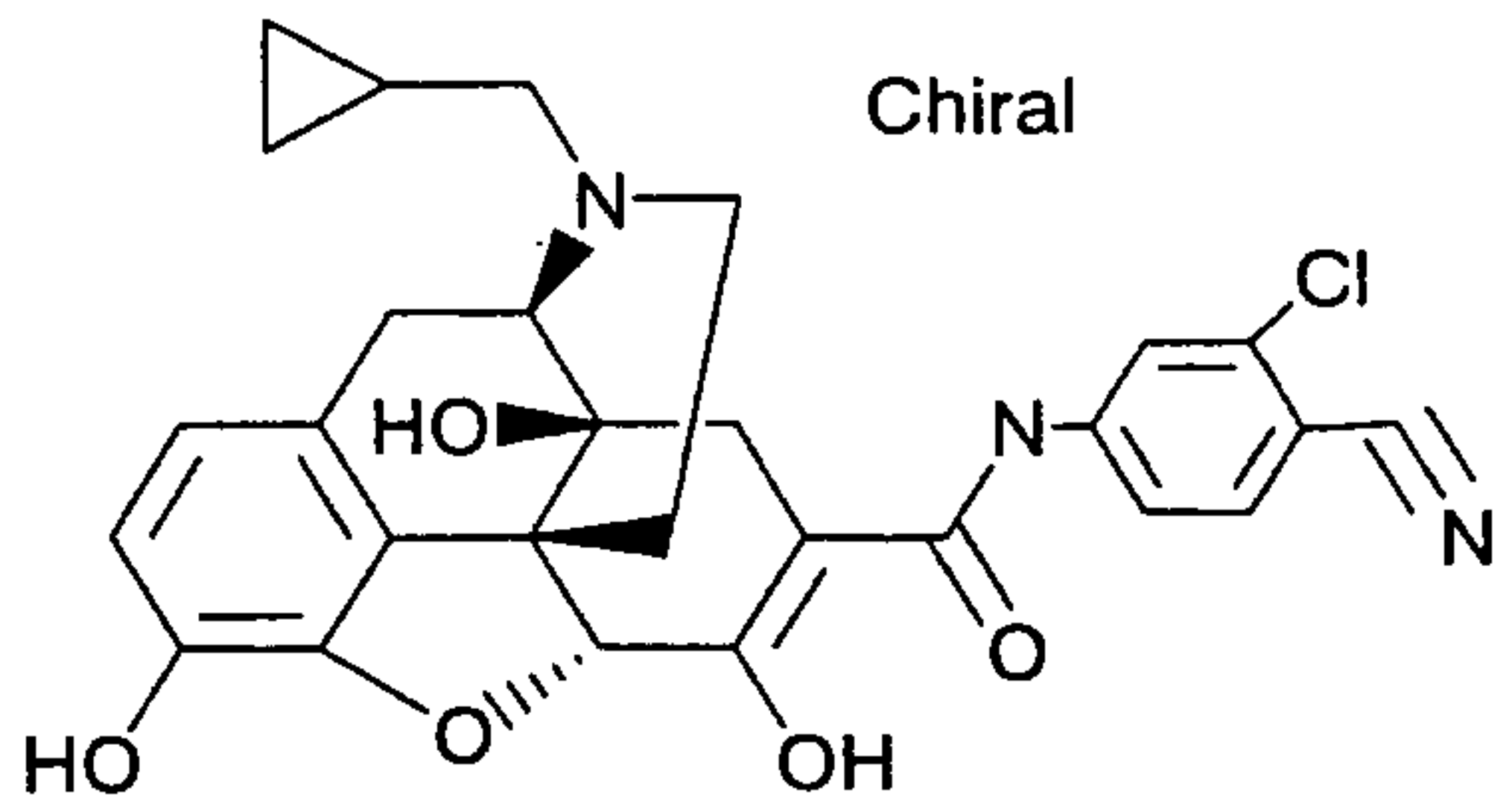
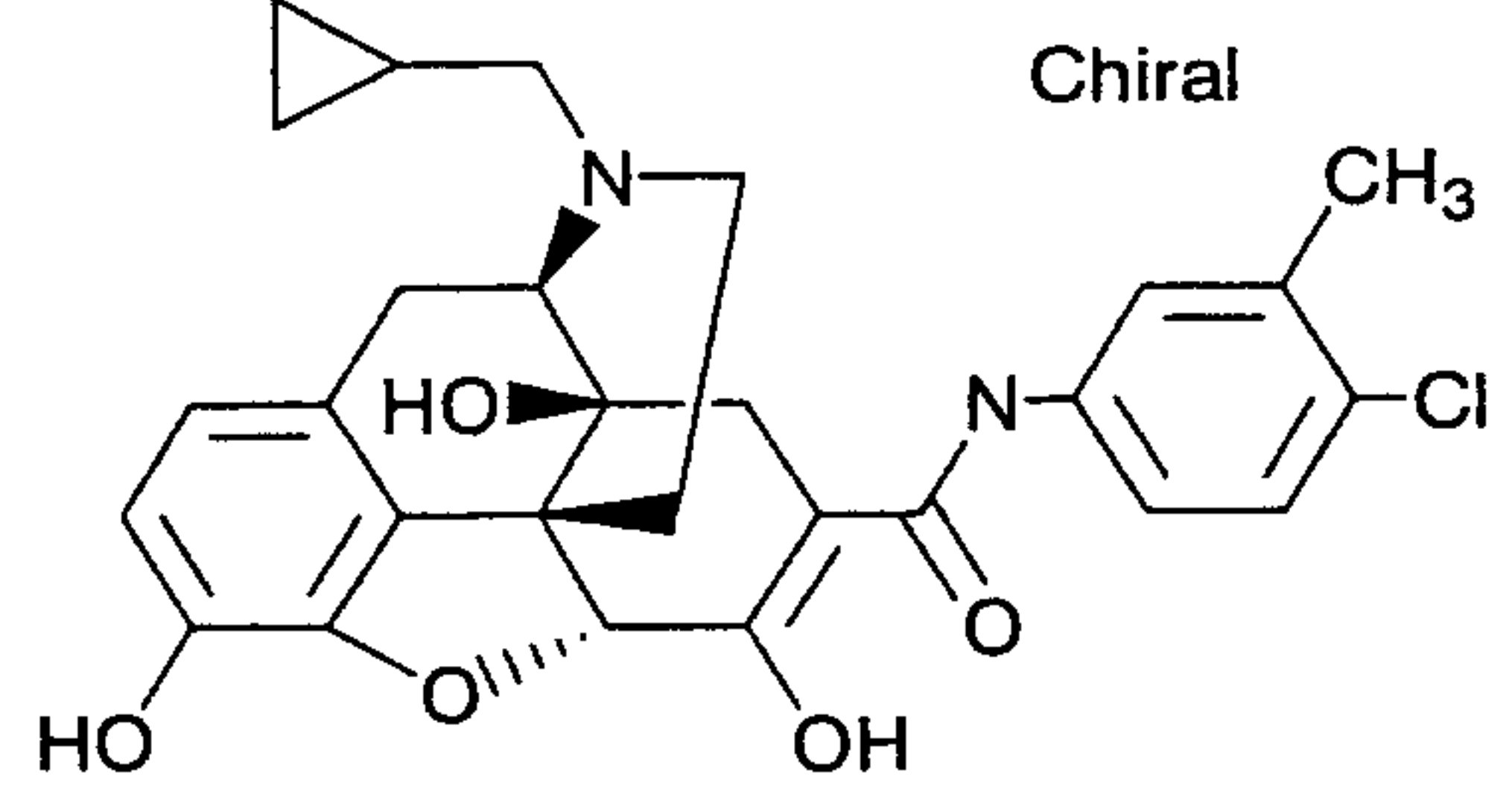
[0080]

[Table 35]

Compound No.	Chemical structure	LC/MS*1	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-133	 Chiral	m/z 511 [M+H] ⁺ 0.97 min	0.12–0.16 (m, 2H), 0.46–0.52 (m, 2H), 0.86 (m, 1H), 1.42 (d, J = 10.5 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06–2.65 (m, 15H), 3.05 (d, J = 18.3 Hz, 1H), 3.26 (d, J = 5.9 Hz, 1H), 3.55 (s, 3H), 4.73 (s 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.76 (brs, 1H), 9.31 (brs, 1H), 13.8 (brs, 1H)
I-134	 Chiral	m/z 498 [M+H] ⁺ 0.96 min	0.13–0.16 (m, 2H), 0.48–0.54 (m, 2H), 0.87 (m, 1H), 1.43 (d, J = 10.5 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06–2.67 (m, 15H), 3.06 (d, J = 18.6 Hz, 1H), 3.27 (d, J = 6.0 Hz, 1H), 4.73 (s 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.72 (brs, 1H), 9.20 (brs, 1H), 14.1 (brs, 1H)
I-135	 Chiral	m/z 483 [M+H] ⁺ 0.87 min	0.12–0.14 (m, 2H), 0.46–0.51 (m, 2H), 0.85 (m, 1H), 1.06–1.09 (m, 2H), 1.35–1.36 (m, 2H), 1.41 (d, J = 11.7 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.17–2.61 (m, 7H), 3.03 (d, J = 18.3 Hz, 1H), 3.17 (d, J = 6.0 Hz, 1H), 3.56 (s, 3H), 4.74 (s, 1H), 4.77 (brs, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 9.17 (brs, 1H), 14.1 (brs, 1H)
I-136	 Chiral	m/z 469 [M+H] ⁺ 0.89 min	0.12–0.16 (m, 2H), 0.43–0.51 (m, 2H), 0.85 (m, 1H), 1.06–1.12 (m, 2H), 1.35–1.36 (m, 2H), 1.42 (d, J = 11.7 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.06–2.63 (m, 7H), 3.02 (d, J = 18.3 Hz, 1H), 3.13 (d, J = 5.4 Hz, 1H), 4.76 (s 1H), 4.77 (brs, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 9.18 (brs, 1H), 14.1 (brs, 1H)

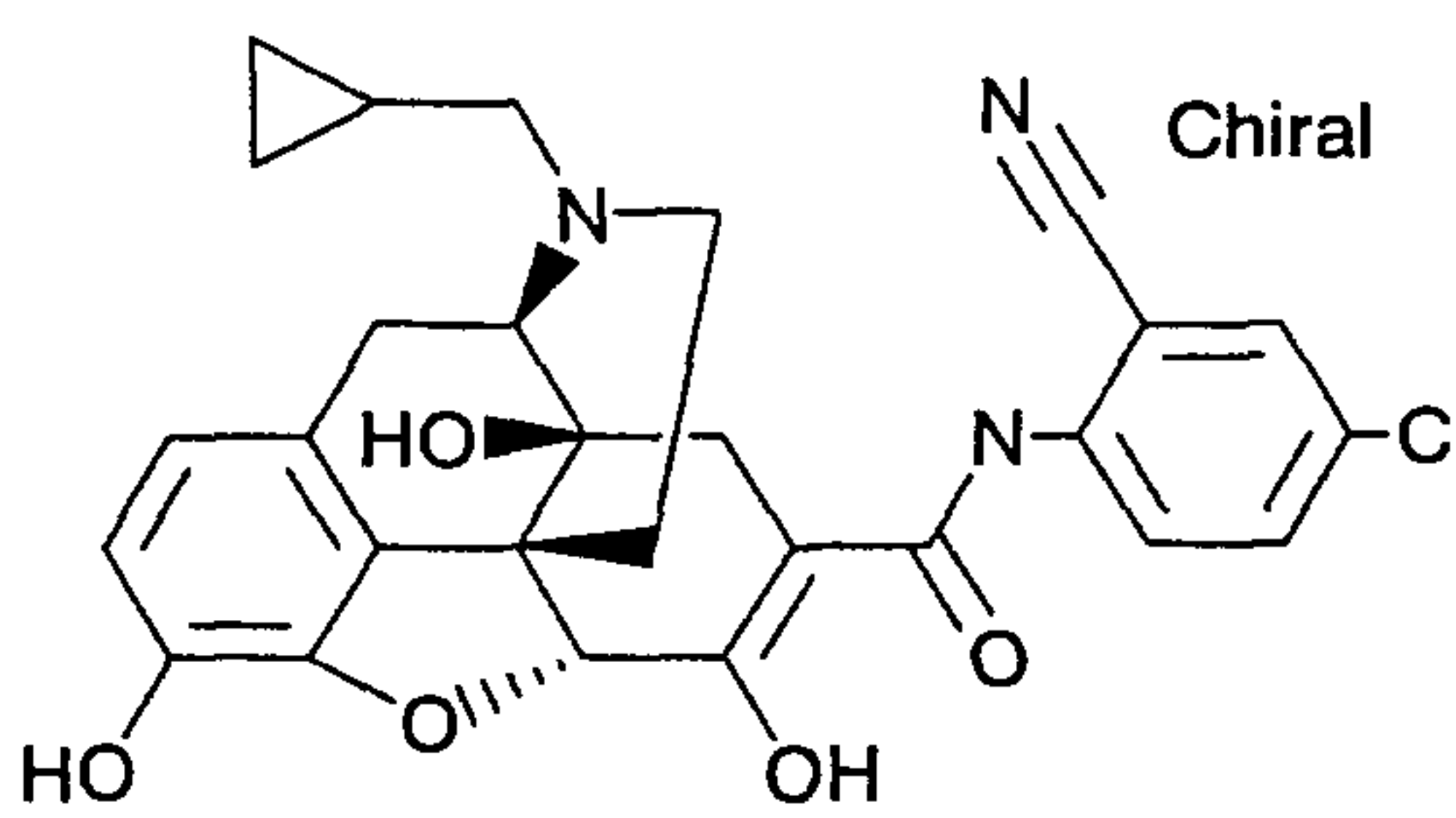
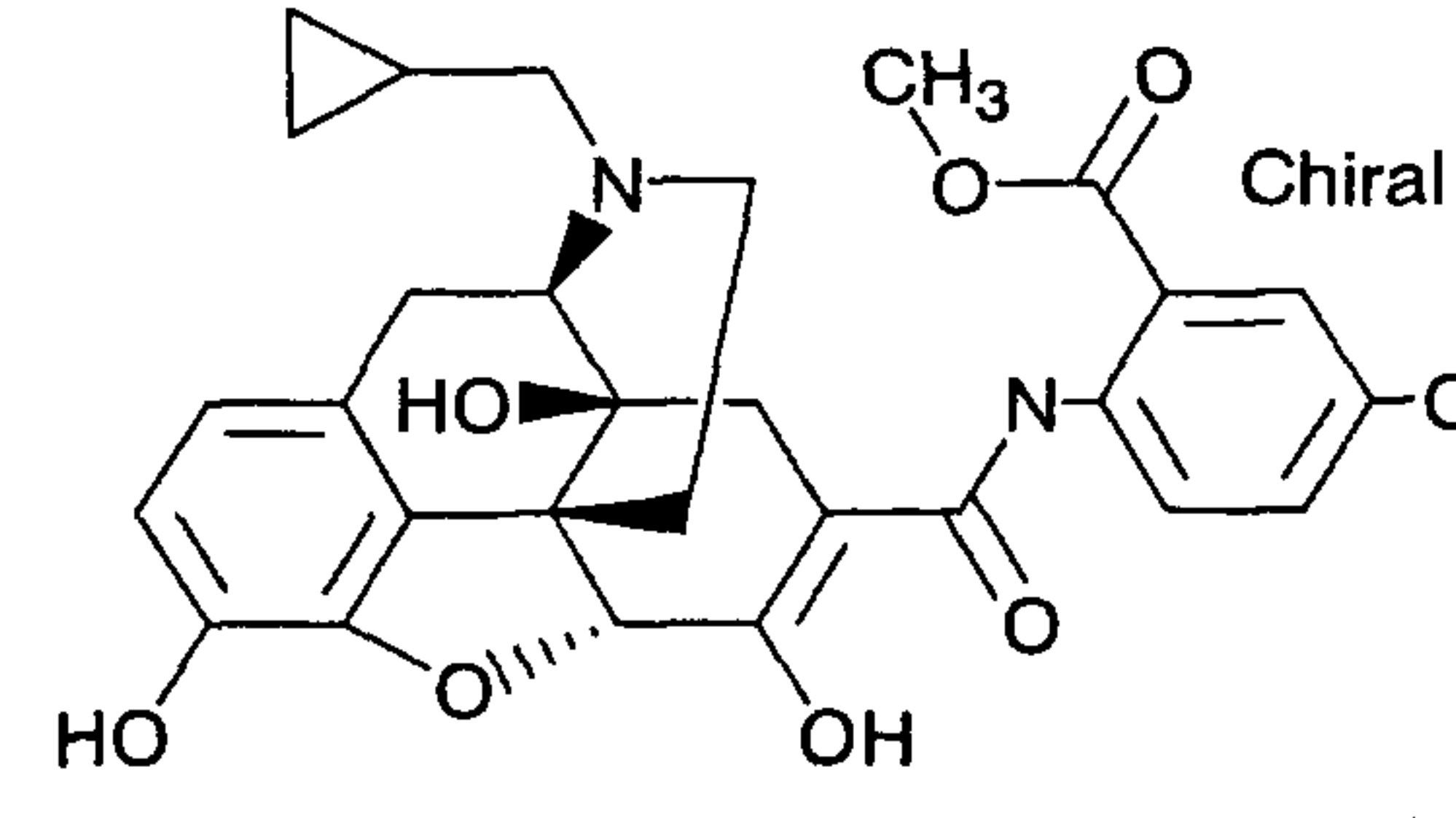
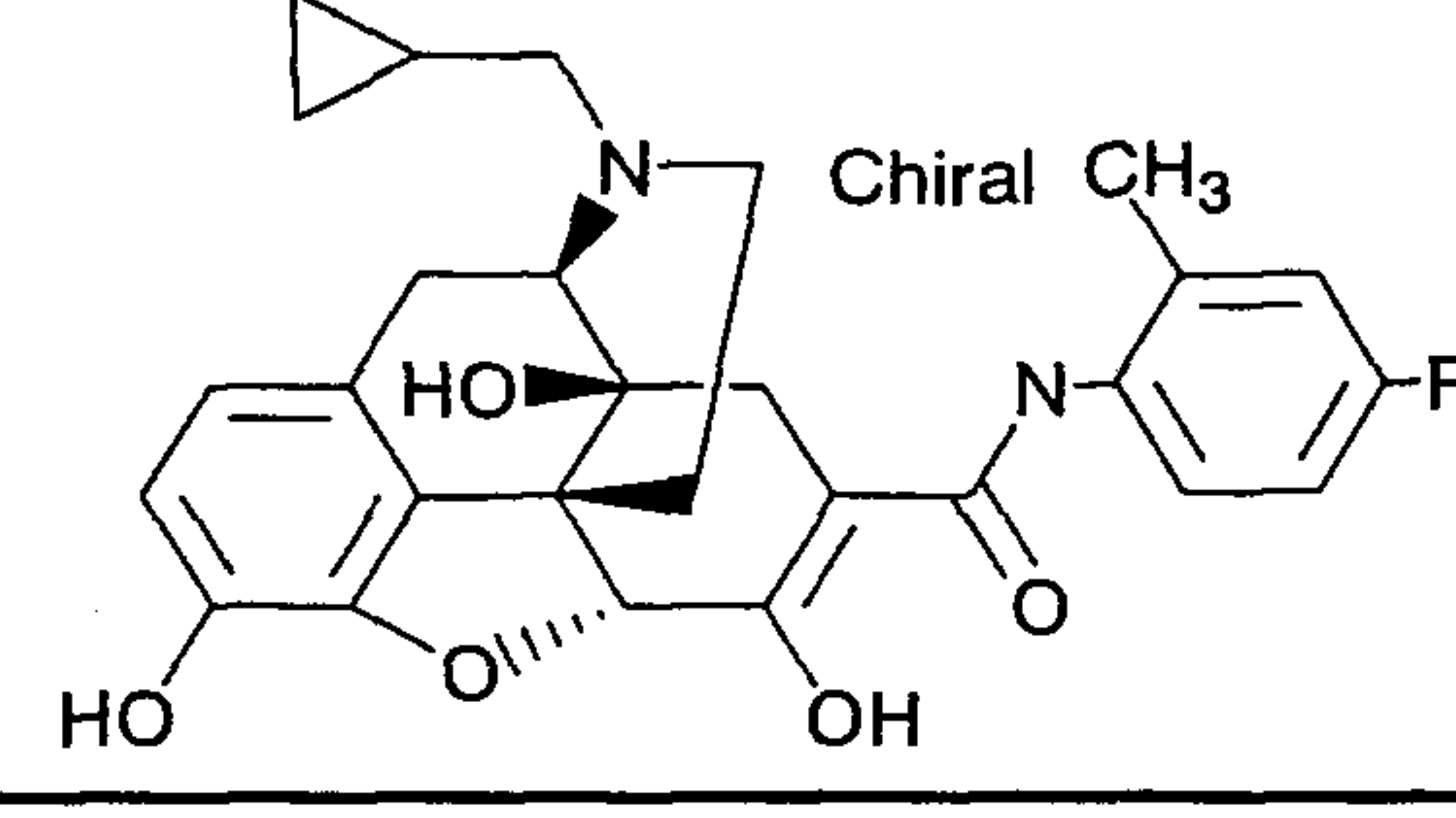
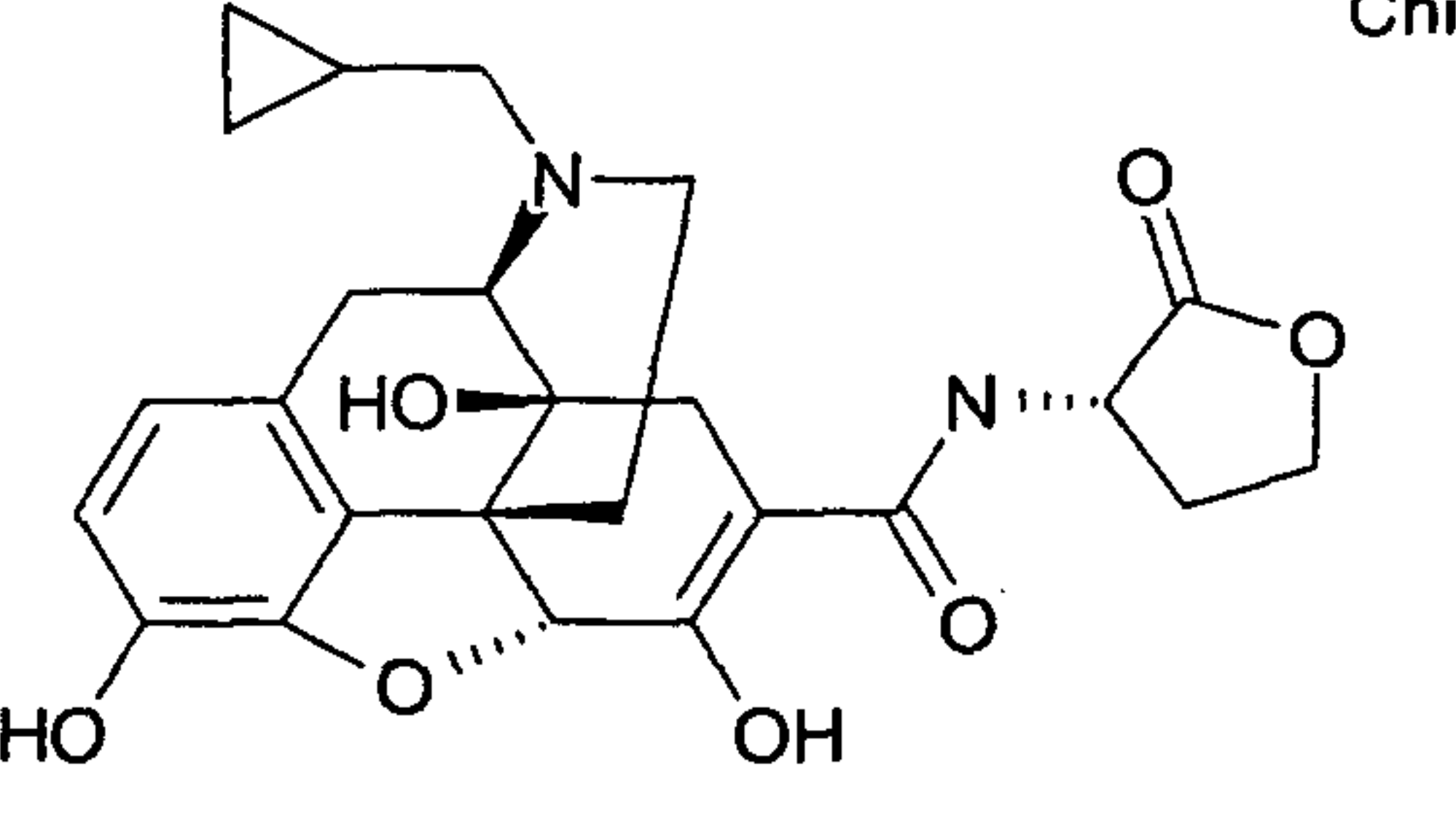
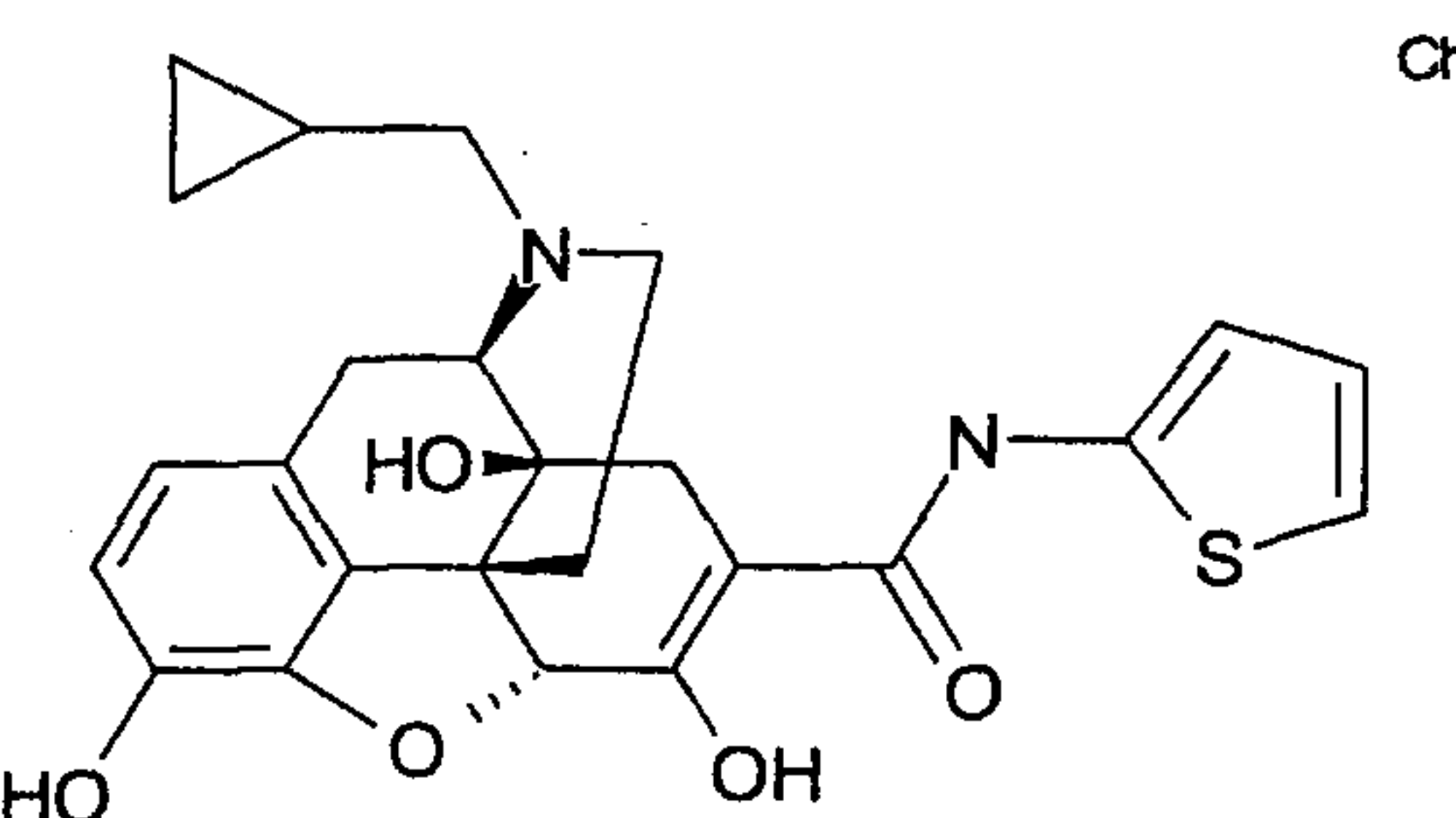
[0081]

[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	
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	

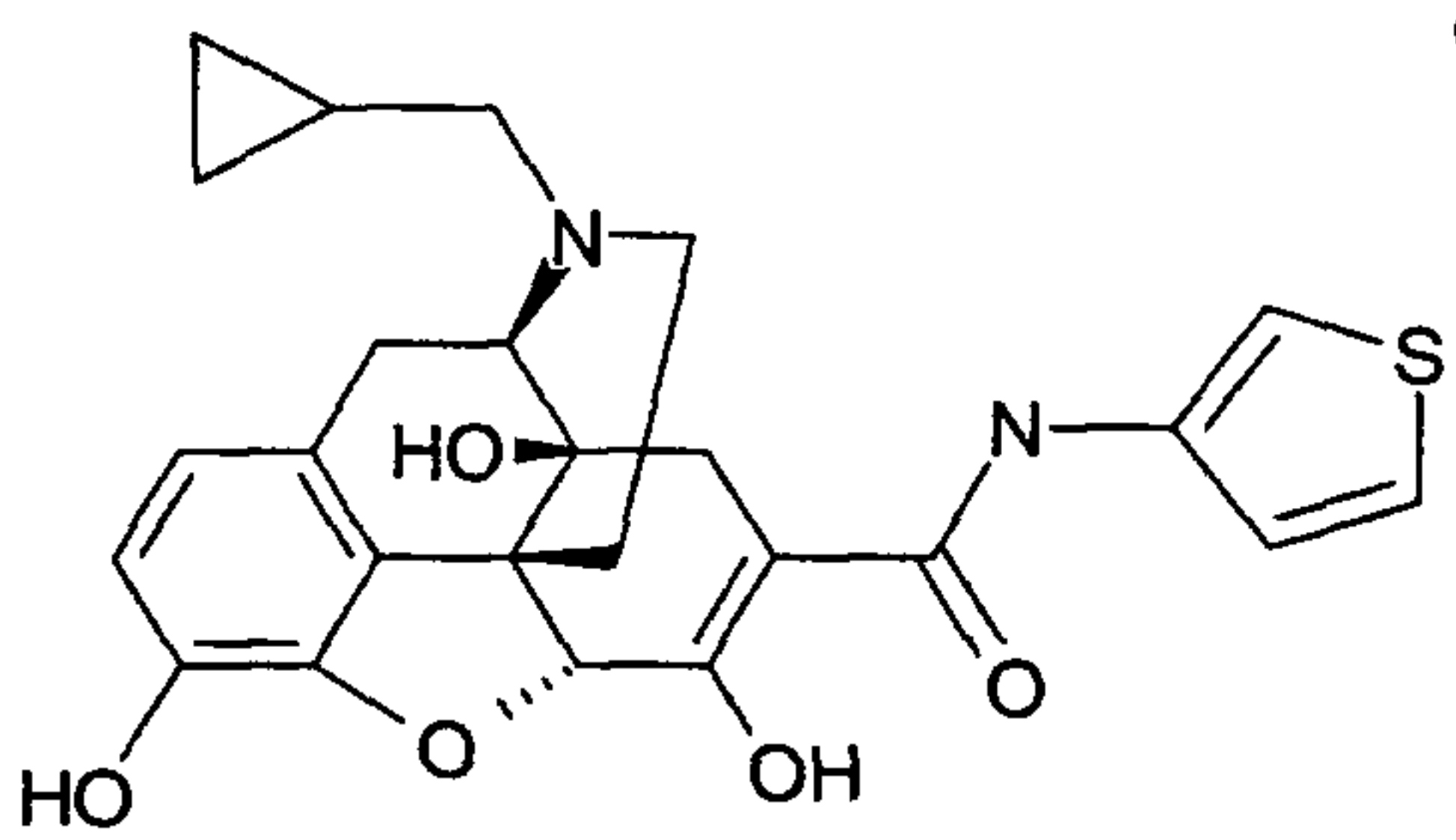
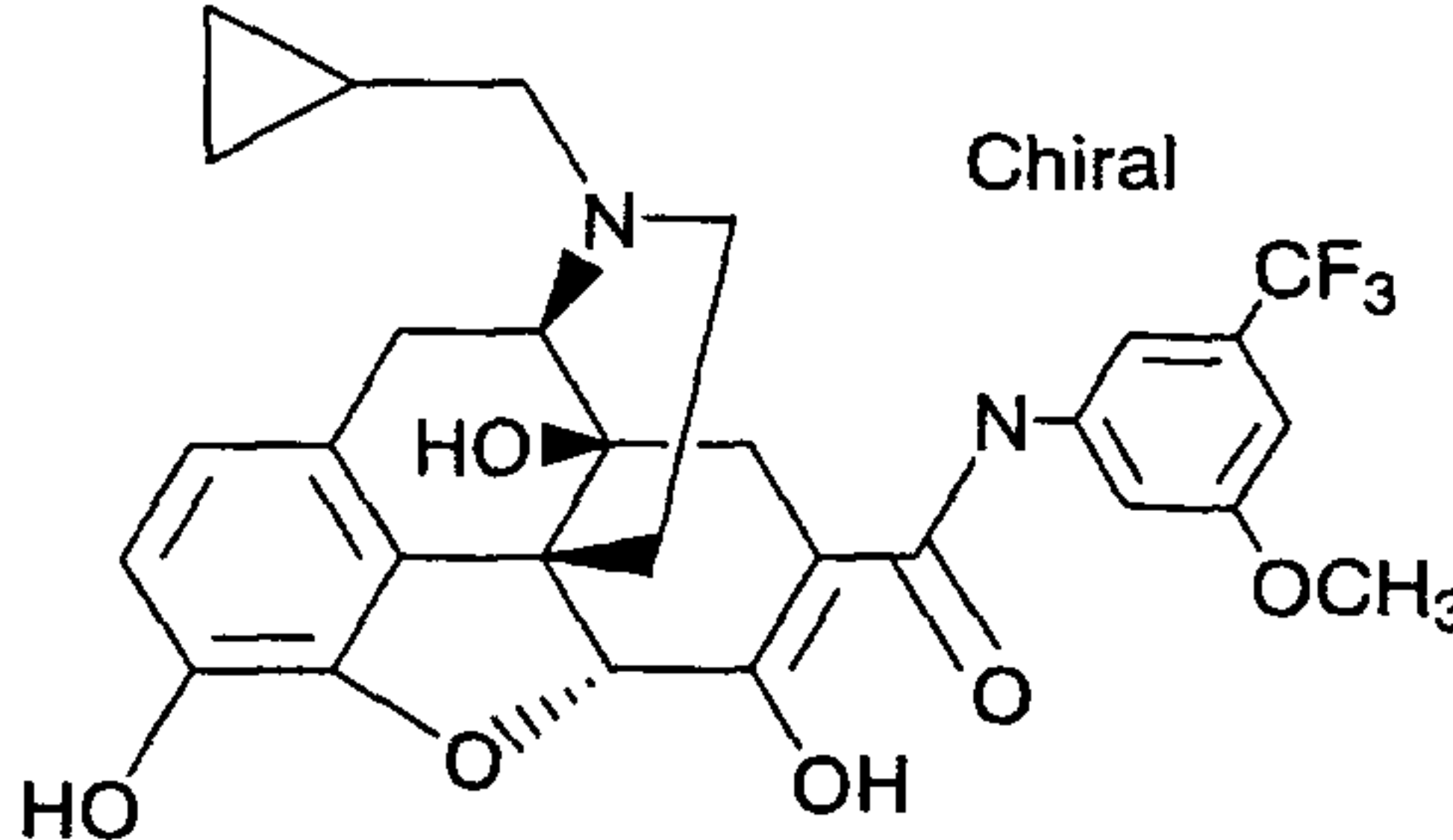
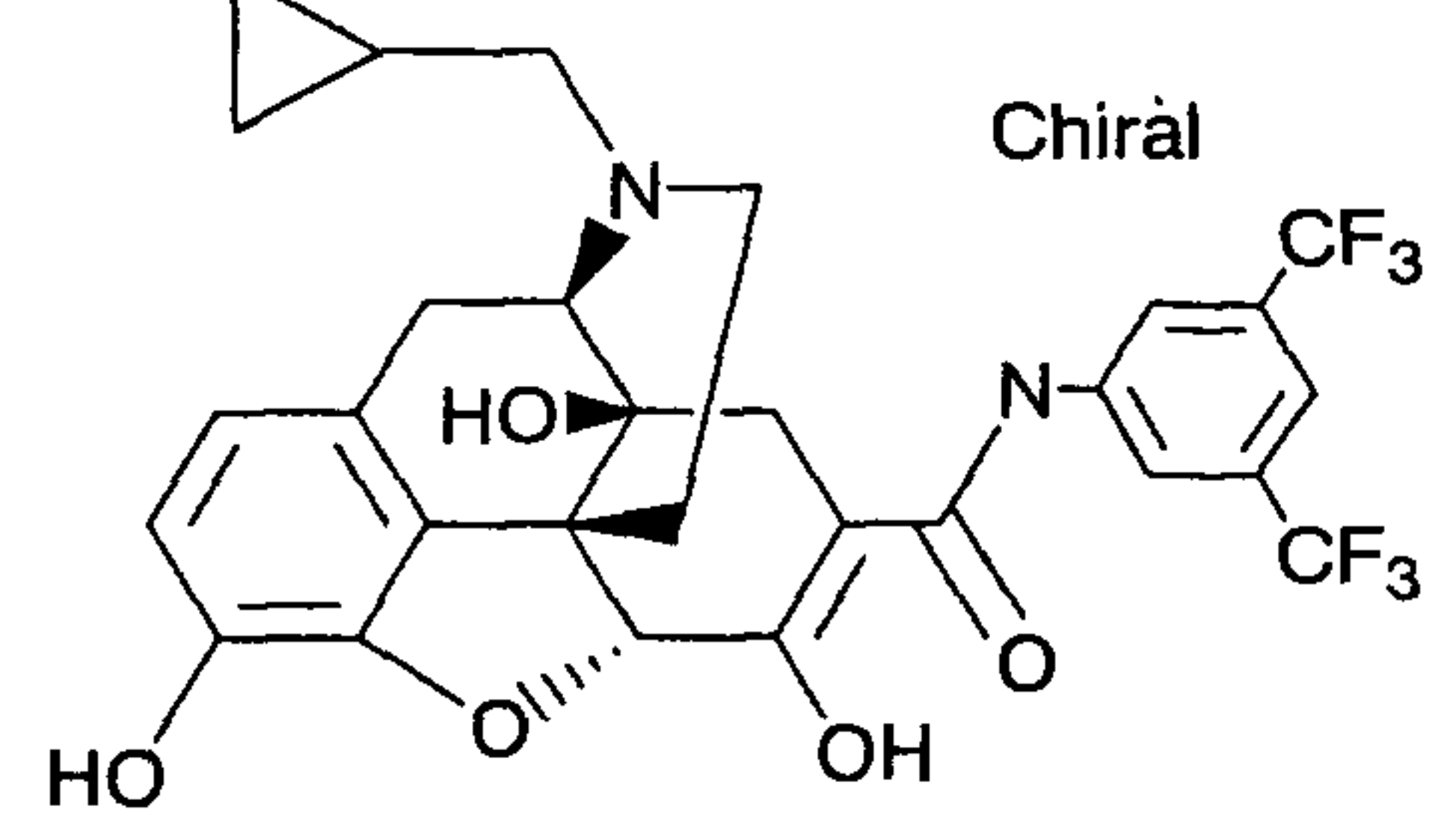
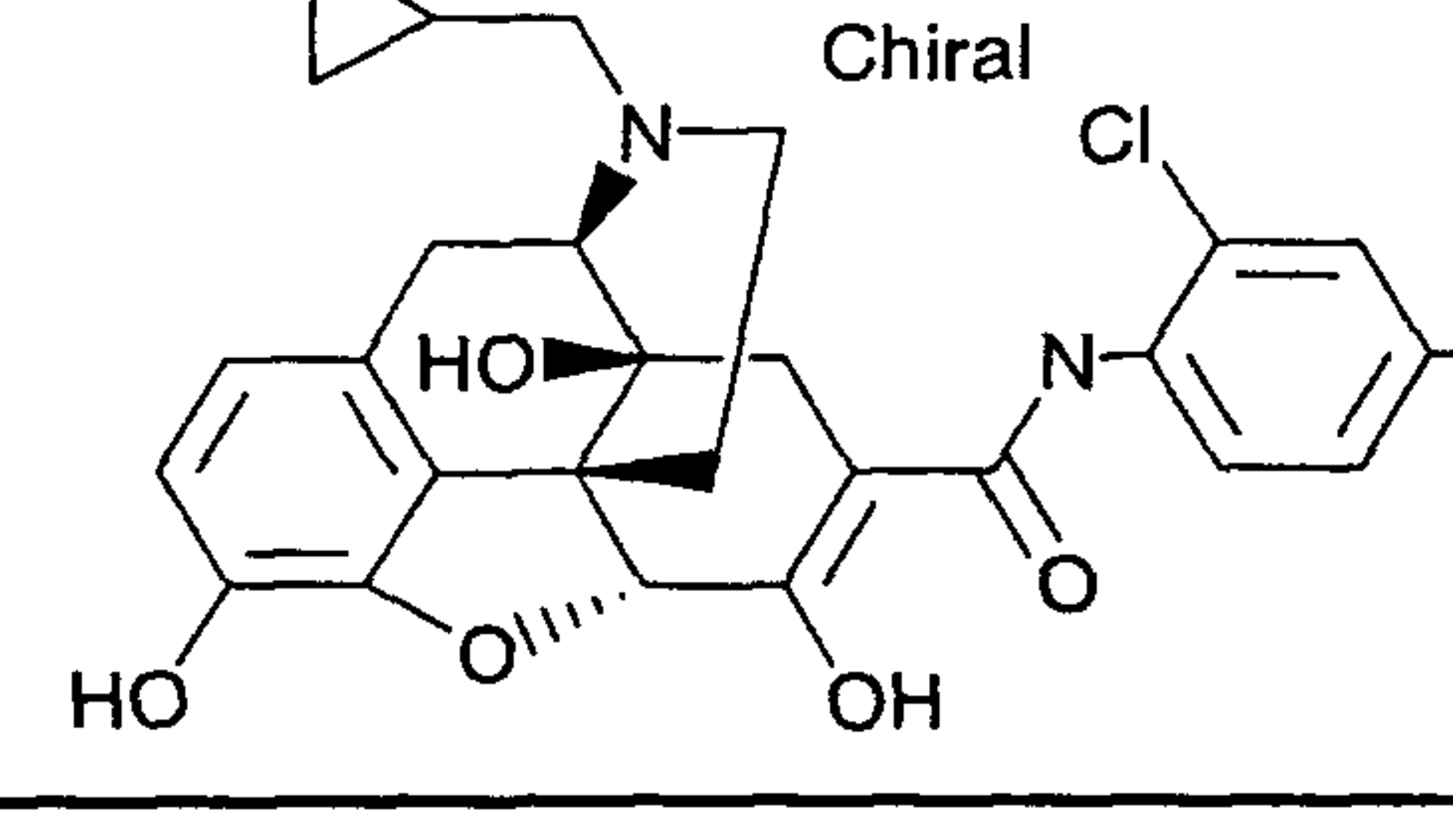
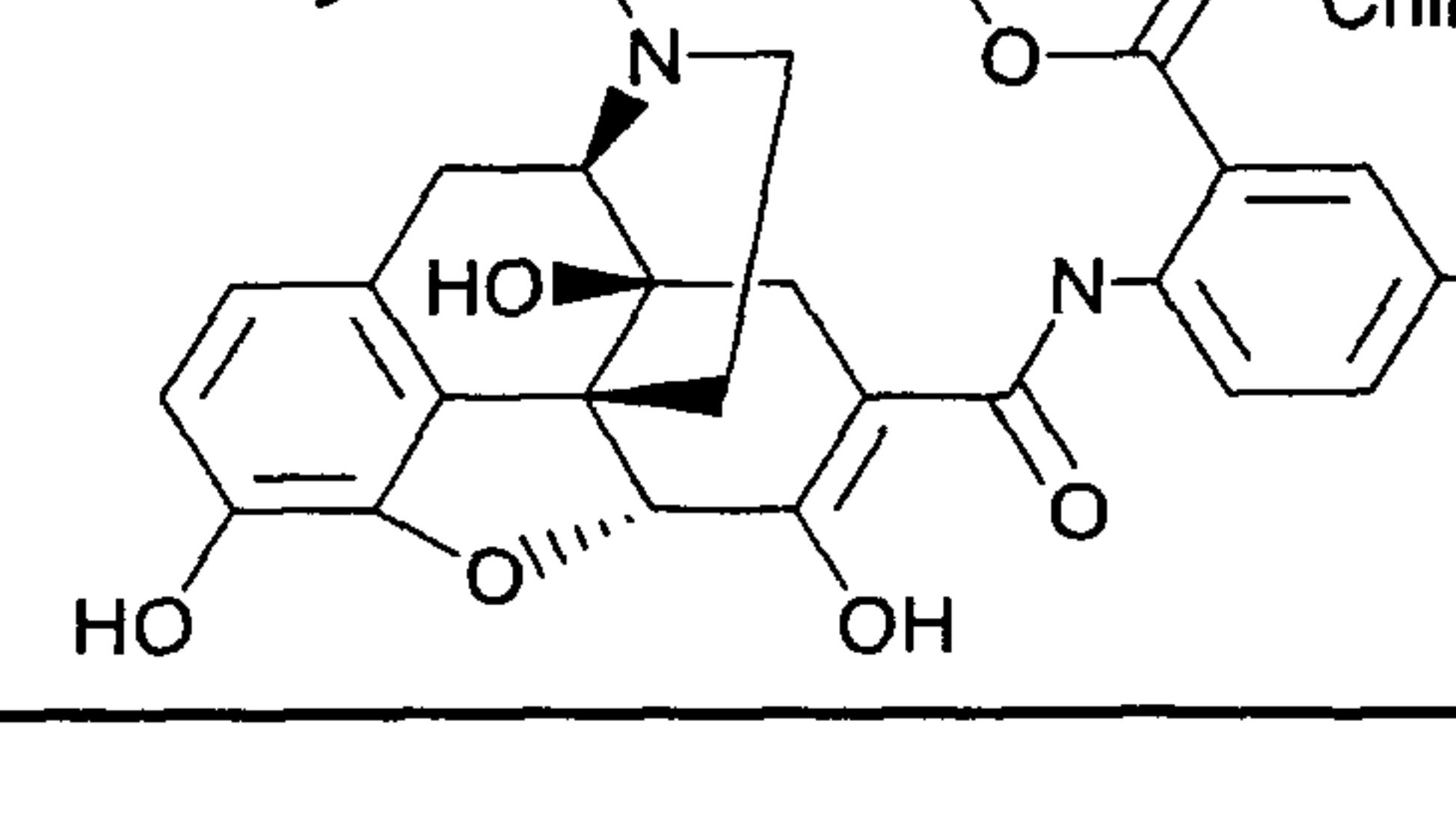
[0082]

[Table 37]

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

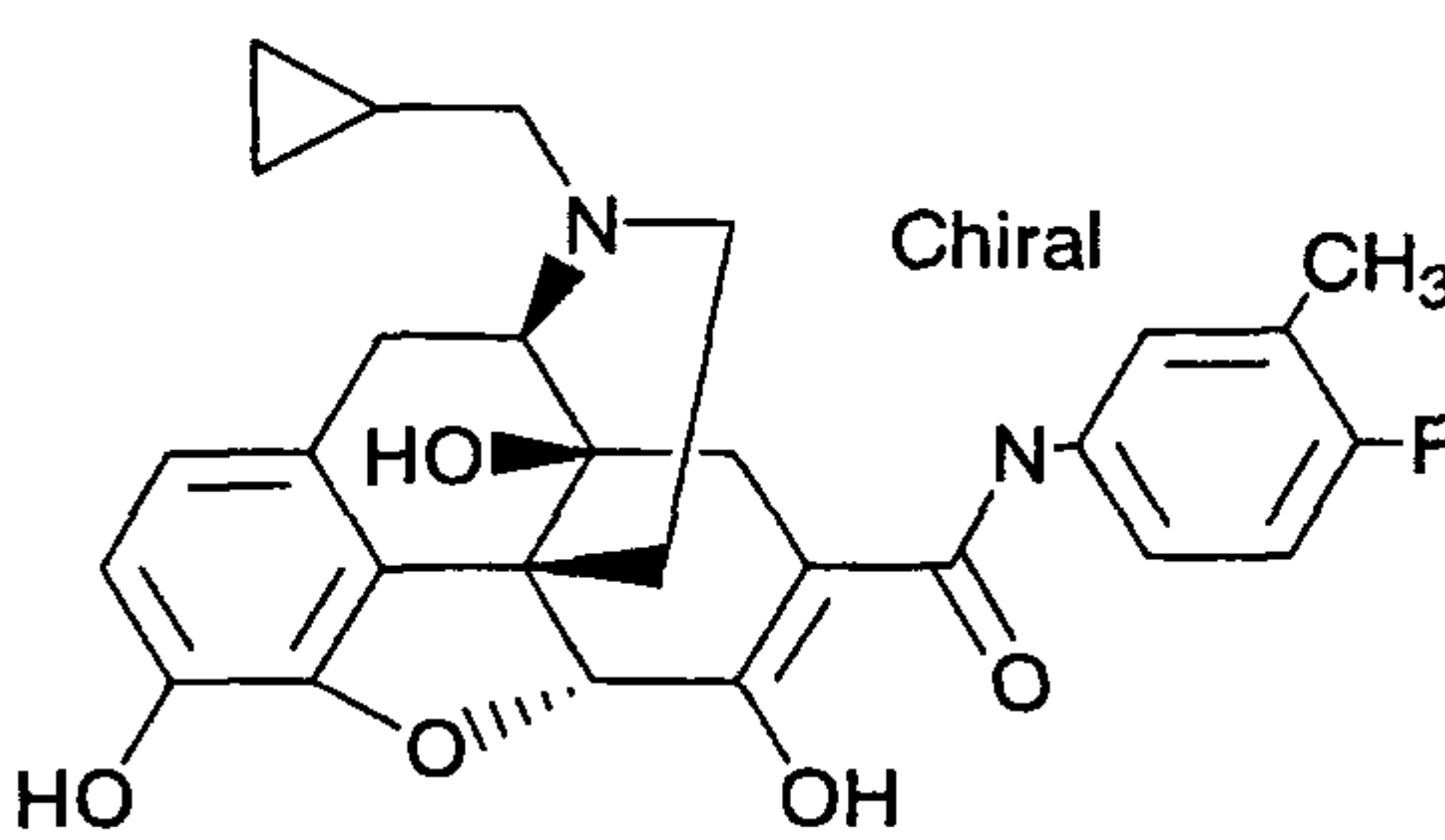
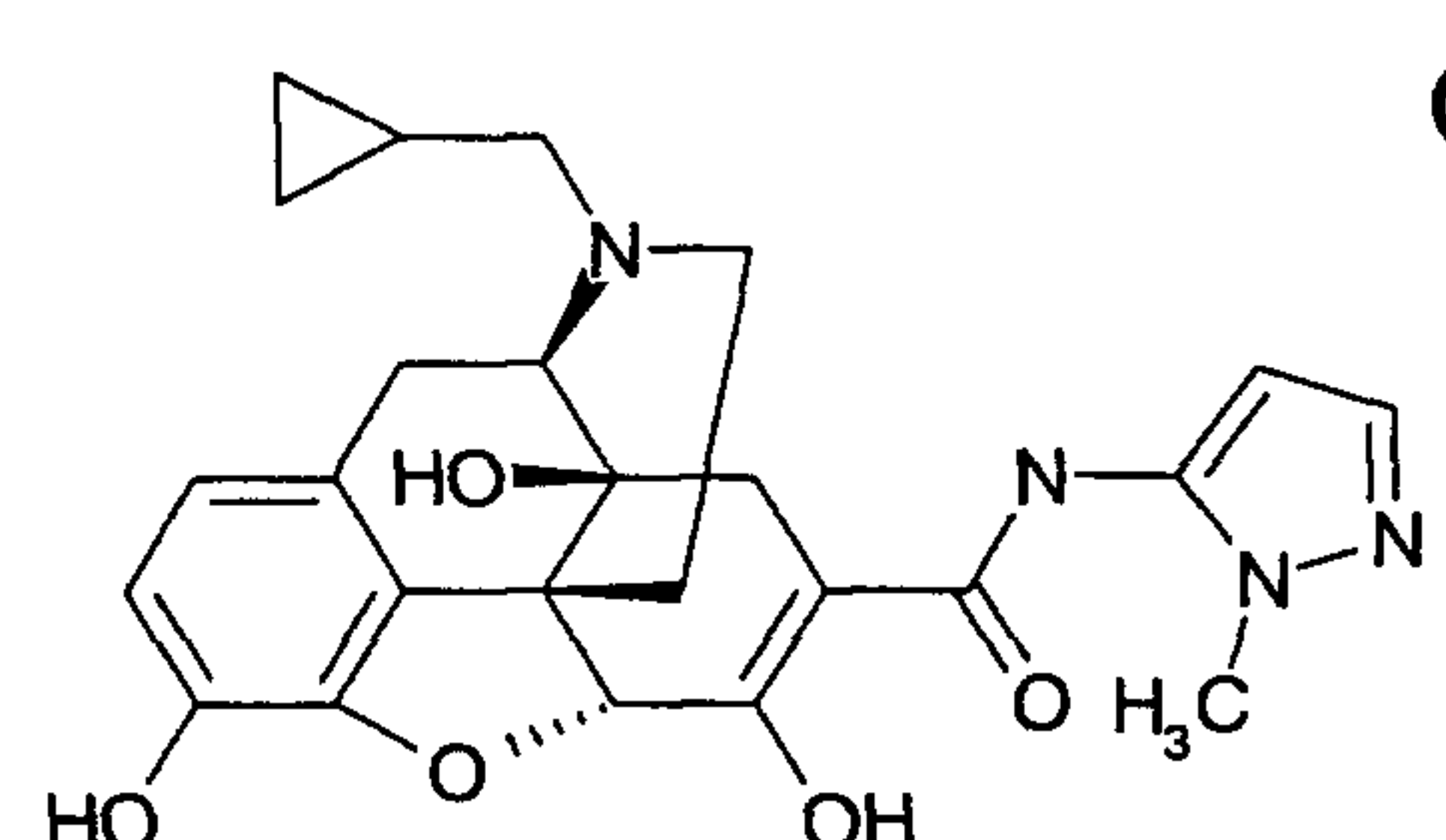
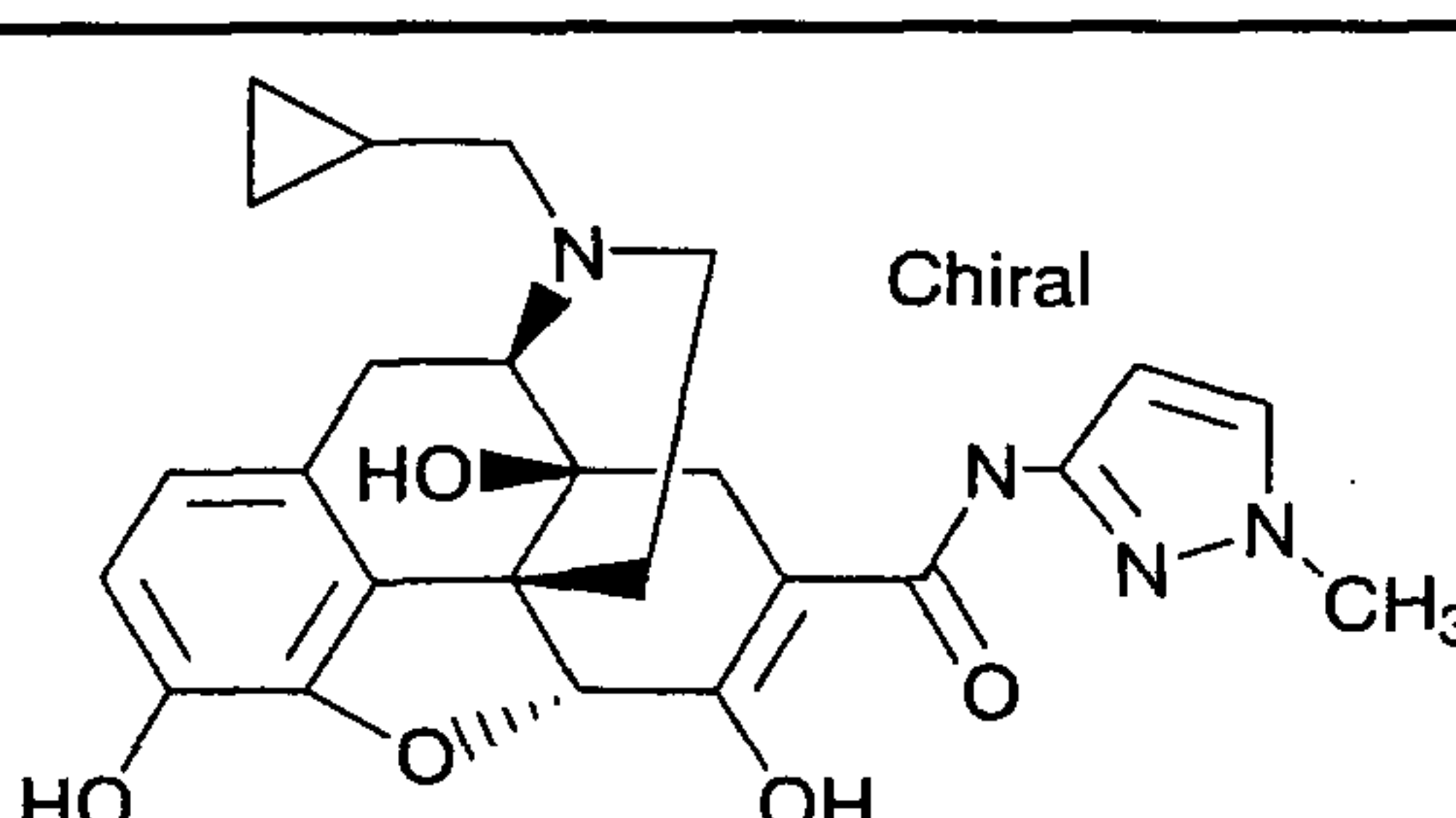
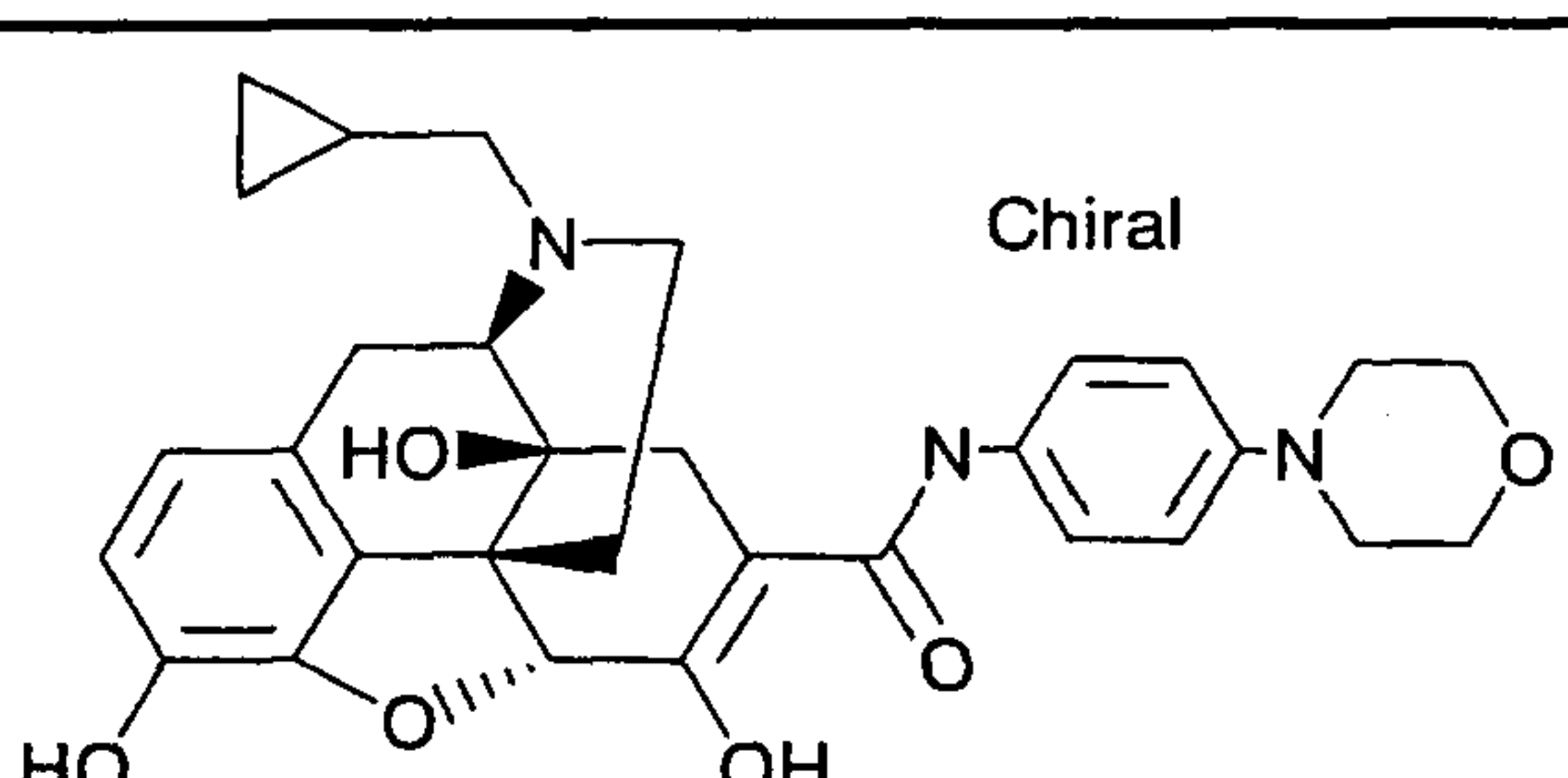
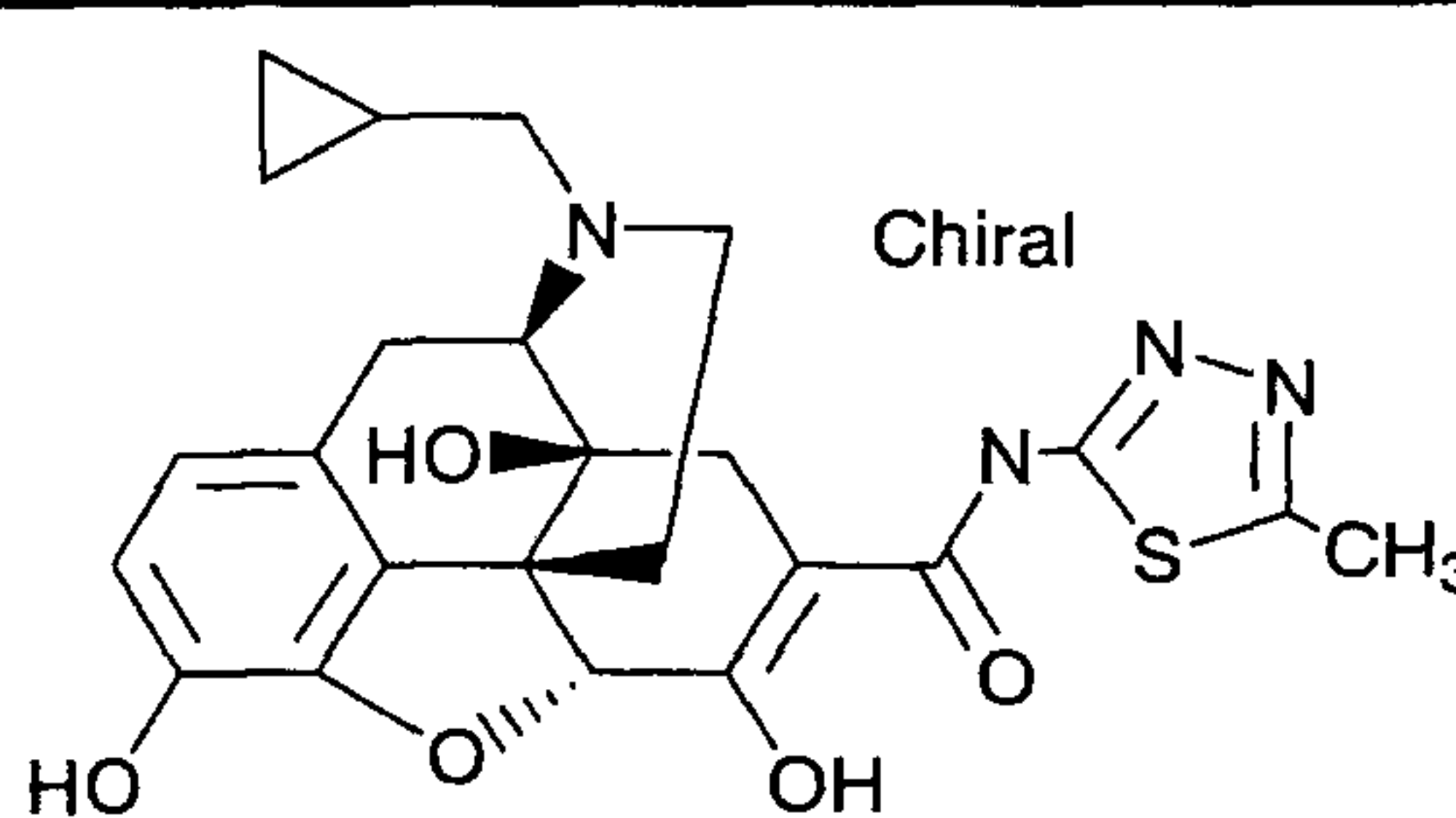
[0083]

[Table 38]

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

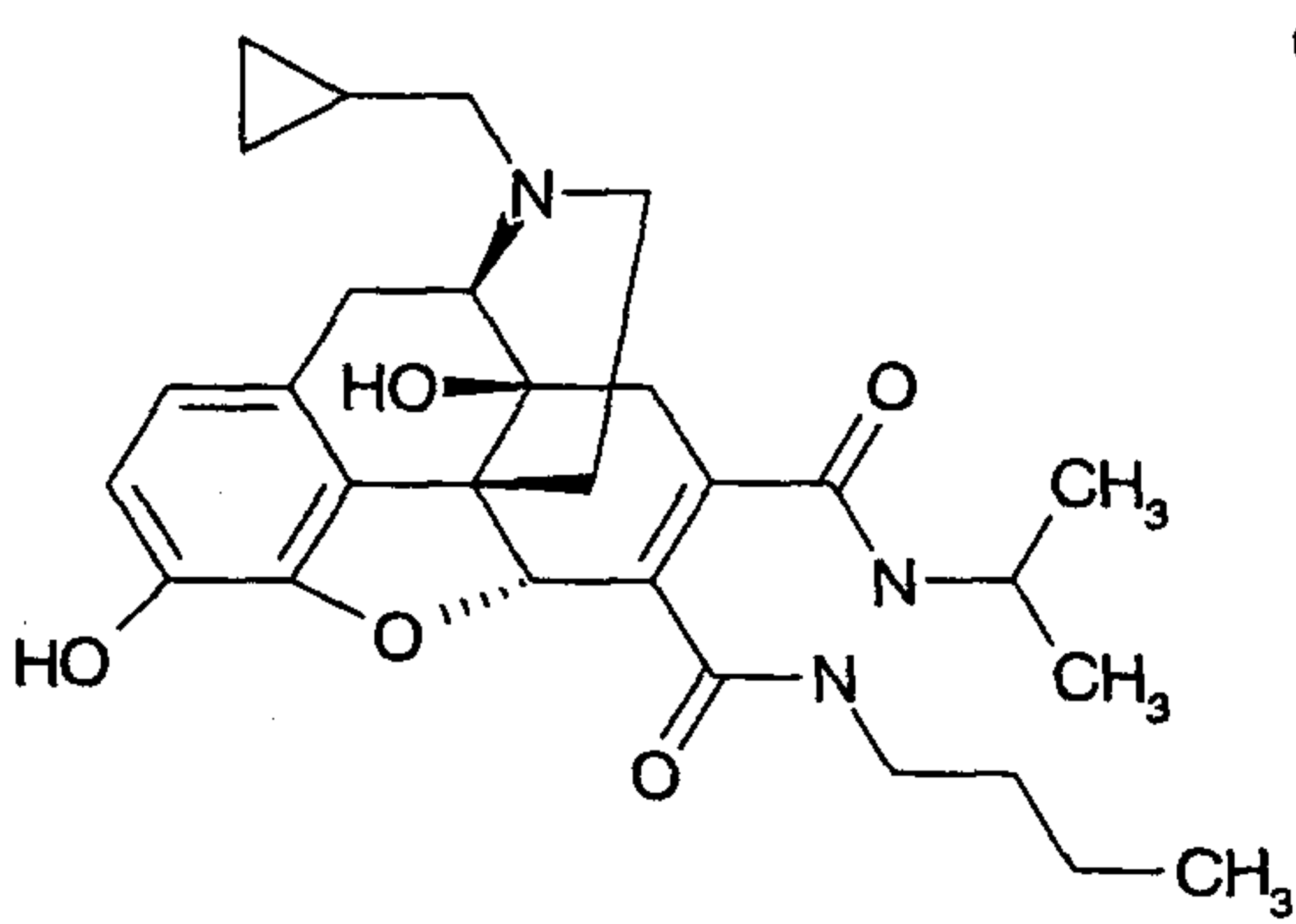
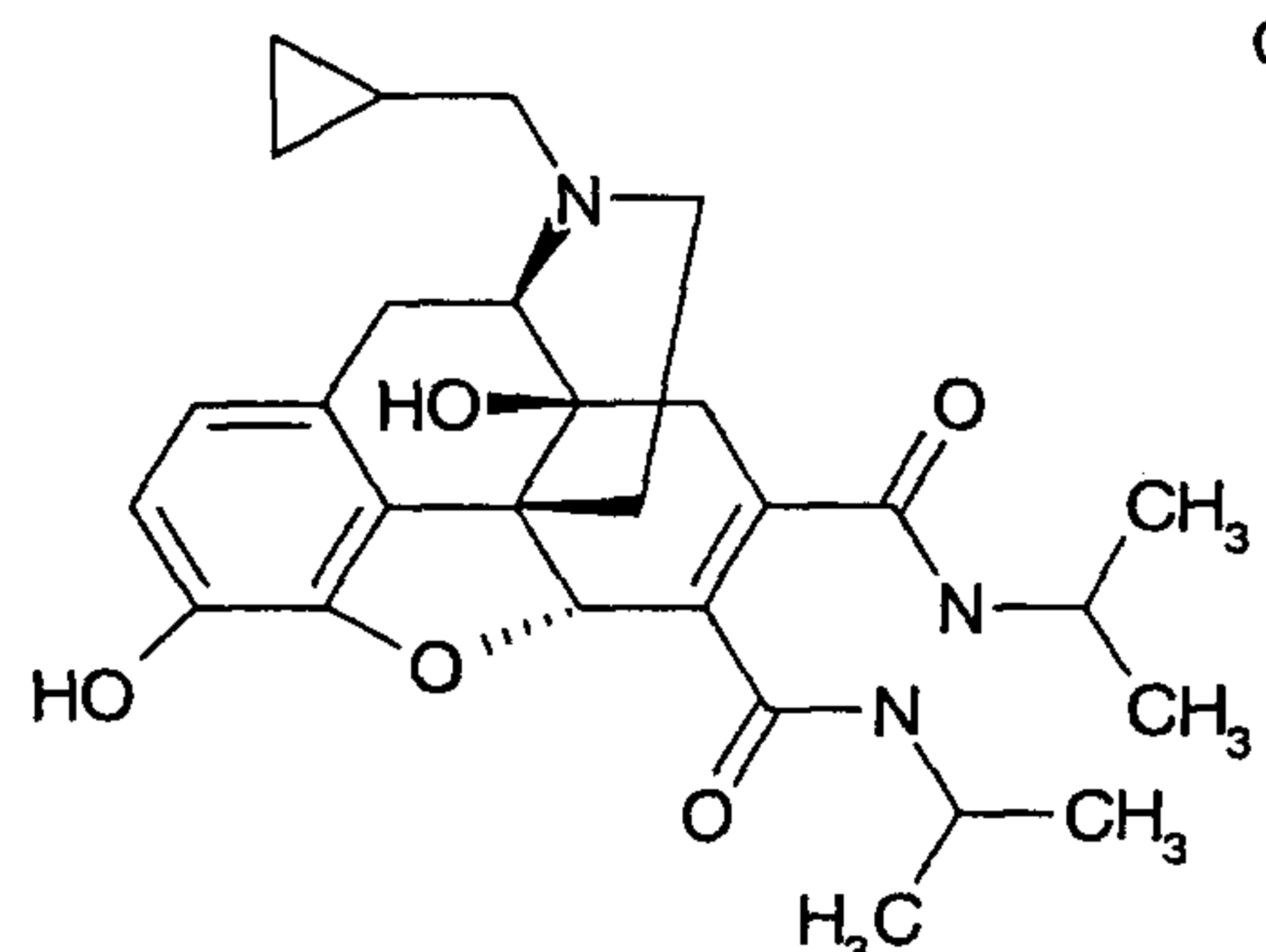
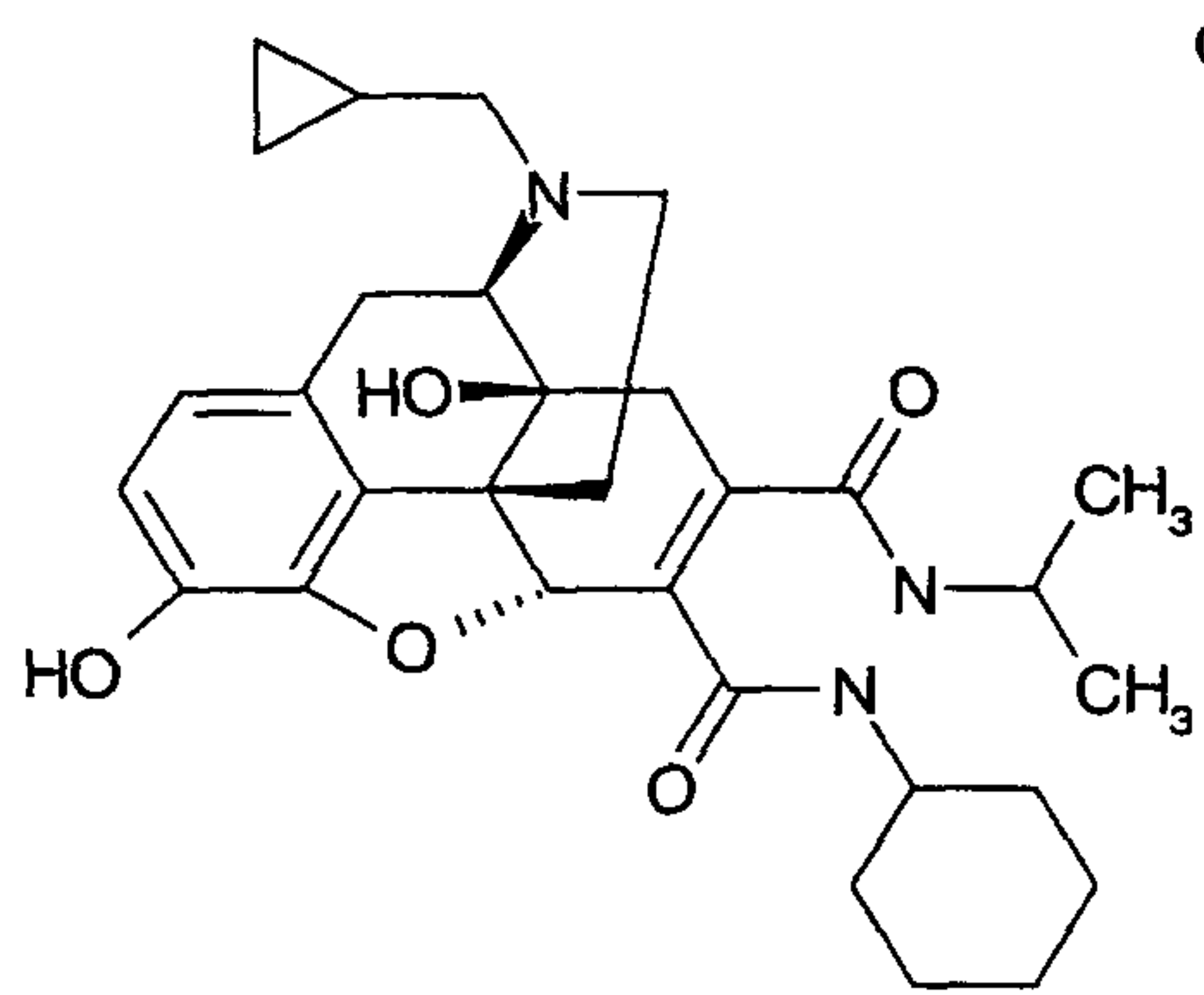
[0084]

[Table 39]

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

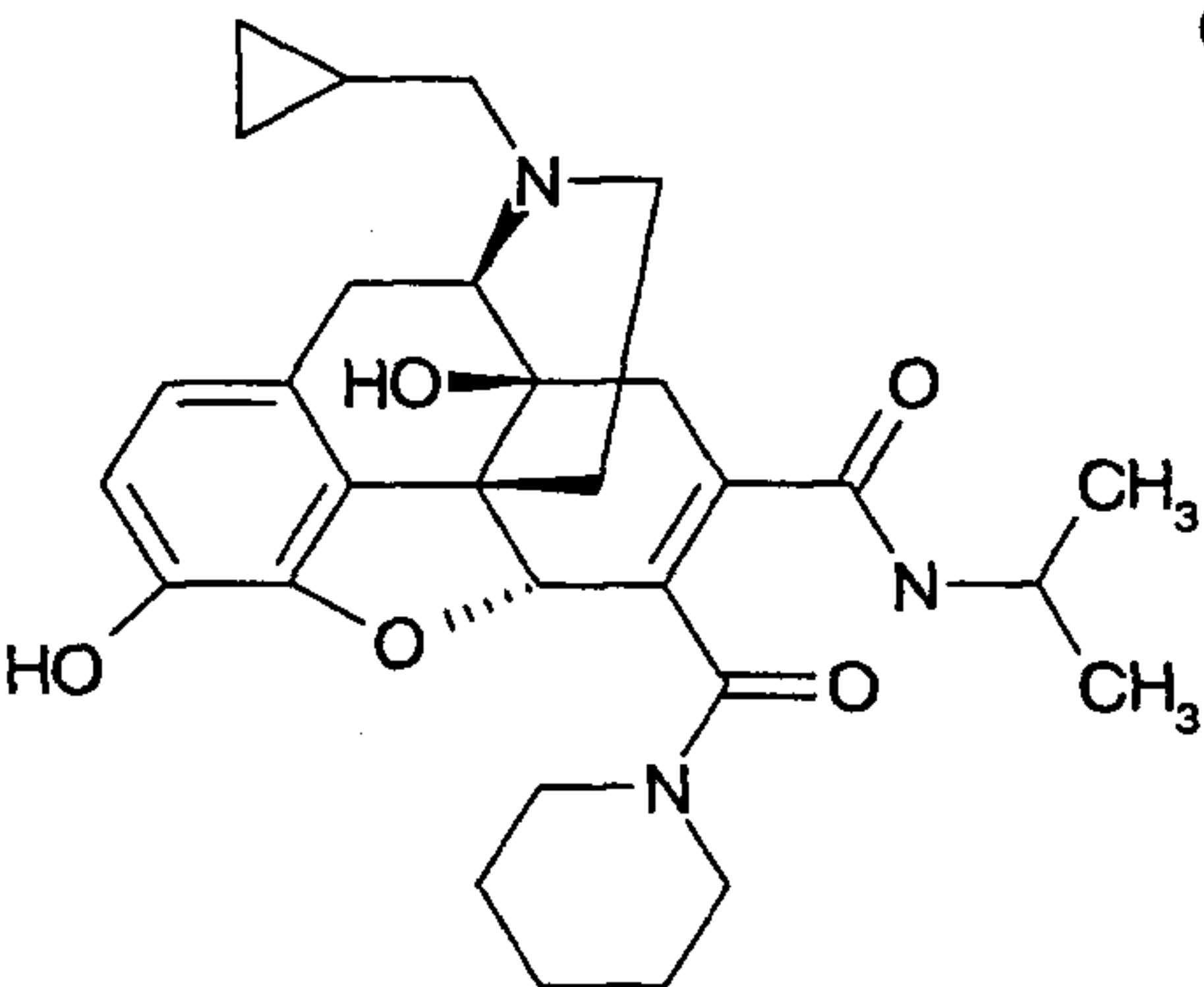
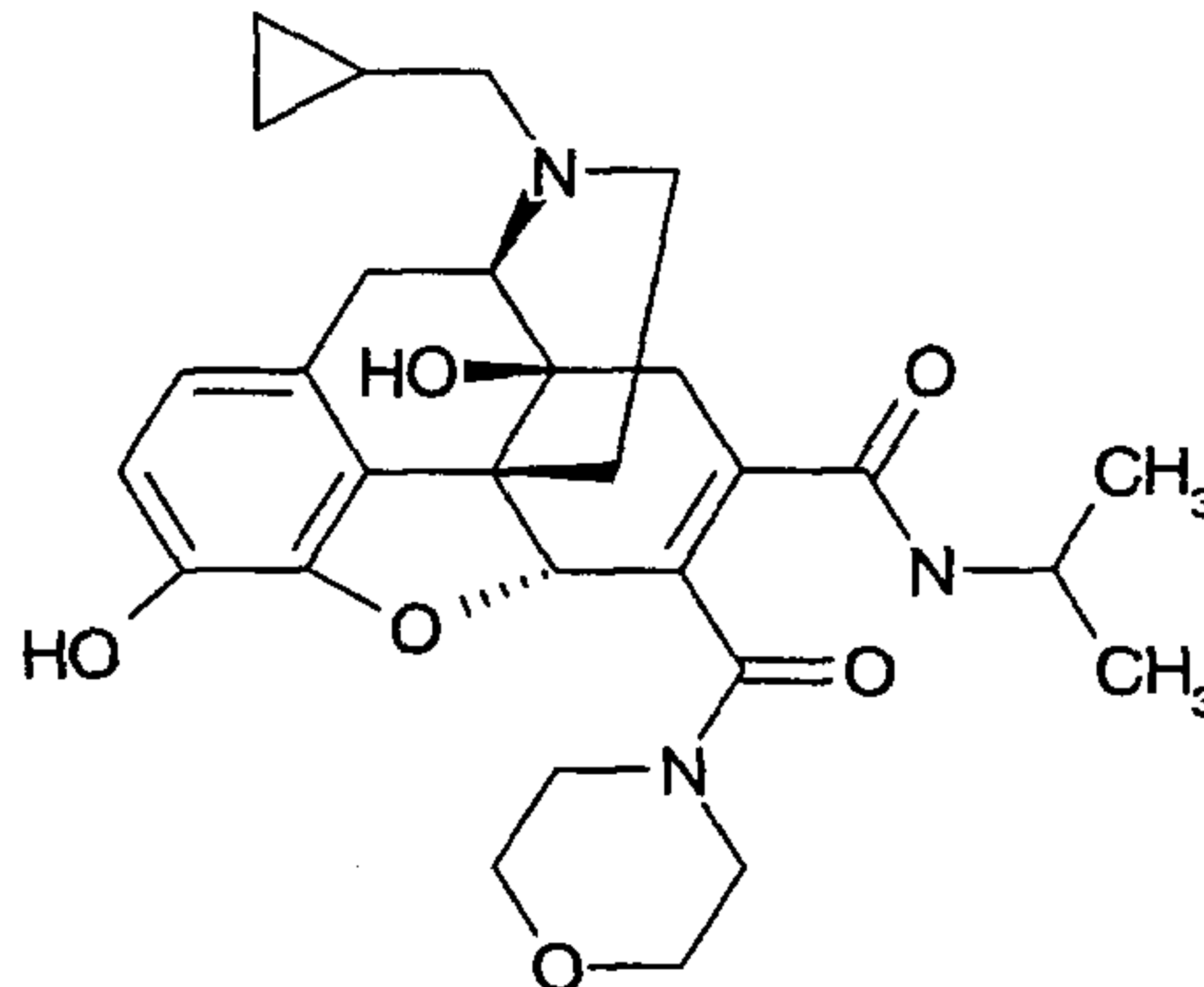
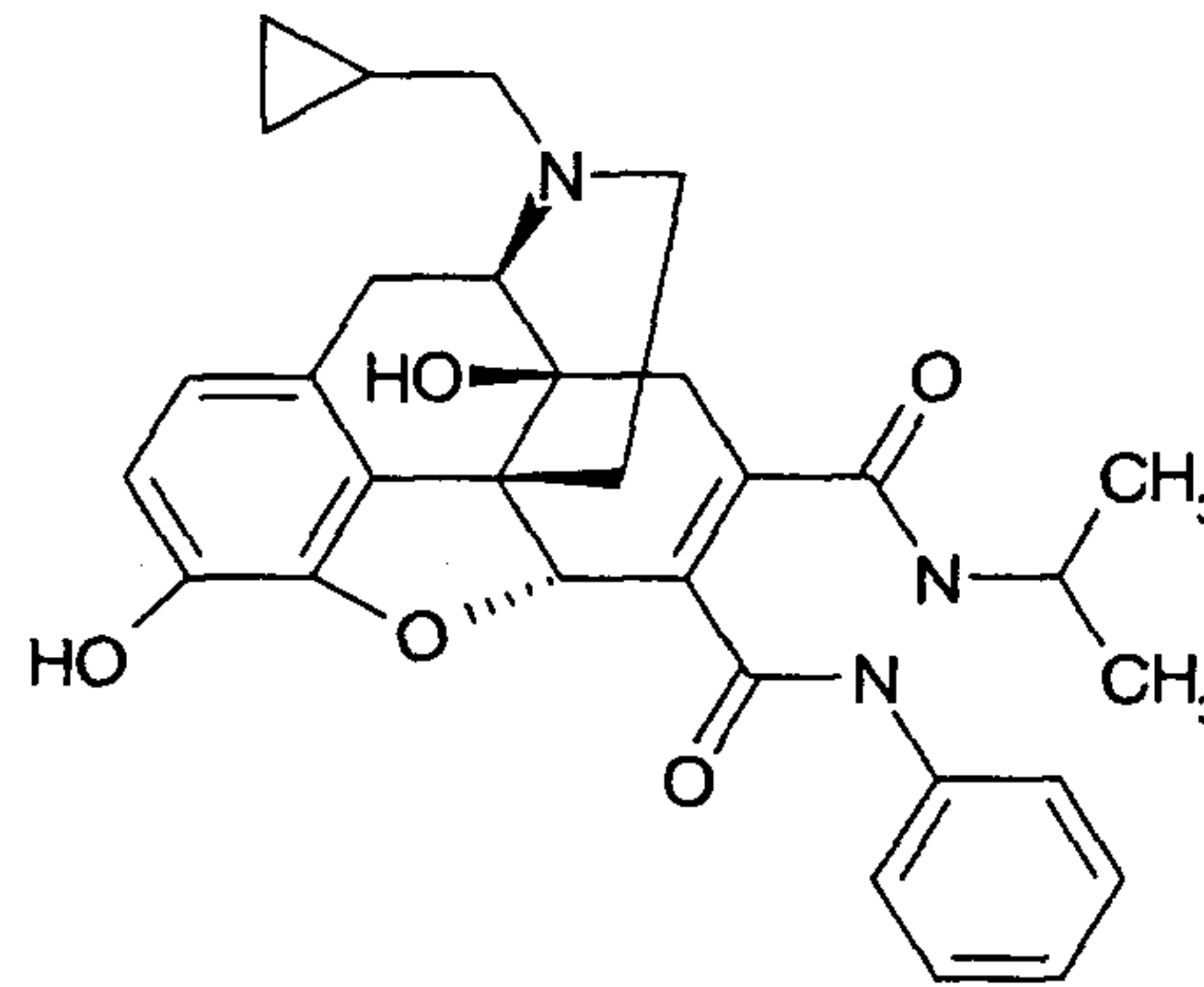
[0085]

[Table 40]

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

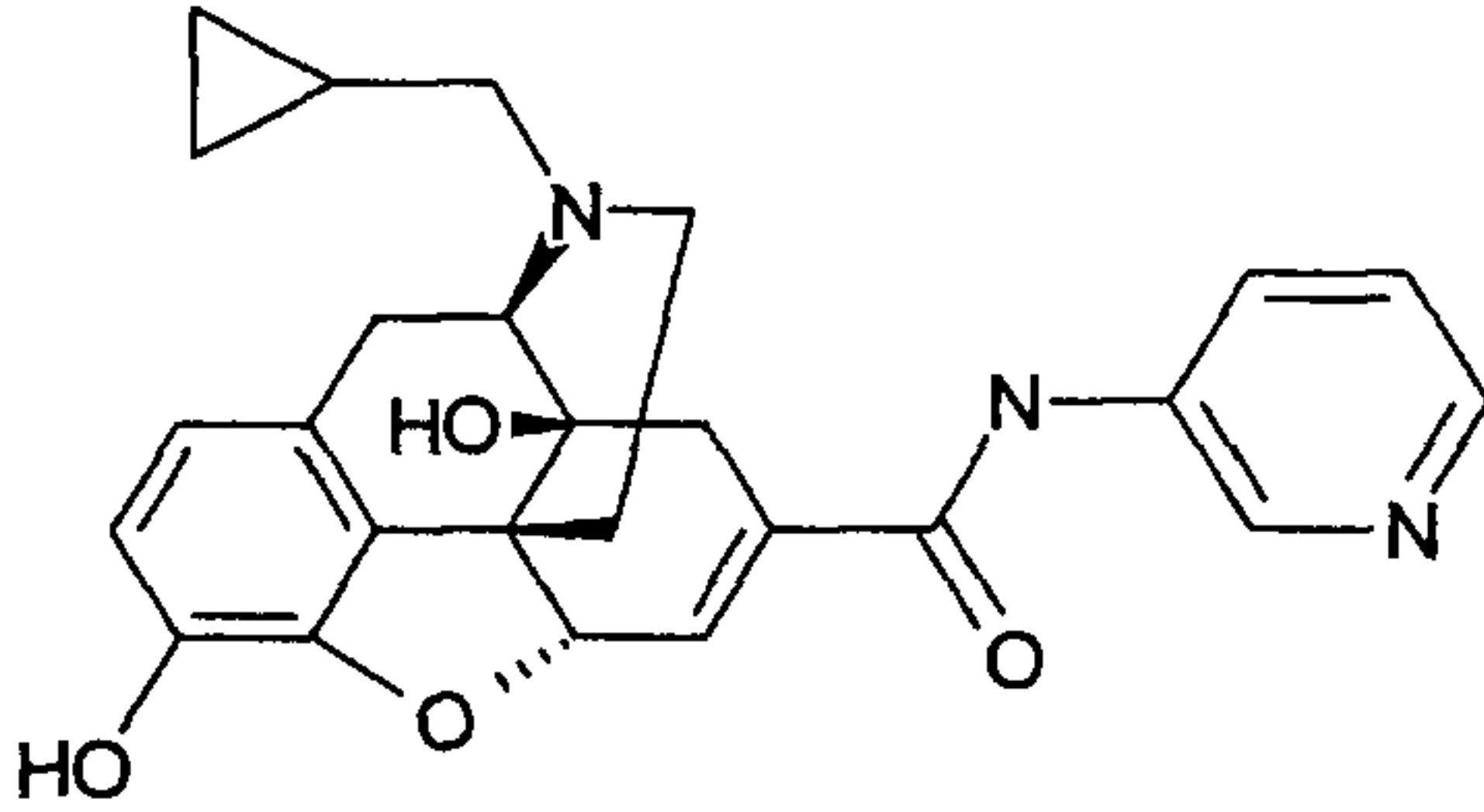
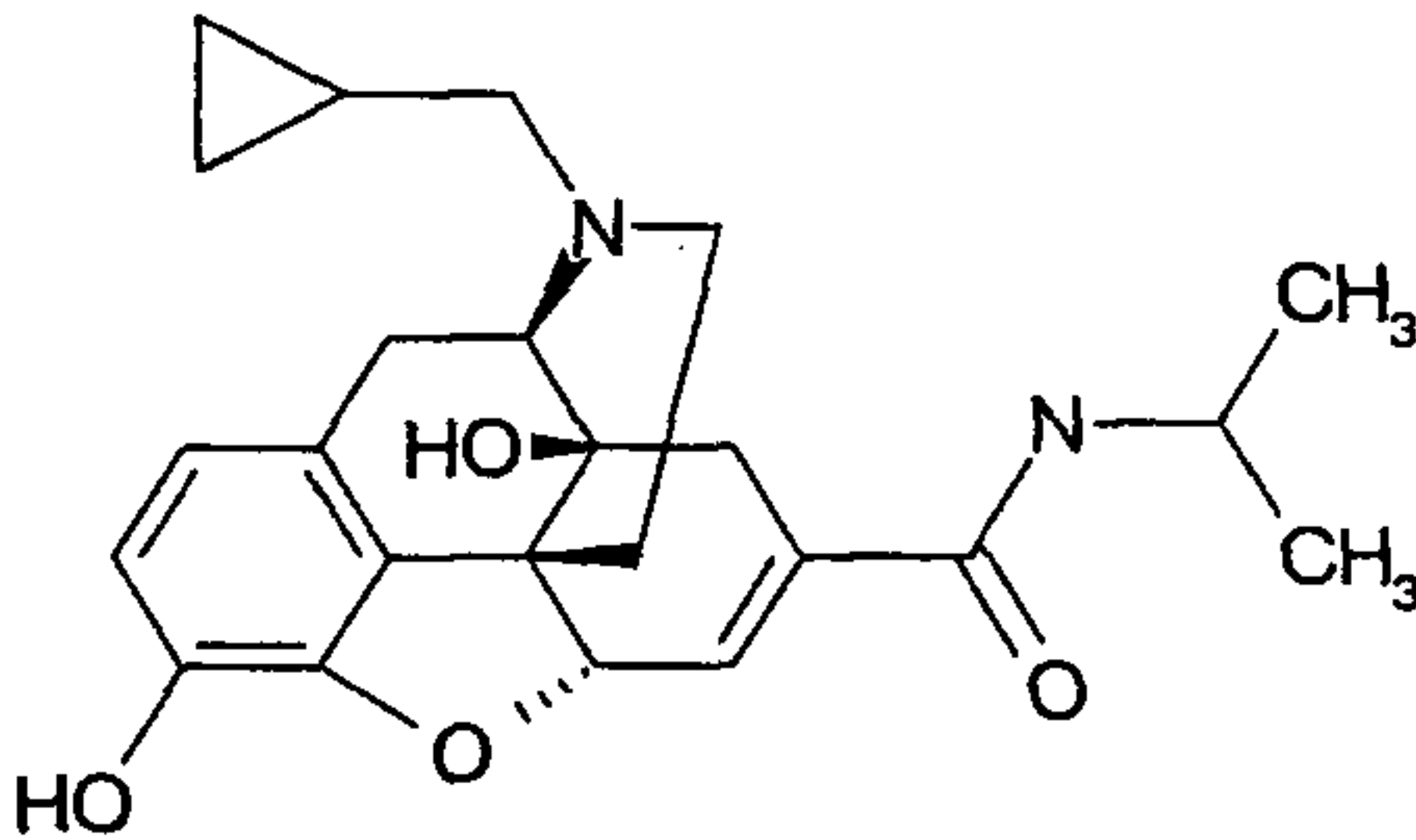
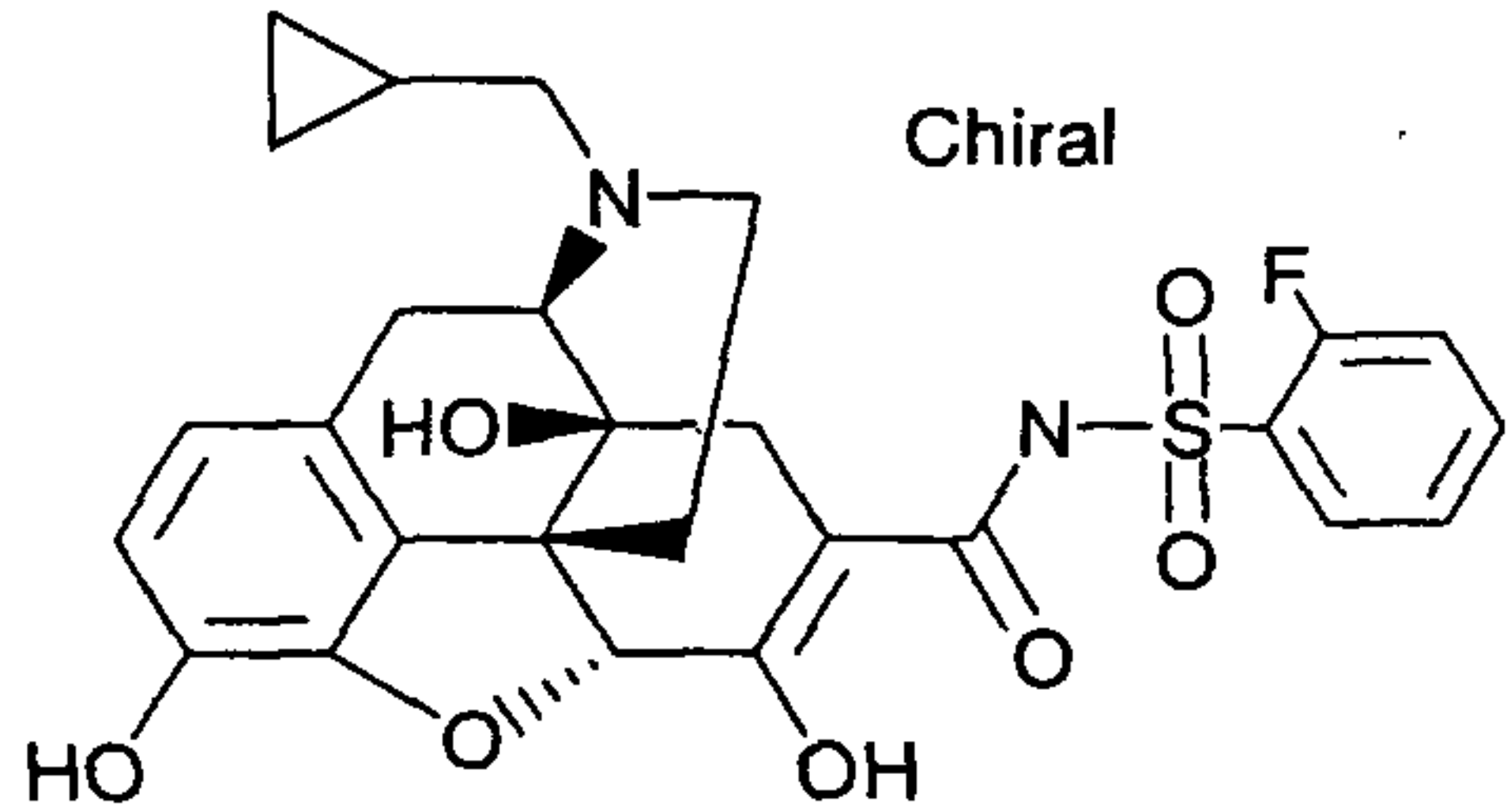
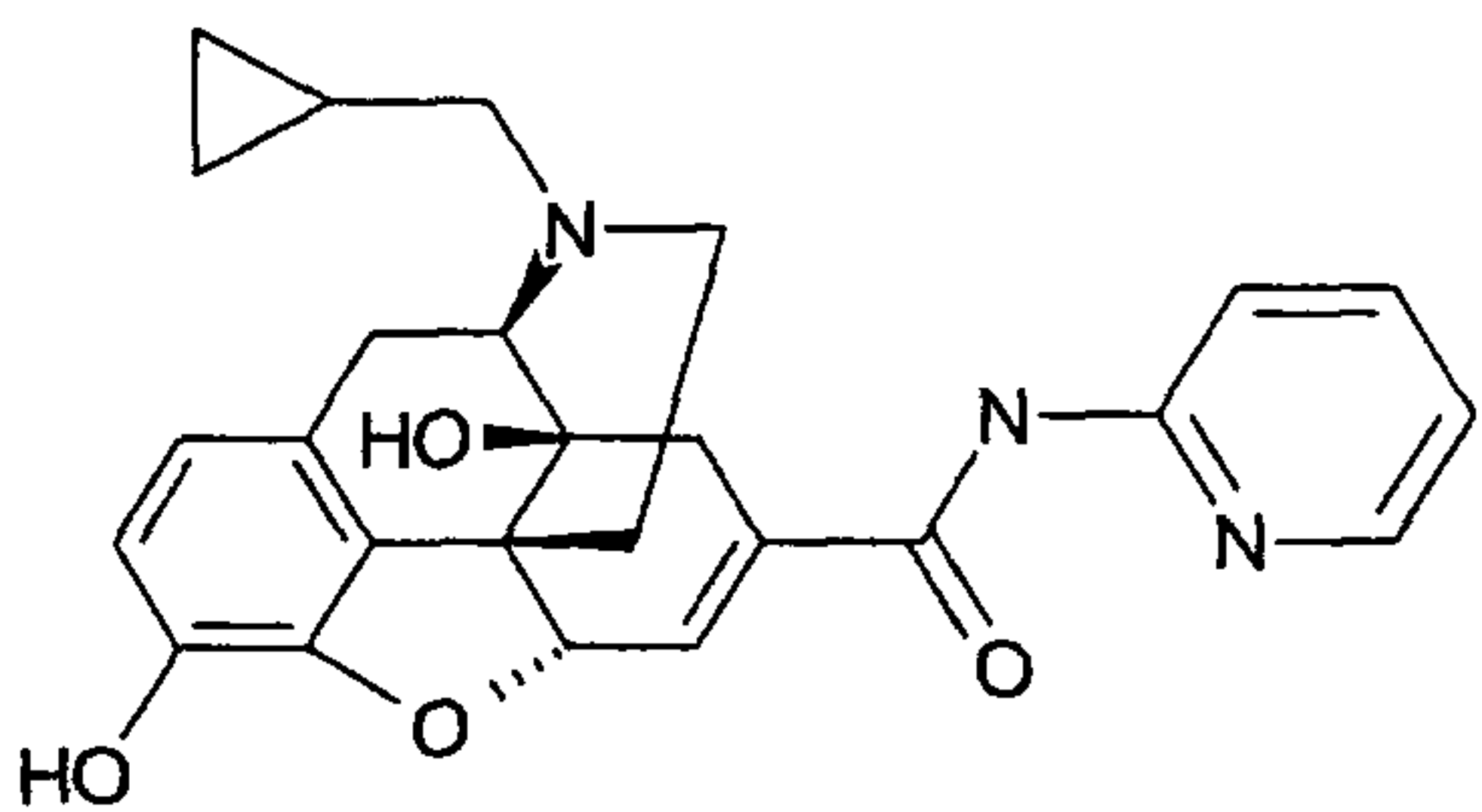
[0086]

[Table 41]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-160	Chiral 	m/z 522 [M+H] ⁺ 1.04 min	0.12-0.13 (m, 2H), 0.46-0.51 (m, 2H), 0.85 (m, 1H), 0.99 (d, J = 3.3 Hz, 3H), 1.01 (d, J = 3.3 Hz, 3H), 1.15-1.49 (m, 7H), 1.91 (d, J = 16.5 Hz, 1H), 2.08-2.65 (m, 7H), 2.98 (d, J = 17.5 Hz, 1H), 3.12 (d, J = 5.7 Hz, 1H), 3.16-3.34 (m, 4H), 3.79 (q, J = 6.9 Hz, 1H), 4.76 (brs, 1H), 5.01 (s, 1H), 6.54 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 9.01 (brs, 1H)
I-161	Chiral 	m/z 524 [M+H] ⁺ 0.92 min	0.12-0.14 (m, 2H), 0.46-0.51 (m, 2H), 0.86 (m, 1H), 0.99 (d, J = 3.3 Hz, 3H), 1.01 (d, J = 3.3 Hz, 3H), 1.41 (d, J = 11.1 Hz, 1H), 1.95 (d, J = 17.1 Hz, 1H), 2.08-2.67 (m, 11H), 2.98 (d, J = 17.5 Hz, 1H), 3.12 (d, J = 5.7 Hz, 1H), 3.49-3.60 (m, 4H), 3.82 (q, J = 6.9 Hz, 1H), 4.78 (brs, 1H), 5.01 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 9.13 (brs, 1H)
I-162	Chiral 	m/z 530 [M+H] ⁺ 0.94 min	0.13-0.14 (m, 2H), 0.47-0.51 (m, 2H), 0.83 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.44 (d, J = 10.5 Hz, 1H), 2.02 (d, J = 16.8 Hz, 1H), 2.11-2.65 (m, 7H), 3.03 (d, J = 18.6 Hz, 1H), 3.17 (d, J = 5.7 Hz, 1H), 3.58 (m, 1H), 3.74 (q, J = 6.3 Hz, 1H), 4.86 (brs, 1H), 5.39 (s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.1 Hz, 2H), 9.01 (brs, 1H), 9.70 (brs, 1H)

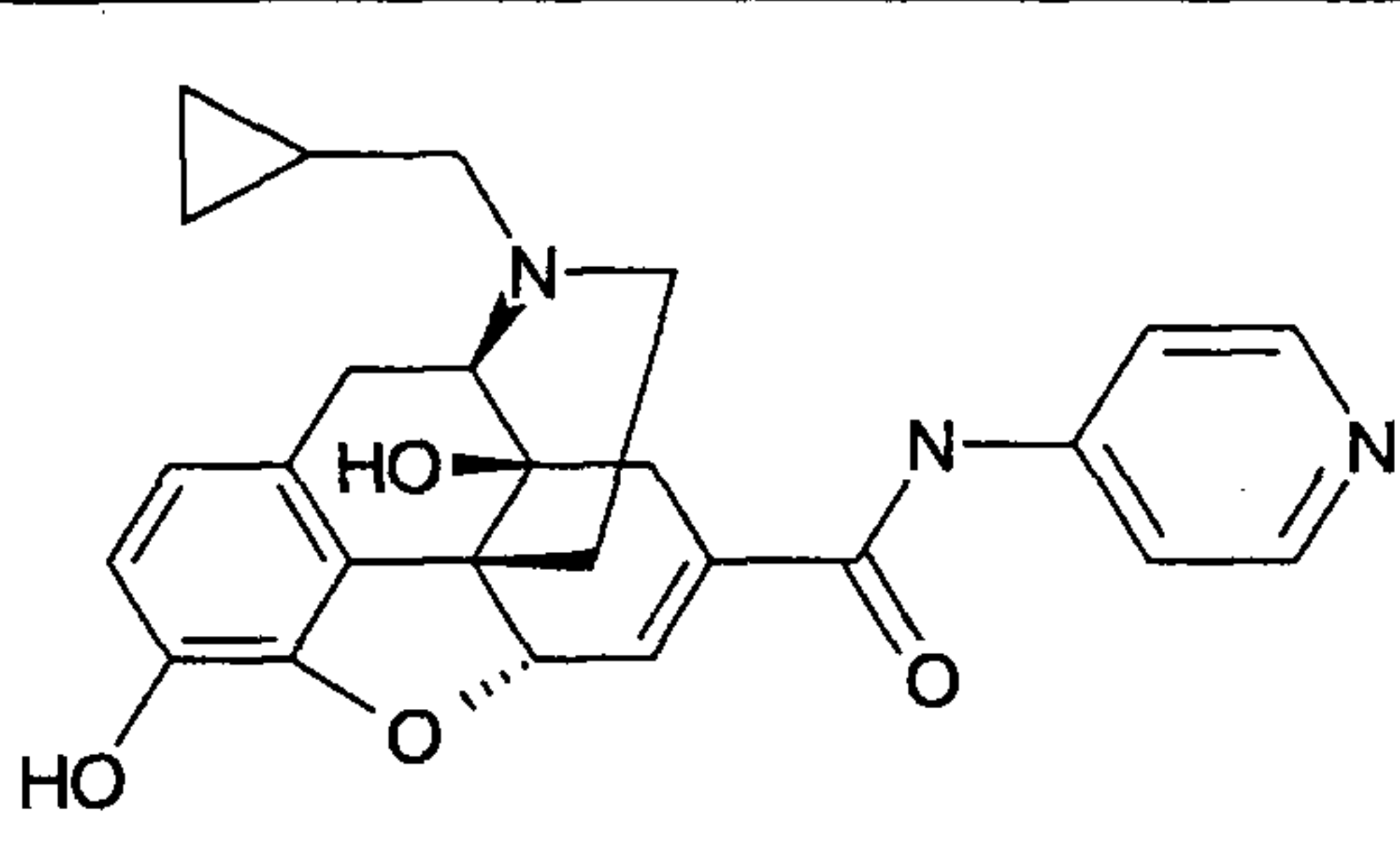
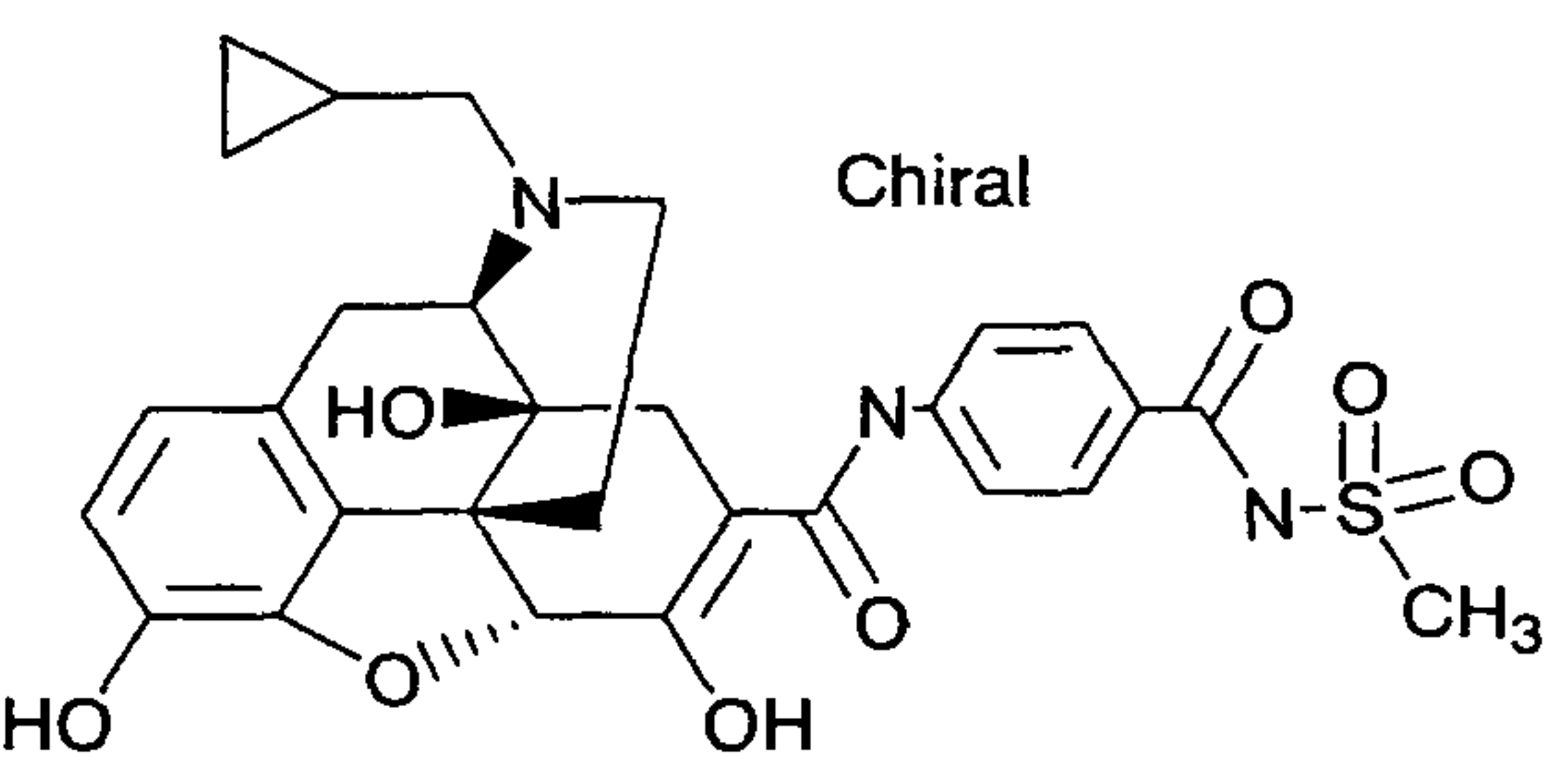
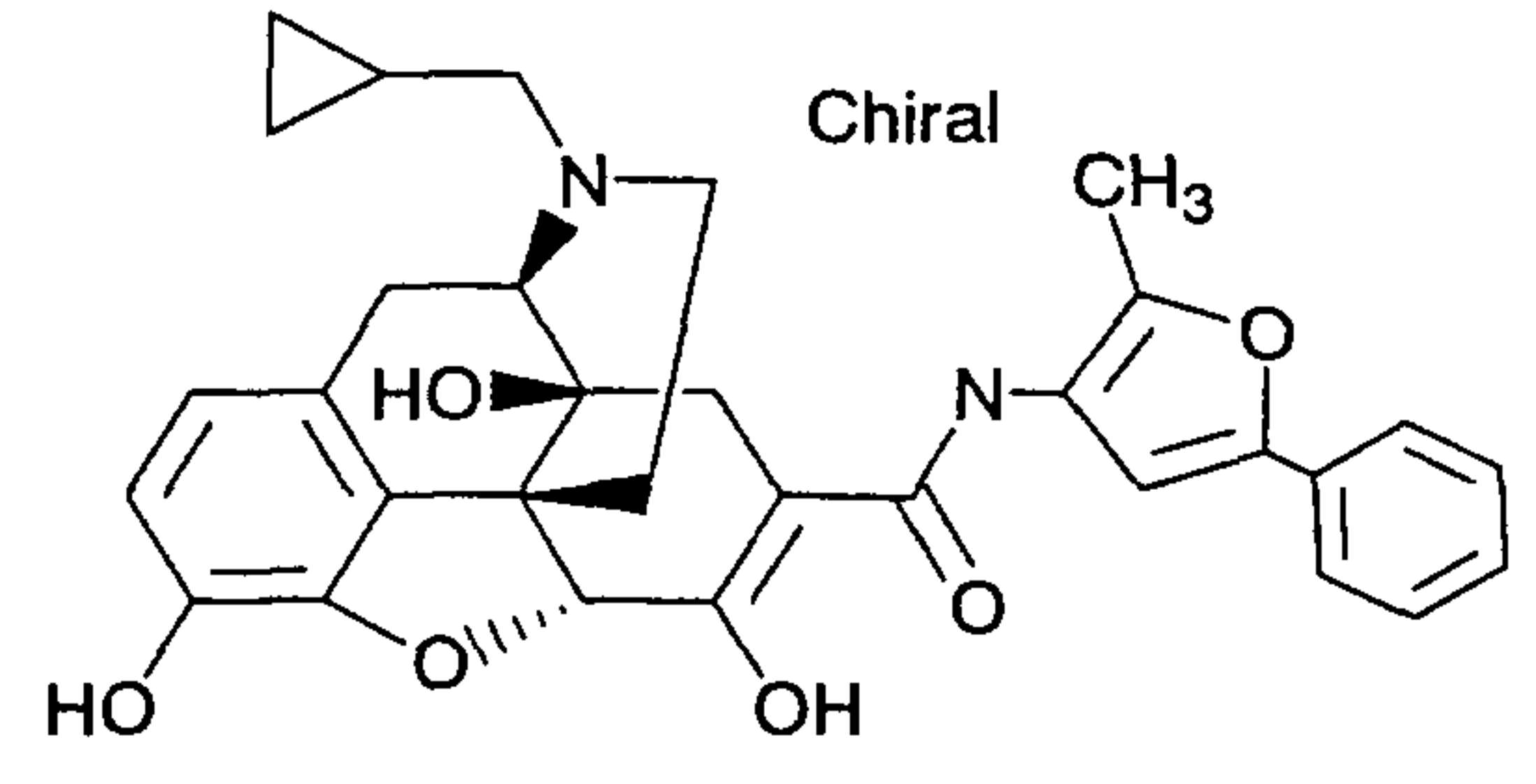
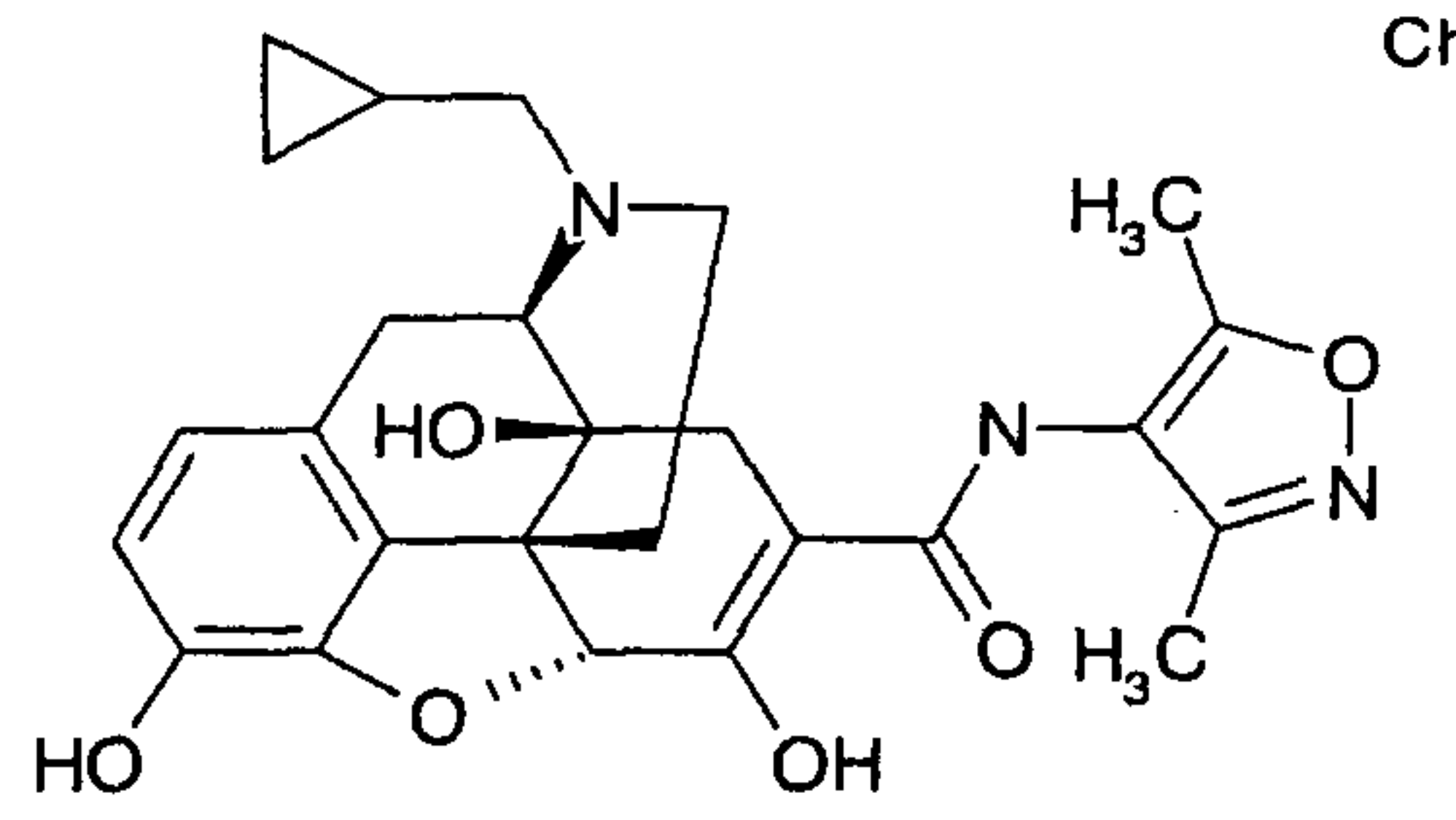
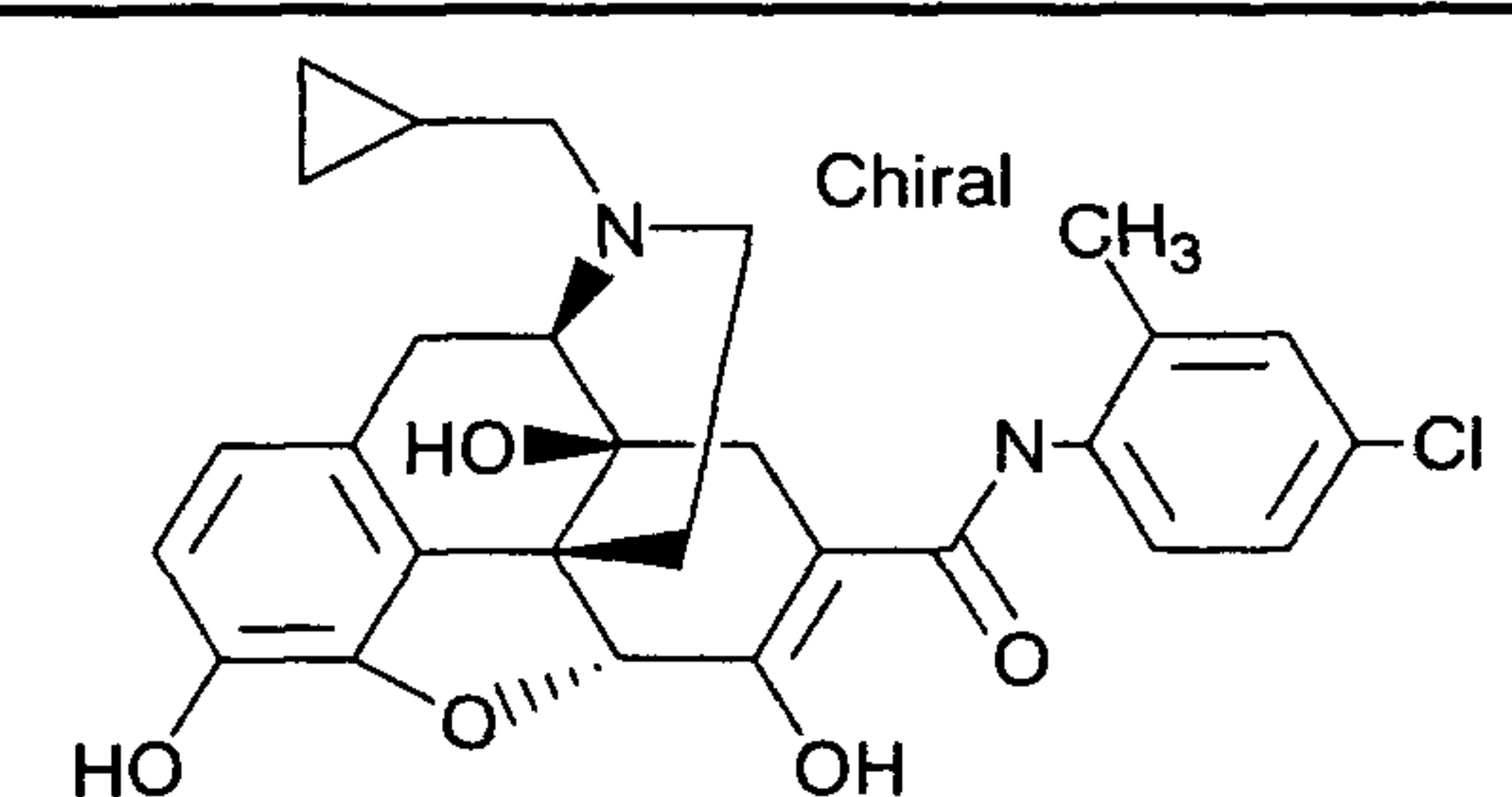
[0087]

[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	
I-164	Chiral 		0.14–0.22 (m, 2H), 0.48–0.61 (m, 2H), 0.91 (m, 1H), 1.12 (d, J = 6.6 Hz, 6H), 1.53–1.66 (m, 1H), 2.15–2.22 (m, 2H), 2.23–2.30 (m, 2H), 2.35–2.49 (m, 2H), 2.70 (d.d, J = 18.9 & 6.6 Hz, 2H), 3.13 (d, J = 18.9 Hz, 1H), 3.27 (d, J = 6.6 Hz, 1H), 3.98 (quintet, J = 6.6 Hz, 1H), 4.99–5.04 (m, 1H), 6.32–6.36 (m, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H).
I-165	Chiral 	m/z 543 [M+H]⁺ 0.63 min	
I-166	Chiral 	m/z 446 [M+H]⁺ 0.94 min	

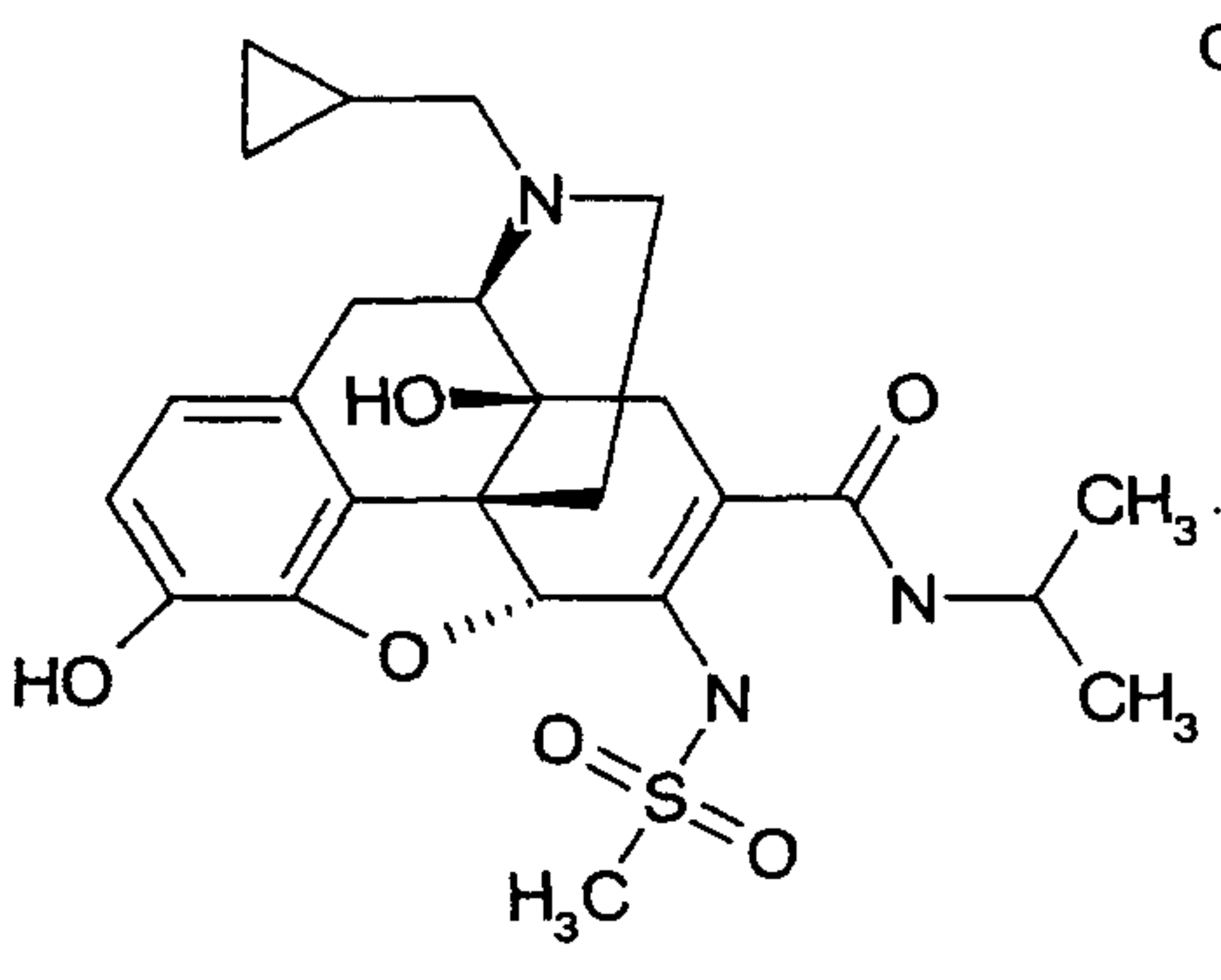
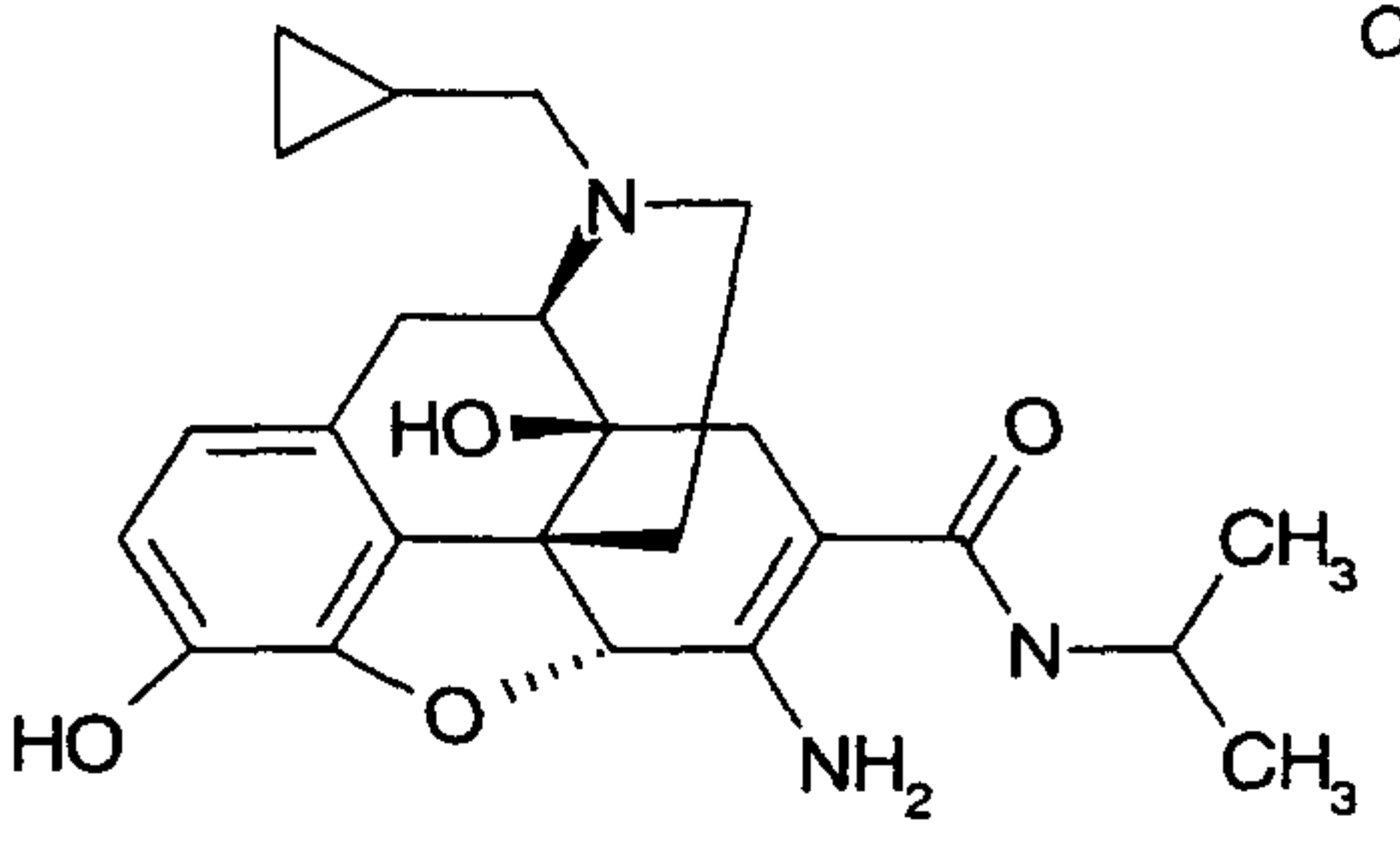
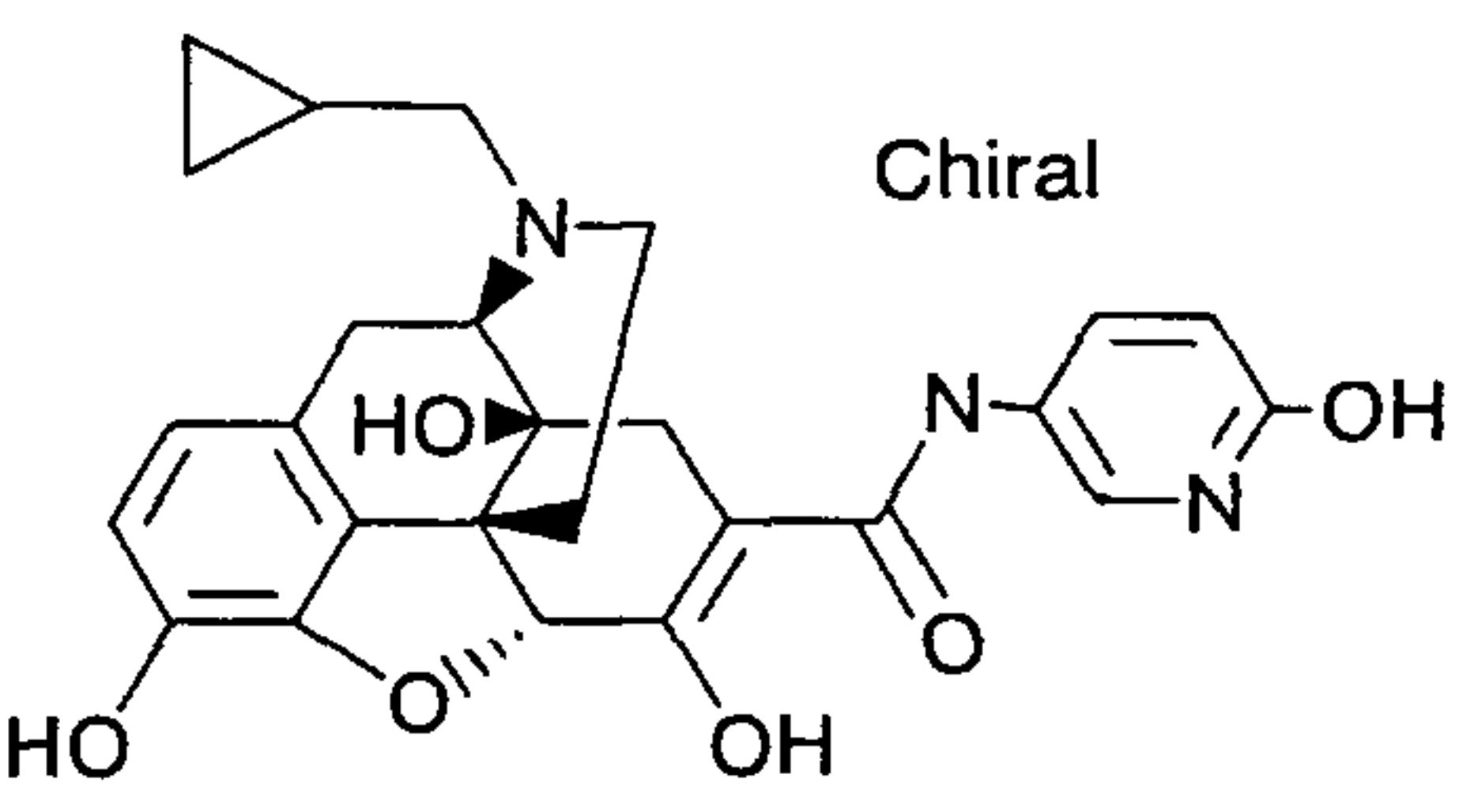
[0088]

[Table 43]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-167	 Chiral		(CD ₃ OD) δ : 0.12–0.22 (m, 2H), 0.48–0.63 (m, 2H), 0.82–1.00 (m, 1H), 1.63 (d, J = 8.1 Hz, 1H), 2.10–2.50 (m, 7H), 2.72 (d.d, J=18.6 & 6.6Hz, 2H), 3.15 (d, J = 18.6 Hz, 1H), 5.10 (brs, 1H), 6.50–6.65 (m, 3H), 7.67 (d.d, J = 4.8 & 1.5Hz, 1H), 8.36 (d.d, J = 4.8 & 1.5Hz, 1H).
I-168	 Chiral	m/z 582 [M+H] ⁺ 0.90 min	
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	

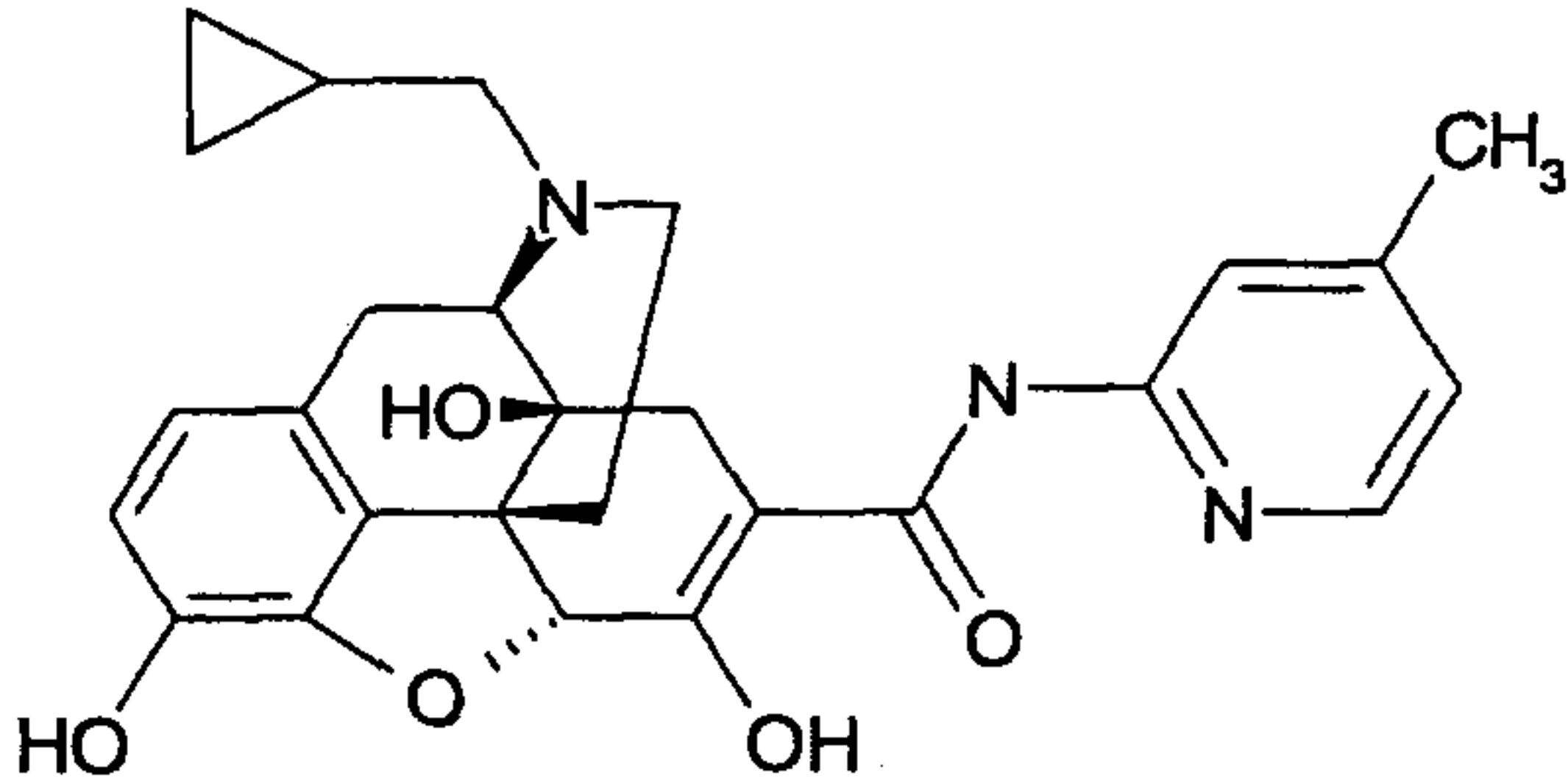
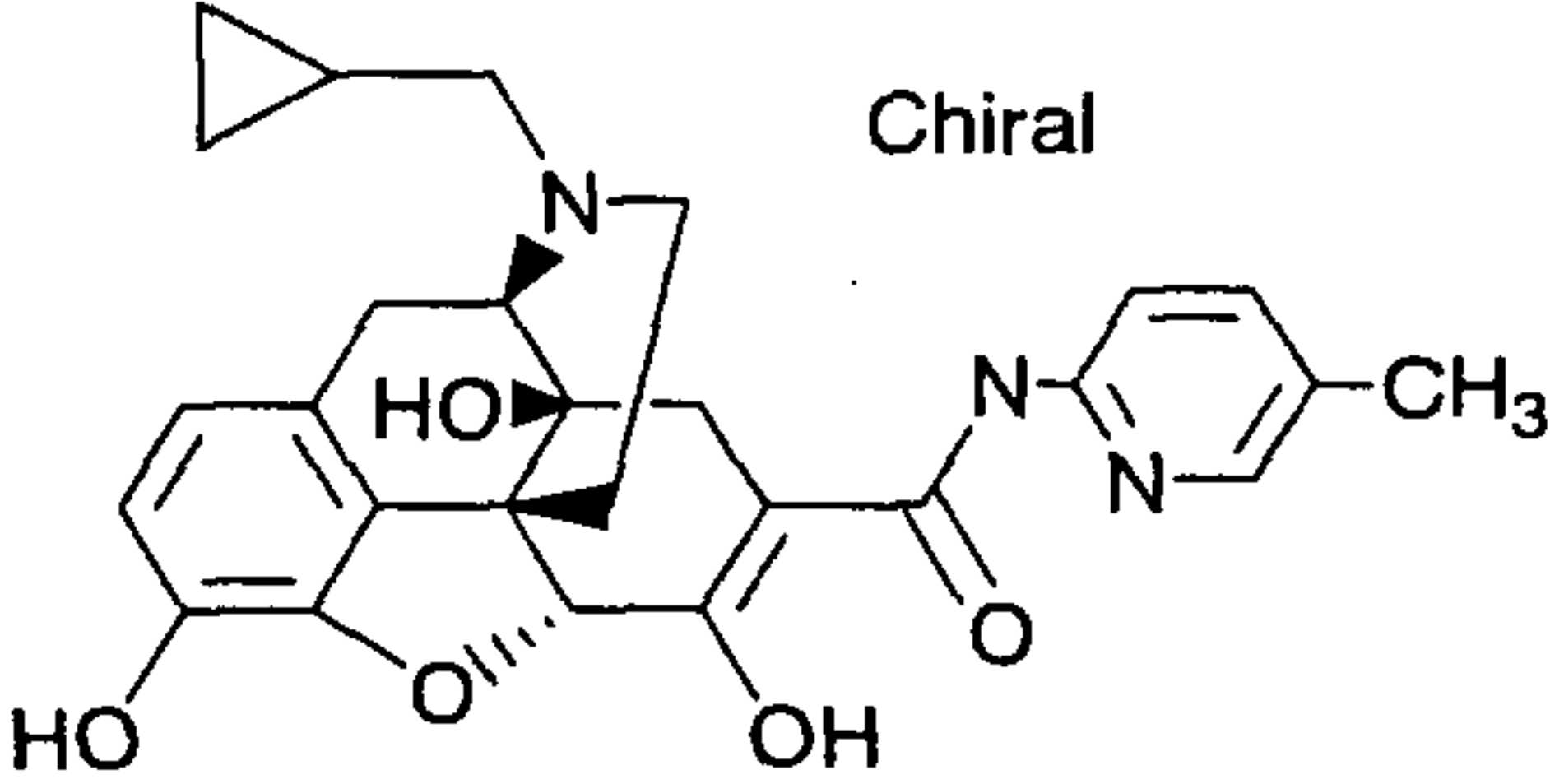
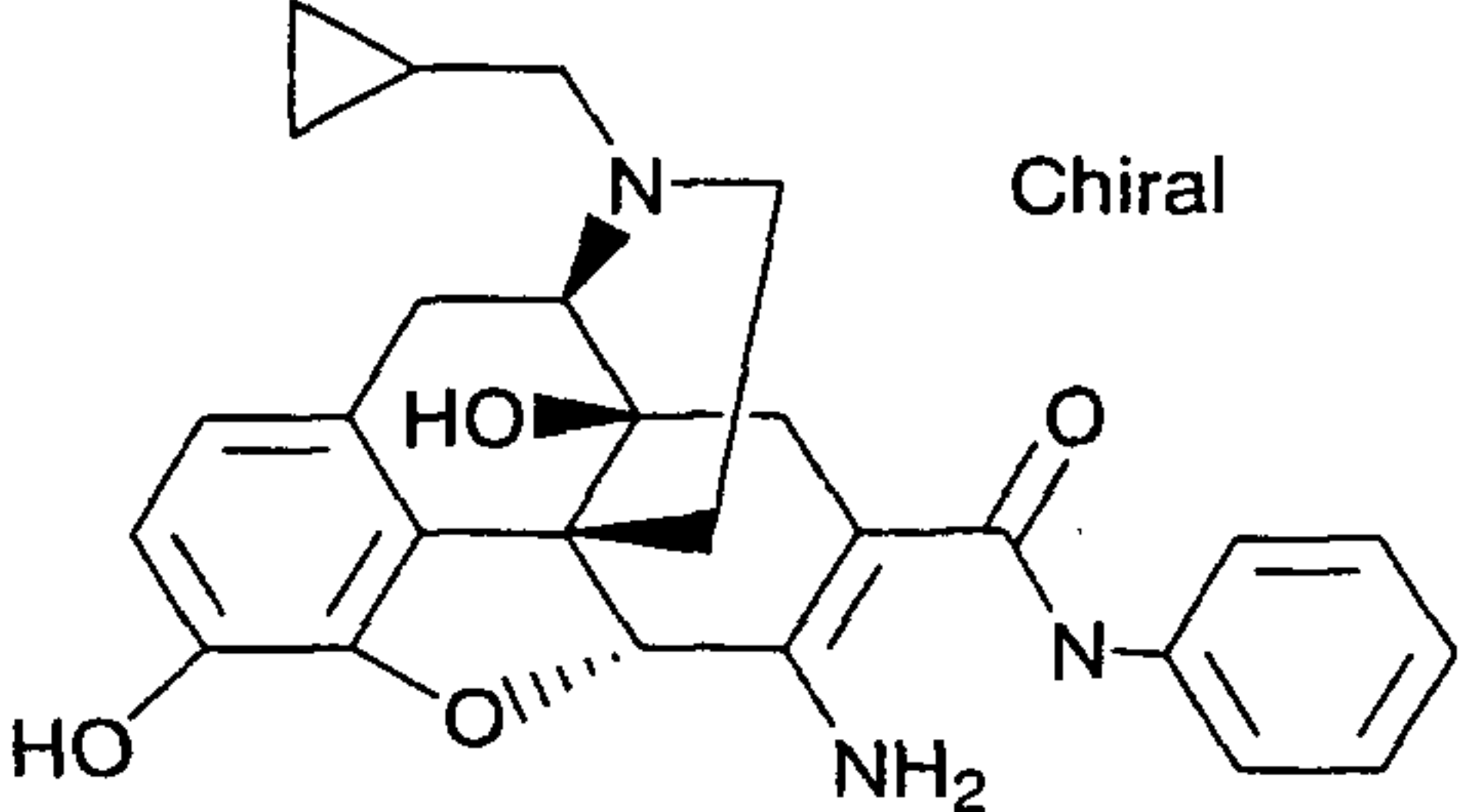
[0089]

[Table 44]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-172	Chiral 	m/z 505 [M+H]⁺ 0.97 min	0.11-0.13 (m, 2H), 0.46-0.50 (m, 2H), 0.84 (m, 1H), 0.98 (d, J = 3.1 Hz, 3H), 1.01 (d, J = 3.1 Hz, 3H), 1.37 (d, J = 10.8 Hz, 1H), 2.08 (d, J = 17.4 Hz, 1H), 2.11-2.24 (m, 2H), 2.35 (d, J = 6.6 Hz, 1H), 2.51-2.63 (m, 2H), 3.01 (d, J = 18.3 Hz, 1H), 3.13 (d, J = 5.7 Hz, 1H), 3.54 (s, 3H), 3.86 (q, J = 7.2 Hz, 1H), 4.79 (brs, 1H), 4.98 (brs, 1H), 5.76 (s, 1H), 6.54 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 9.16 (brs, 1H)
I-173	Chiral 	m/z 426 [M+H]⁺ 0.90 min	0.12-0.14 (m, 2H), 0.46-0.52 (m, 2H), 0.85 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.38 (d, J = 10.2 Hz, 1H), 1.86 (d, J = 15.0 Hz, 1H), 2.02 (d, J = 15.0 Hz, 1H), 2.10-2.17 (m, 2H), 2.28 (dd, J = 6.9, 6.9 Hz, 1H), 2.43 (dd, J = 6.9, 8.4 Hz, 1H), 2.54-2.62 (m, 2H), 3.01 (d, J = 18.3 Hz, 1H), 3.17 (d, J = 5.7 Hz, 1H), 3.58 (m, 1H), 3.88 (q, J = 7.2 Hz, 1H), 4.62 (brs, 1H), 4.68 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.94 (brs, 1H), 9.06 (brs, 1H)
I-174	Chiral 		(CD₃OD) δ: 0.10-0.25 (m, 2H), 0.48-0.63 (m, 2H), 0.83-1.00 (m, 1H), 1.55 (d, J = 8.1 Hz, 1H), 2.01 (d, J = 15.6 Hz, 1H), 2.22-2.57 (m, 6H), 2.70 (d.d, J = 18.3 & 7.2 Hz, 2H), 3.12 (d, J = 18.3 Hz, 1H), 4.67 (s, 1H), 6.44-6.62 (m, 3H), 7.54 (d.d, J = 9.6 & 3.6 Hz, 1H), 8.00 (d, J = 3.6 Hz, 1H).

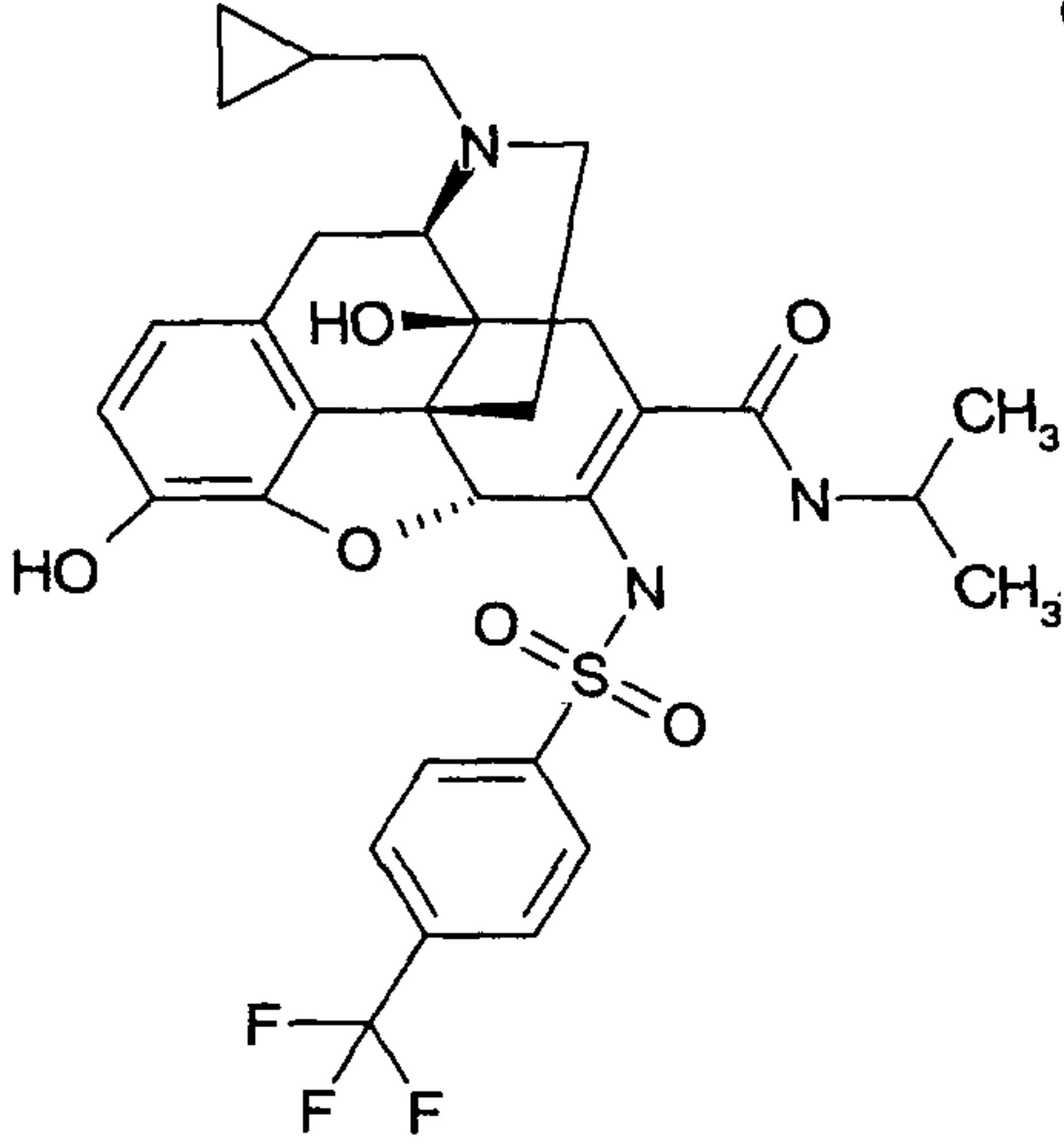
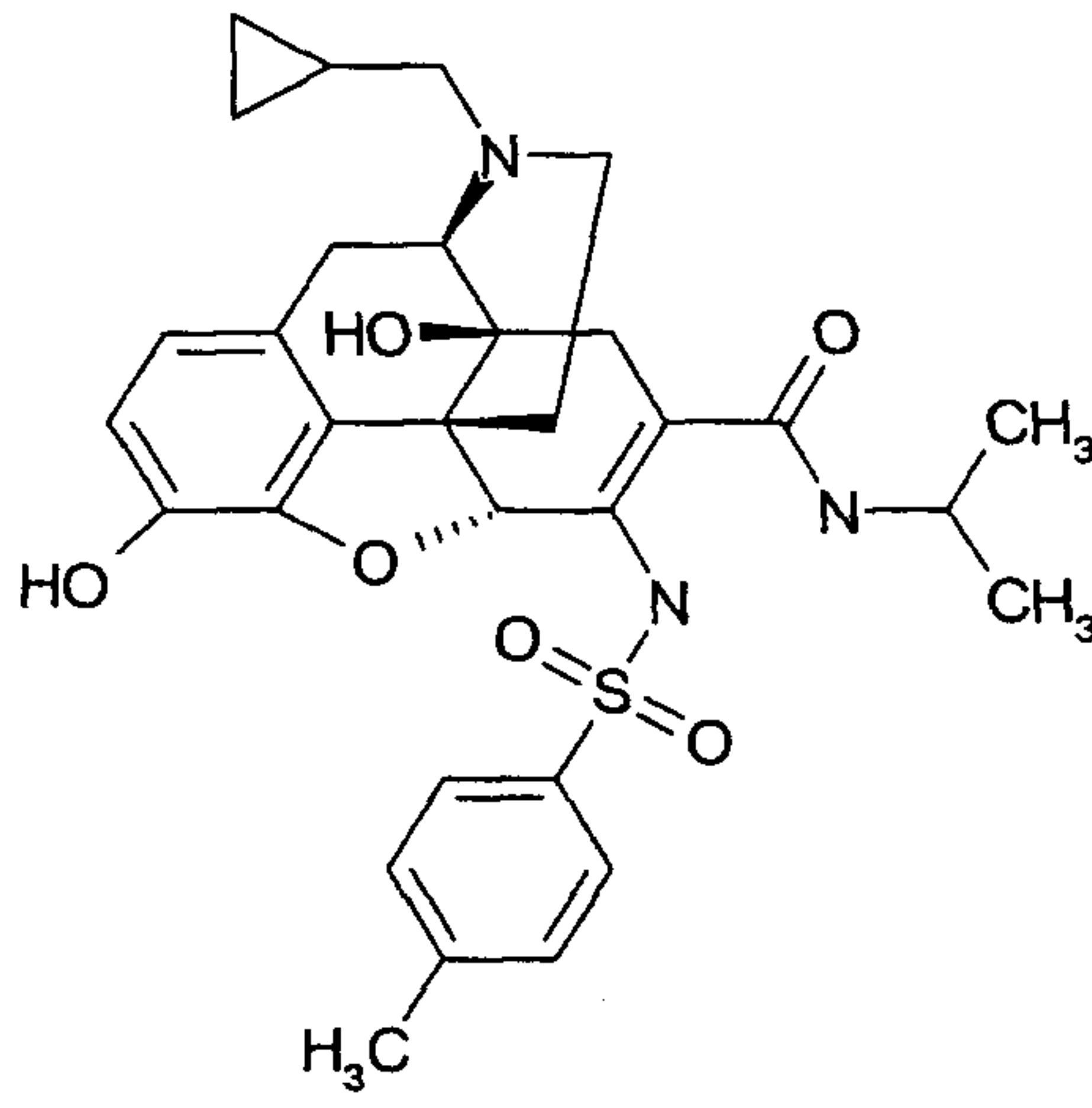
[0090]

[Table 45]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-175		m/z 458 [M+H] ⁺ 0.86 min	
I-176		ESI : m/z 458 [M+H] ⁺	
I-177		m/z 460 [M+H] ⁺ 1.20 min	0.13-0.17 (m, 2H), 0.47-0.50 (m, 2H), 0.87 (m, 1H), 1.41 (d, J = 10.5 Hz, 1H), 2.07 (d, J = 15.0 Hz, 1H), 2.10-2.25 (m, 2H), 2.32 (dd, J = 5.7, 6.9 Hz, 1H), 2.45 (dd, J = 5.7, 6.0 Hz, 1H), 2.63 (dt, J = 6.3, 11.7, 2H), 3.05 (d, J = 18.3 Hz, 1H), 3.19 (d, J = 6.0 Hz, 1H), 4.67 (brs, 1H), 4.75 (s, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 3.6 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 8.38 (brs, 1H), 9.07 (brs, 1H)

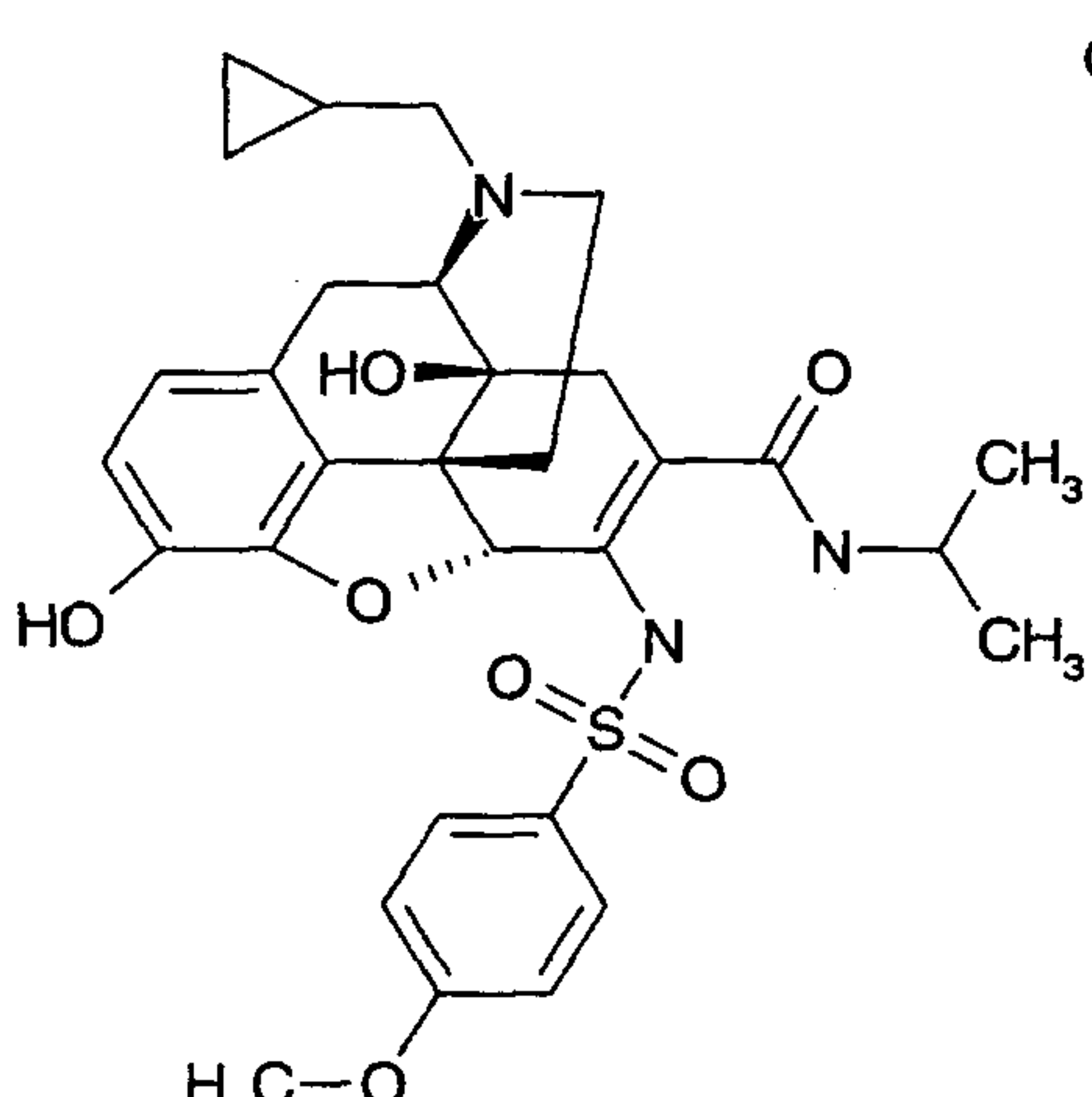
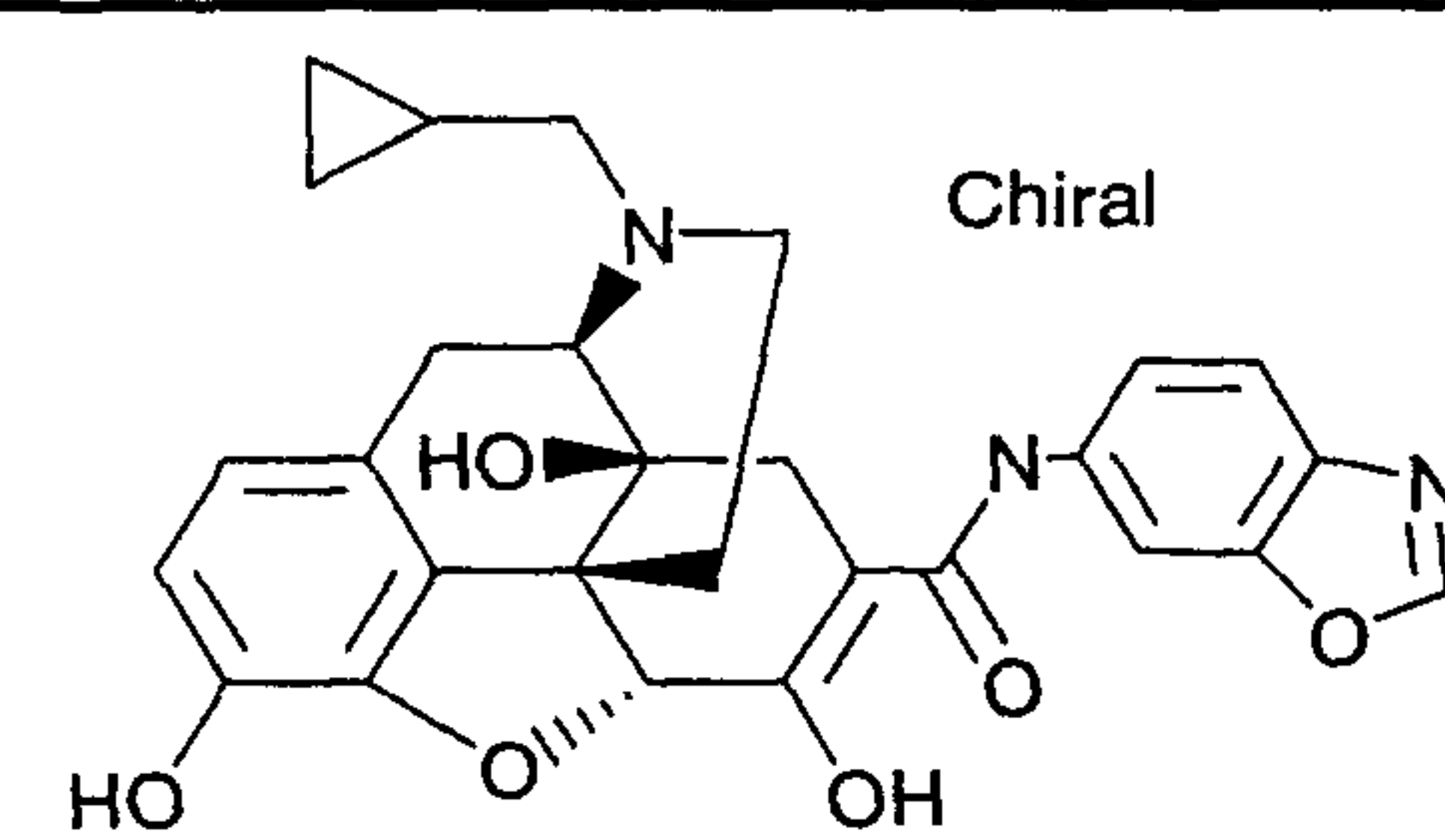
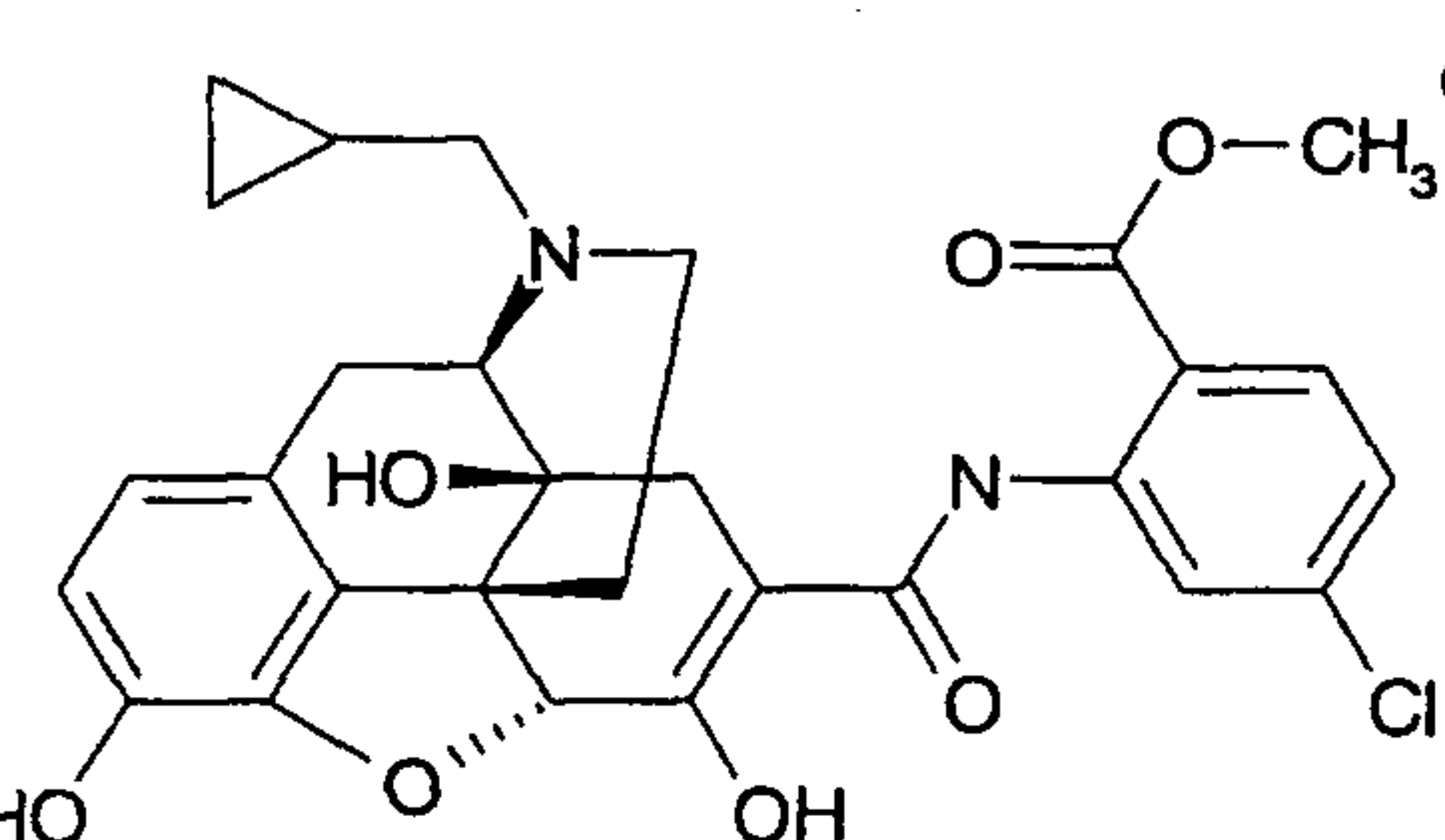
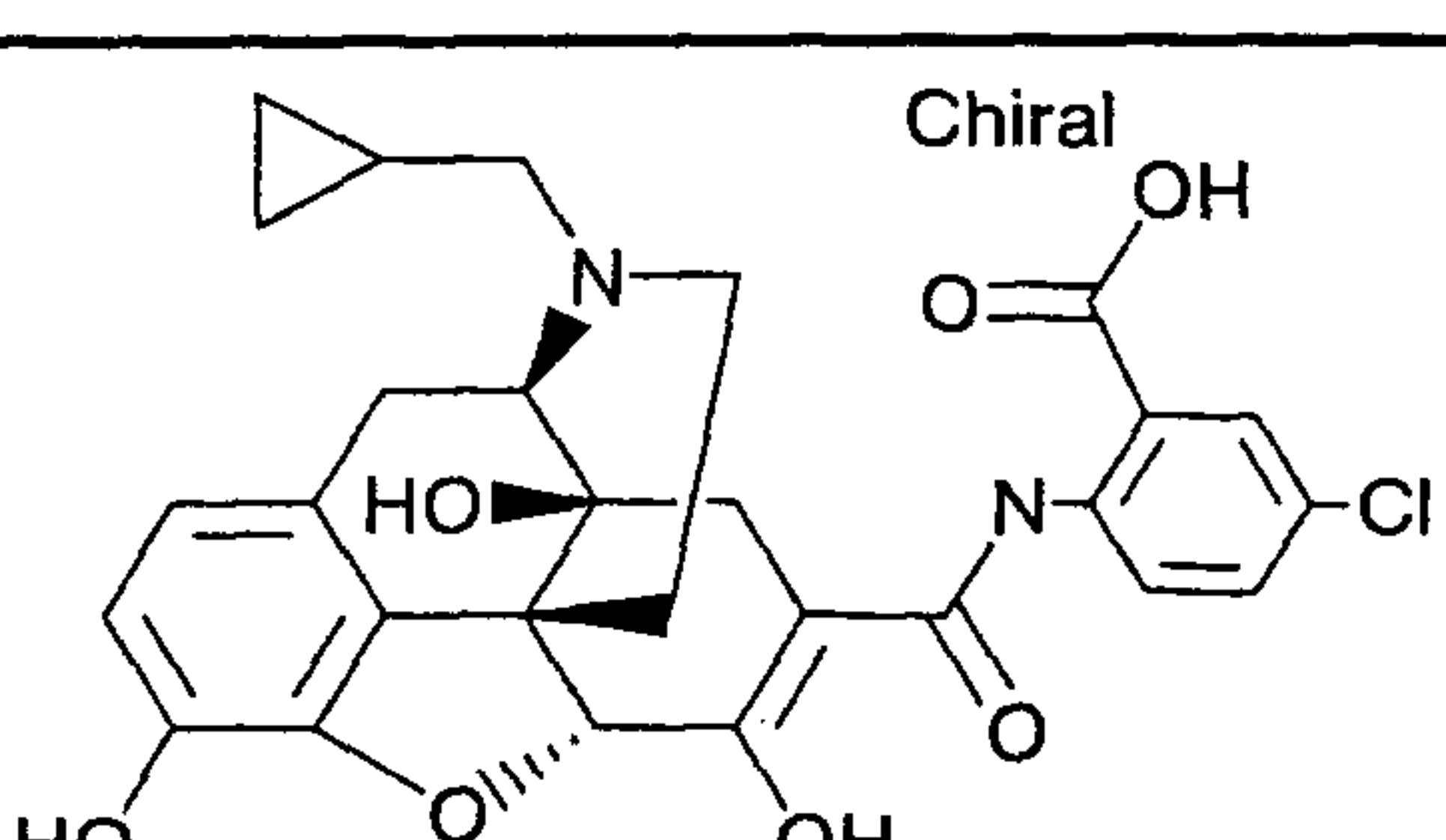
[0091]

[Table 46]

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

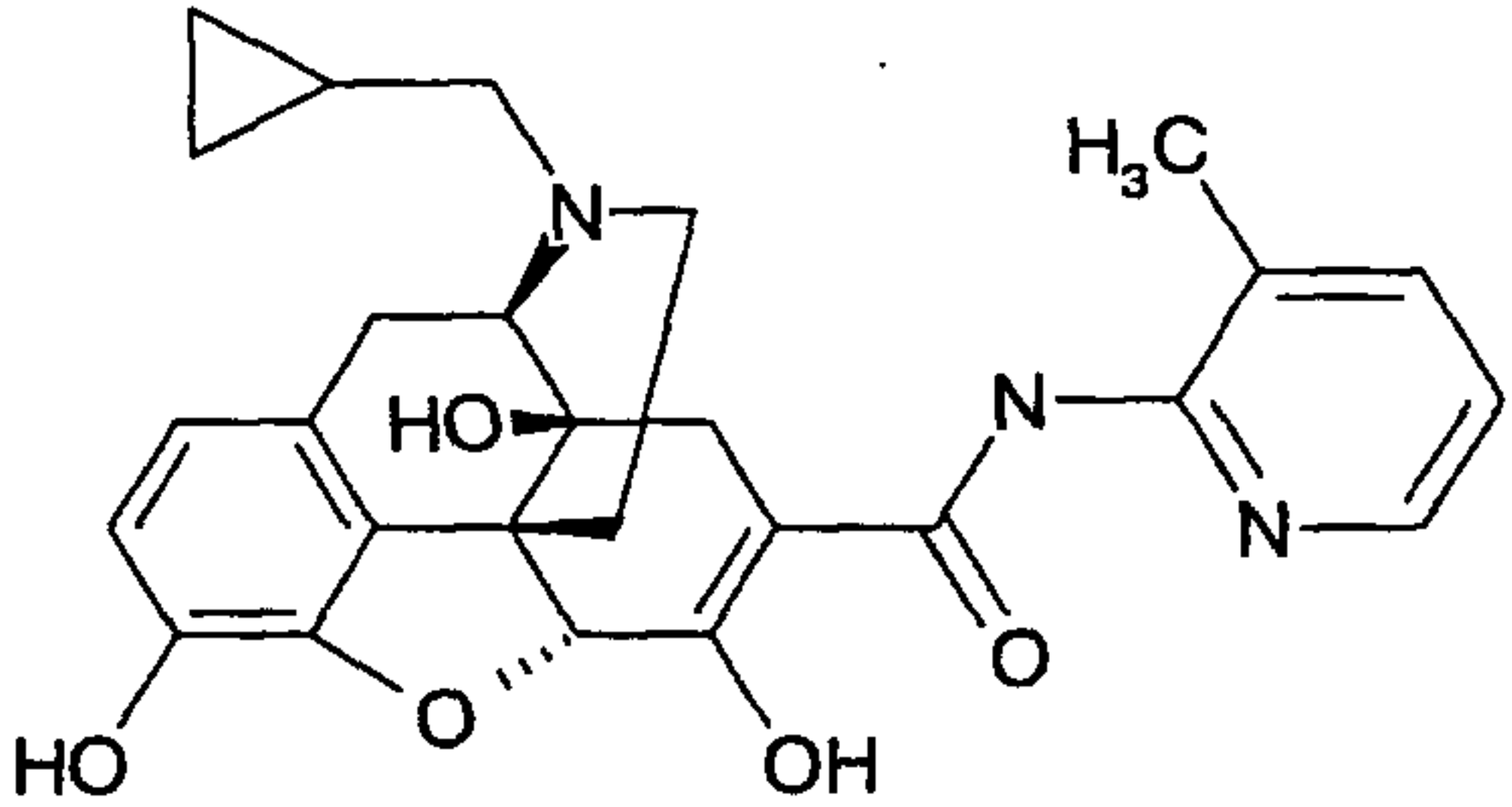
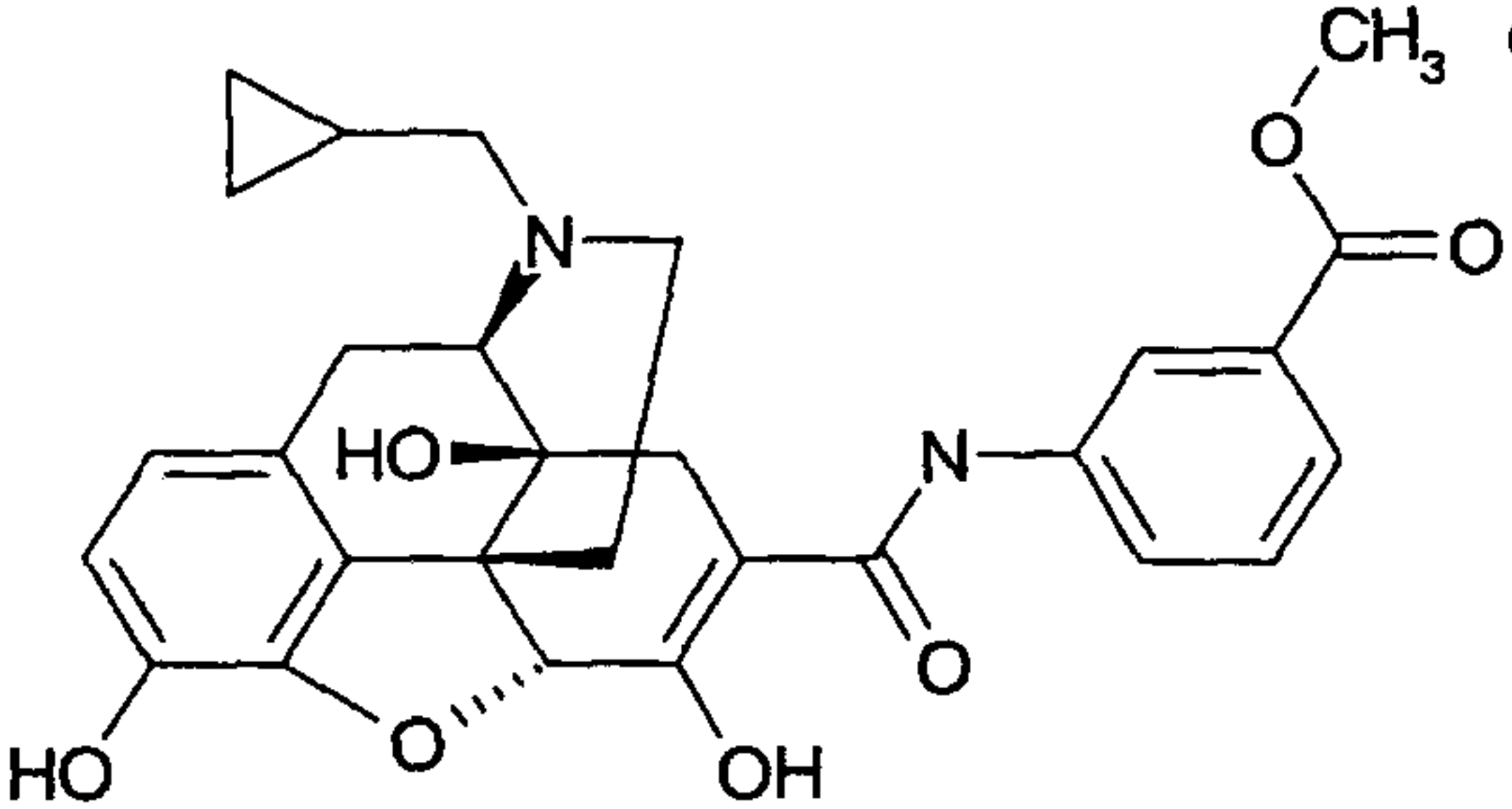
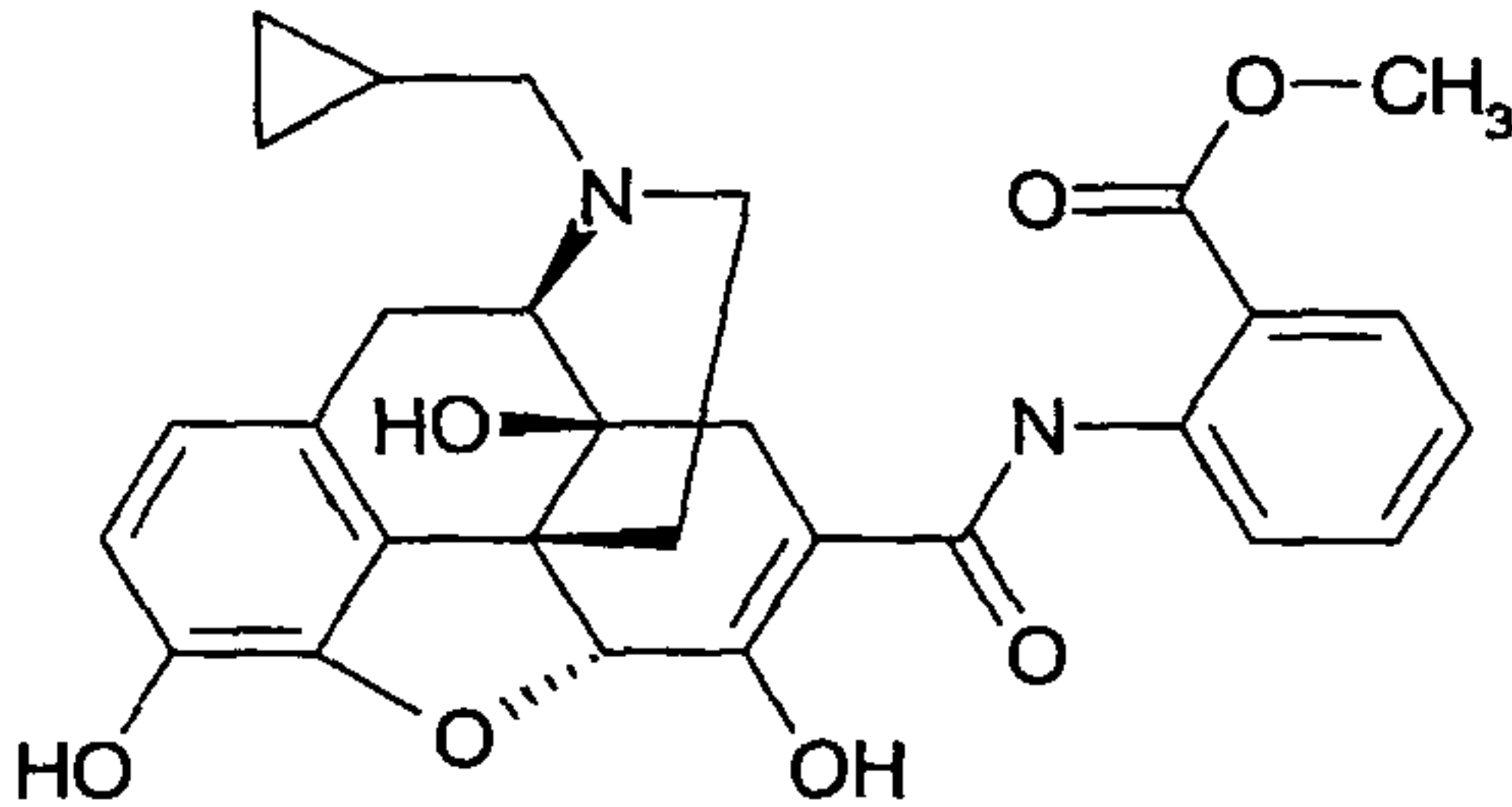
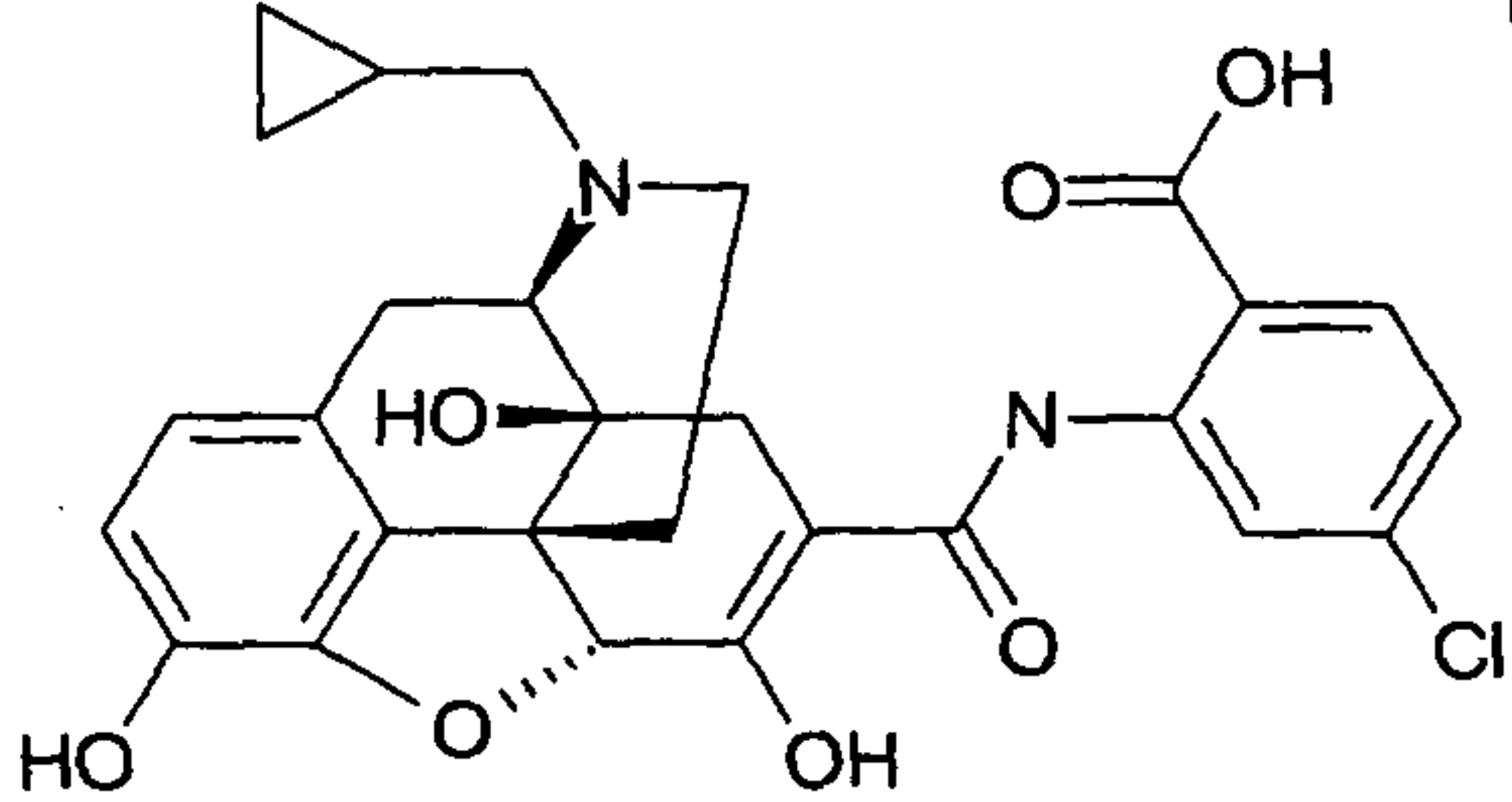
[0092]

[Table 47]

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

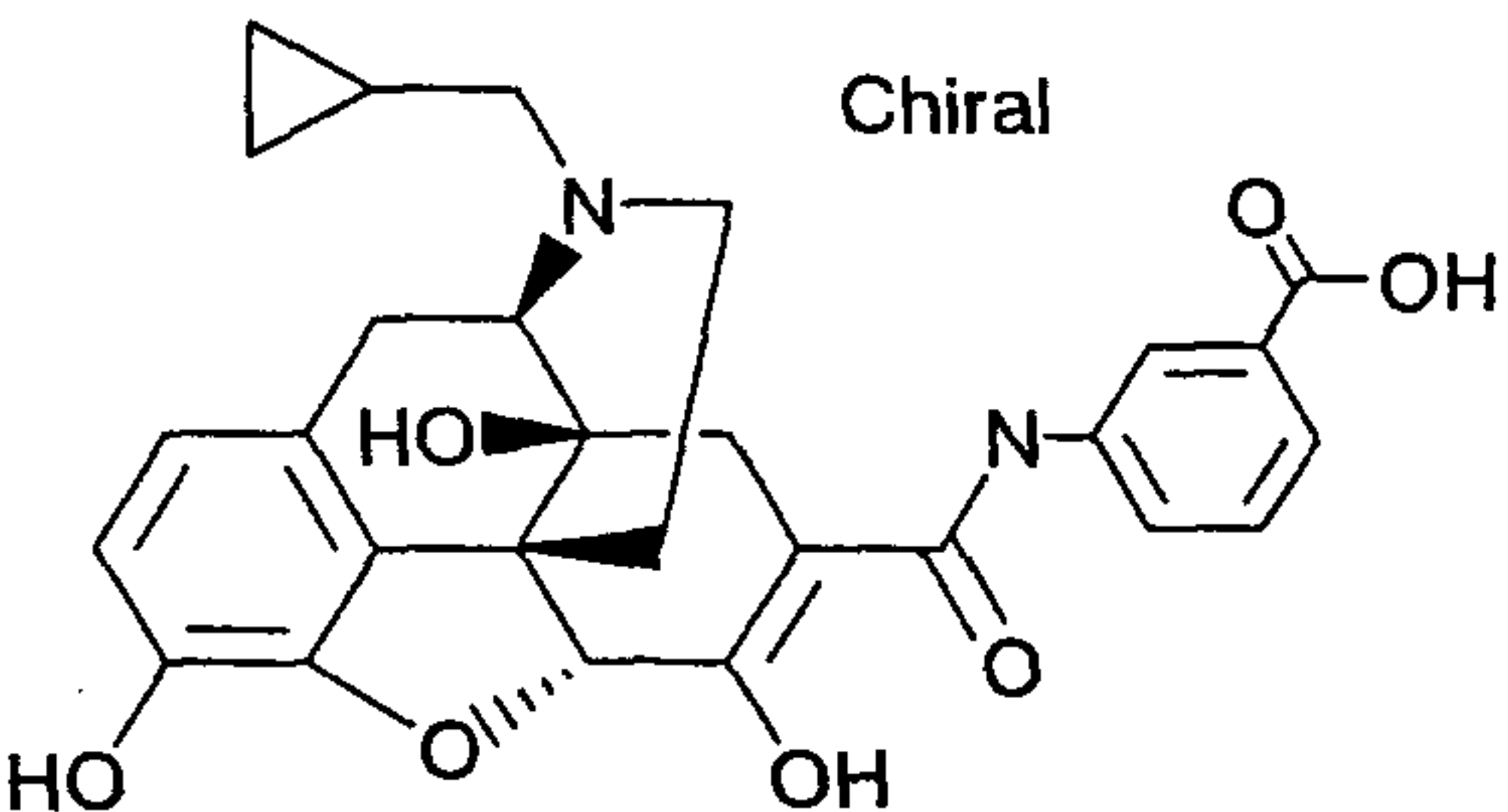
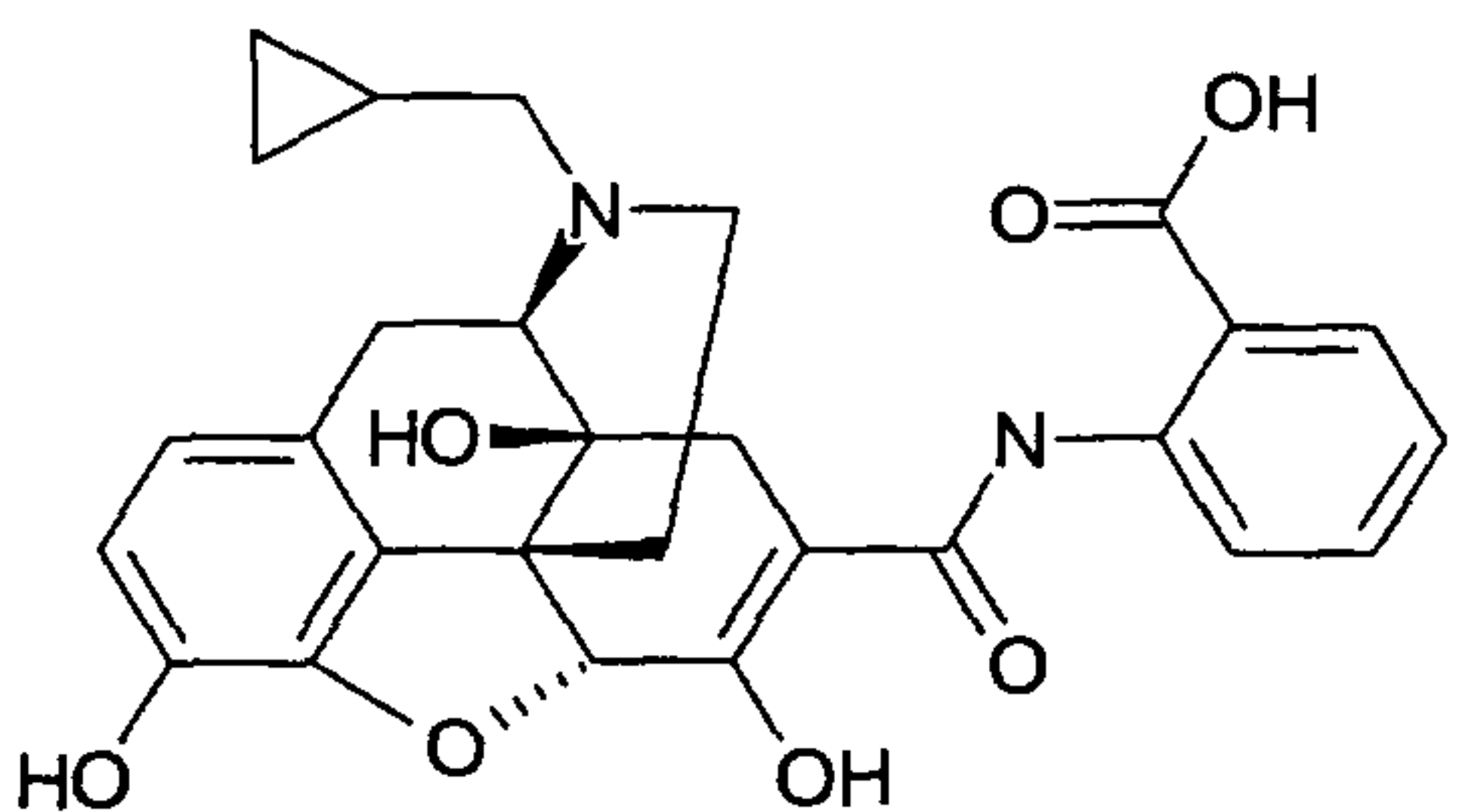
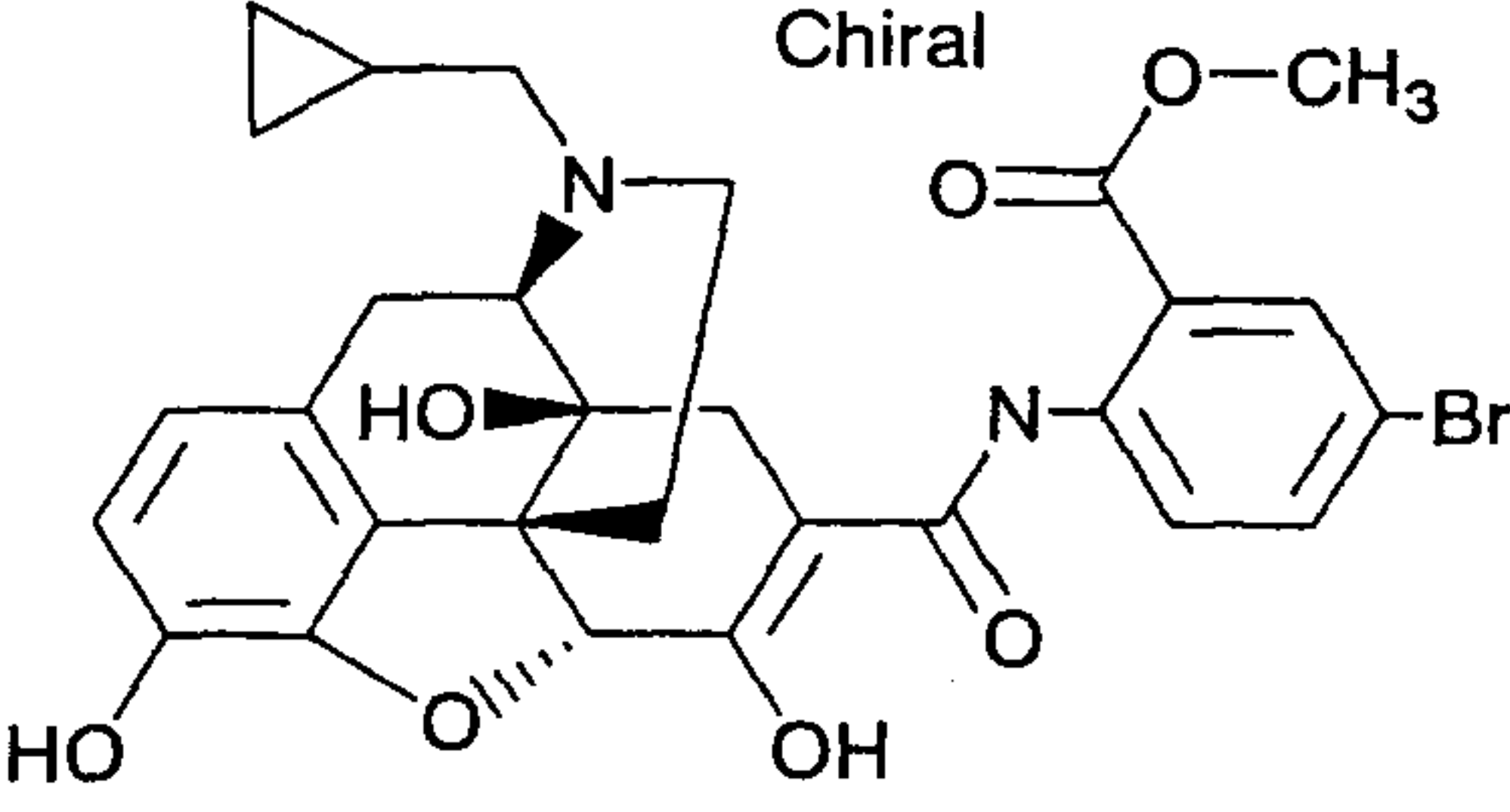
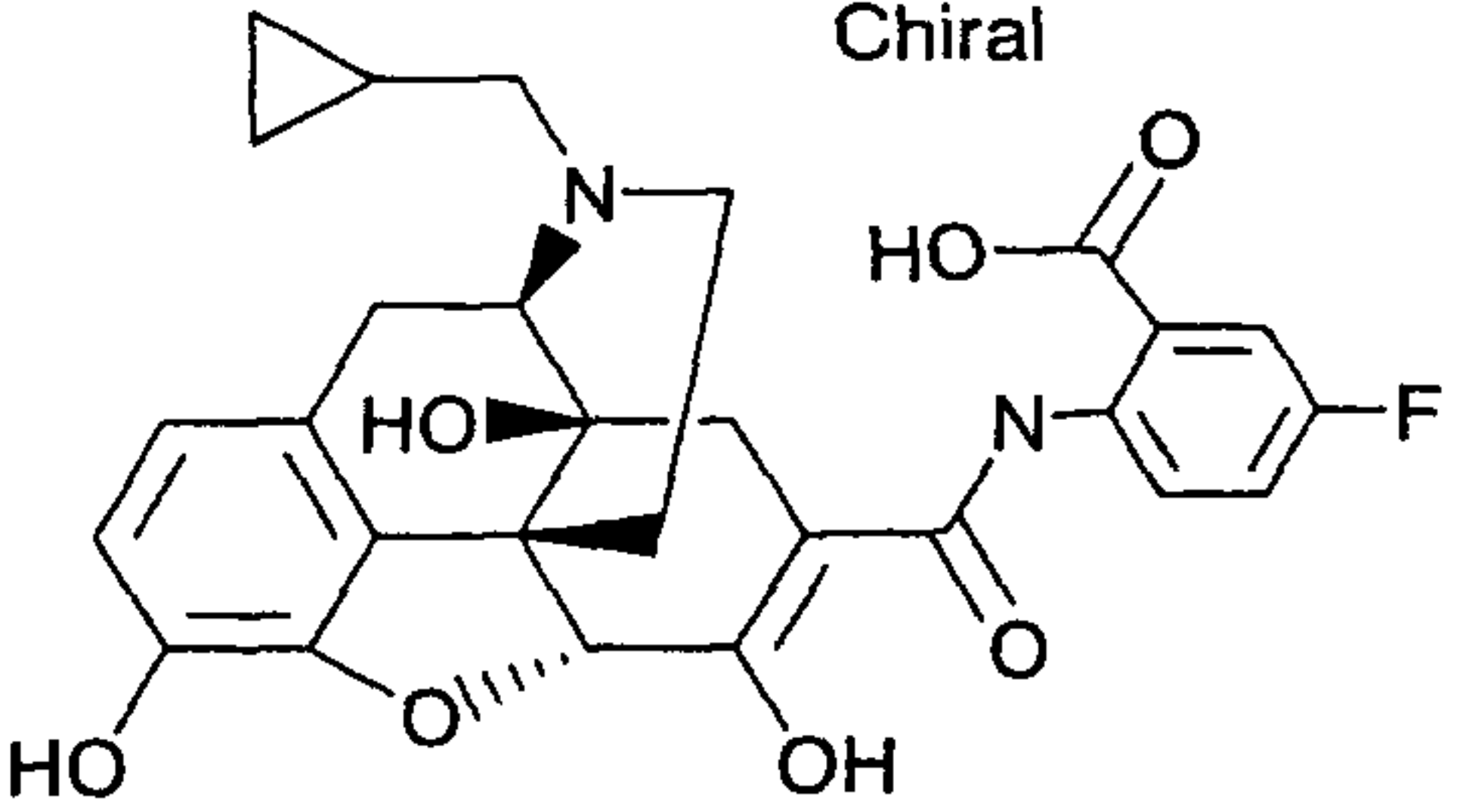
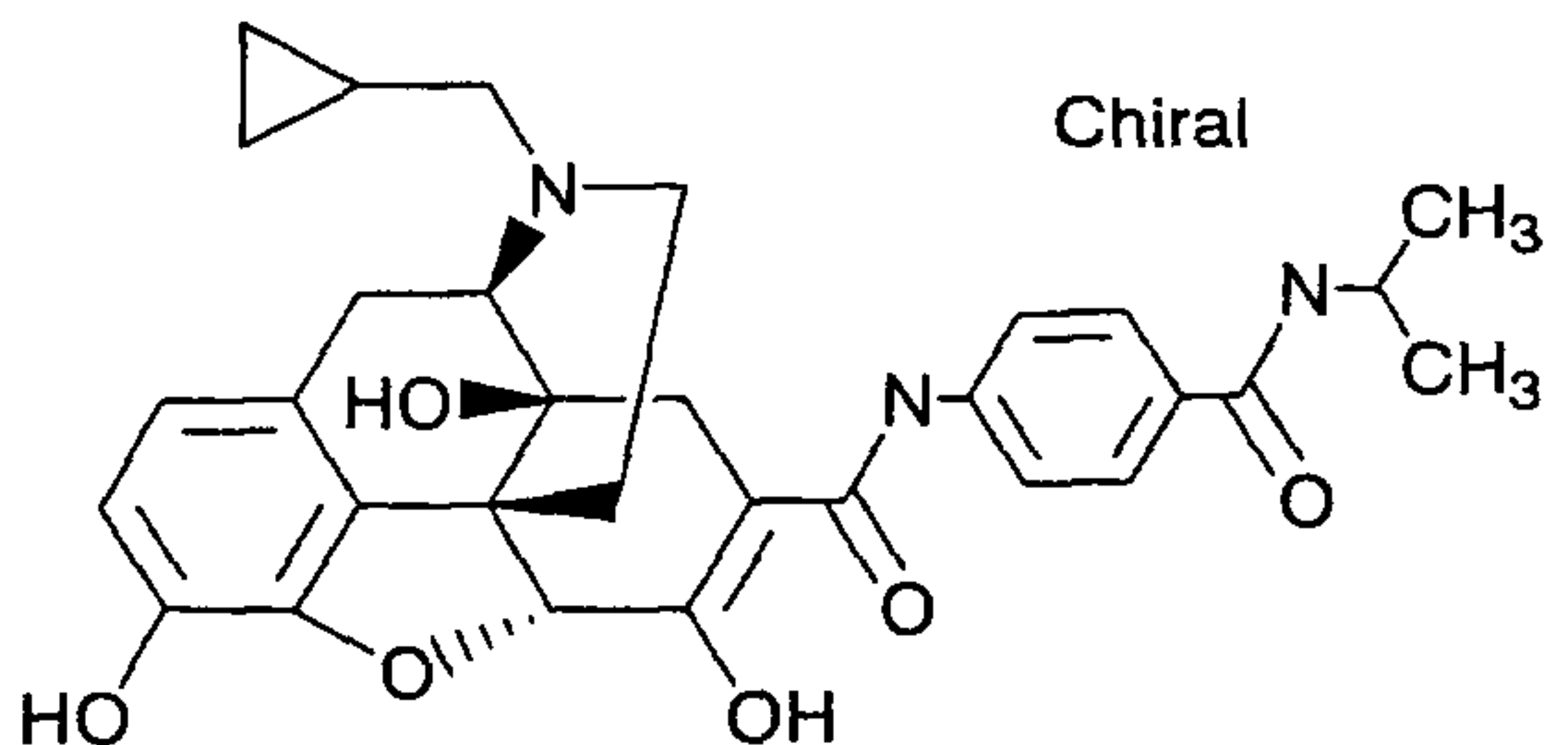
[0093]

[Table 48]

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

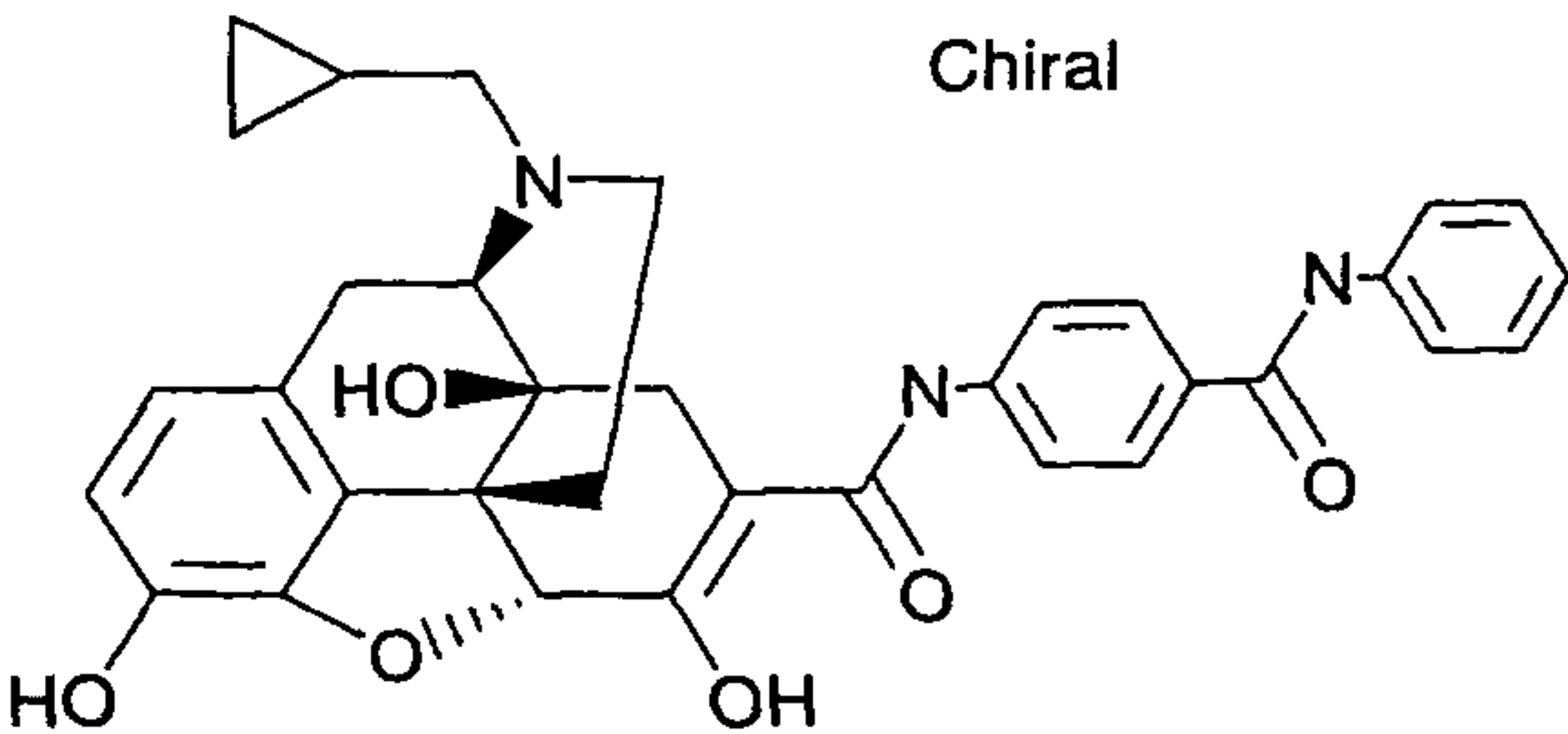
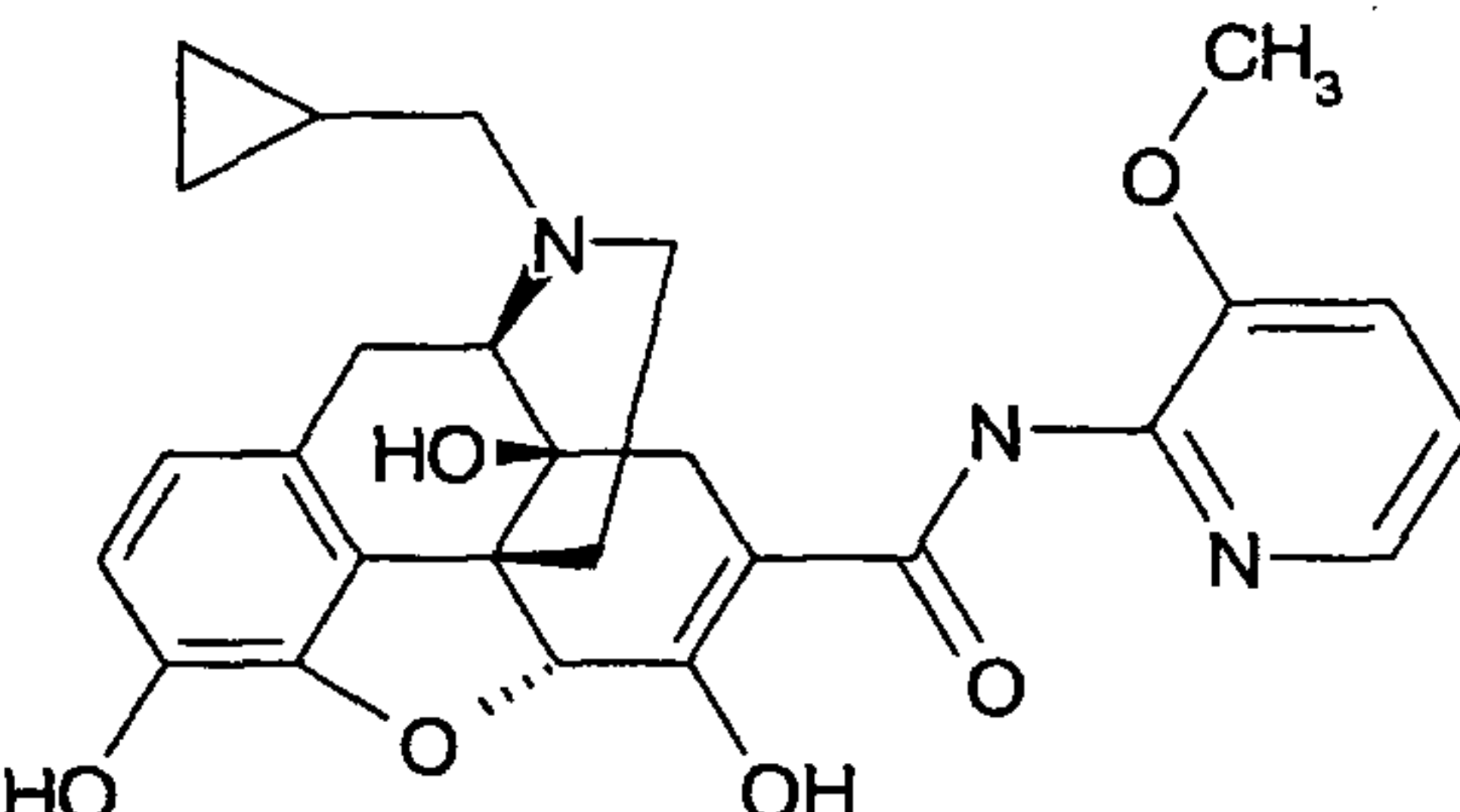
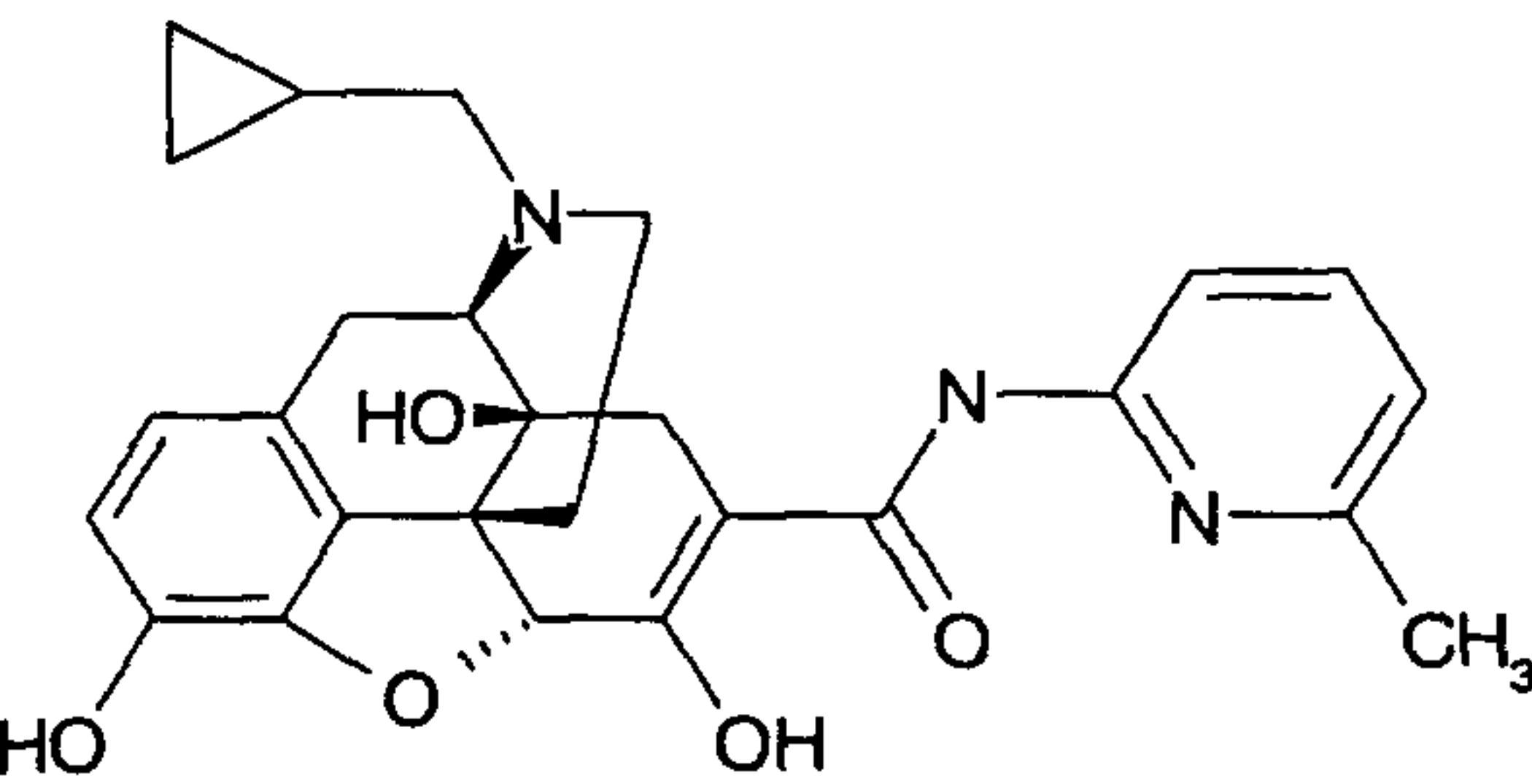
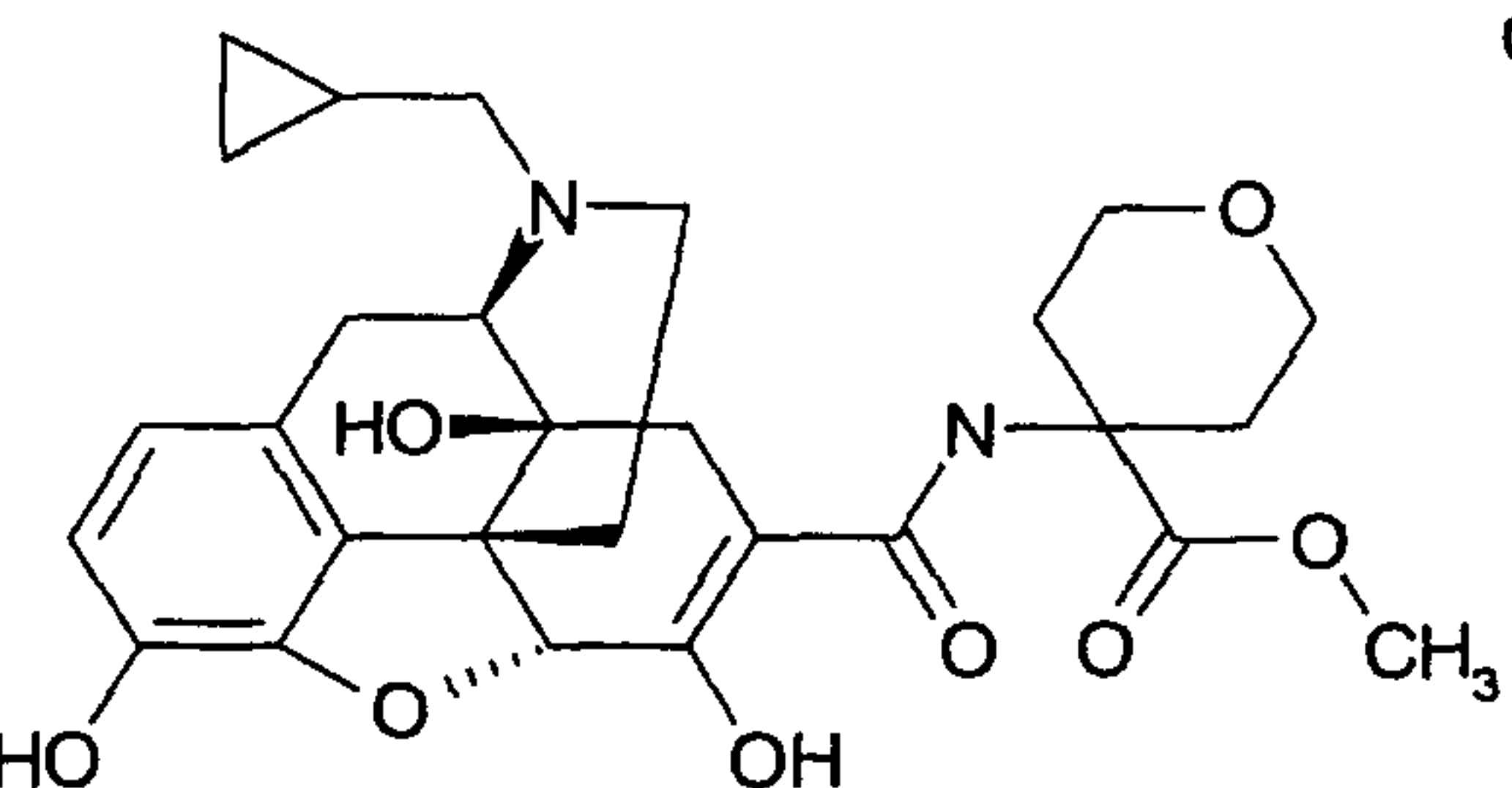
[0094]

[Table 49]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-188	 Chiral	m/z 505 [M+H] ⁺ 0.35 min	
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	

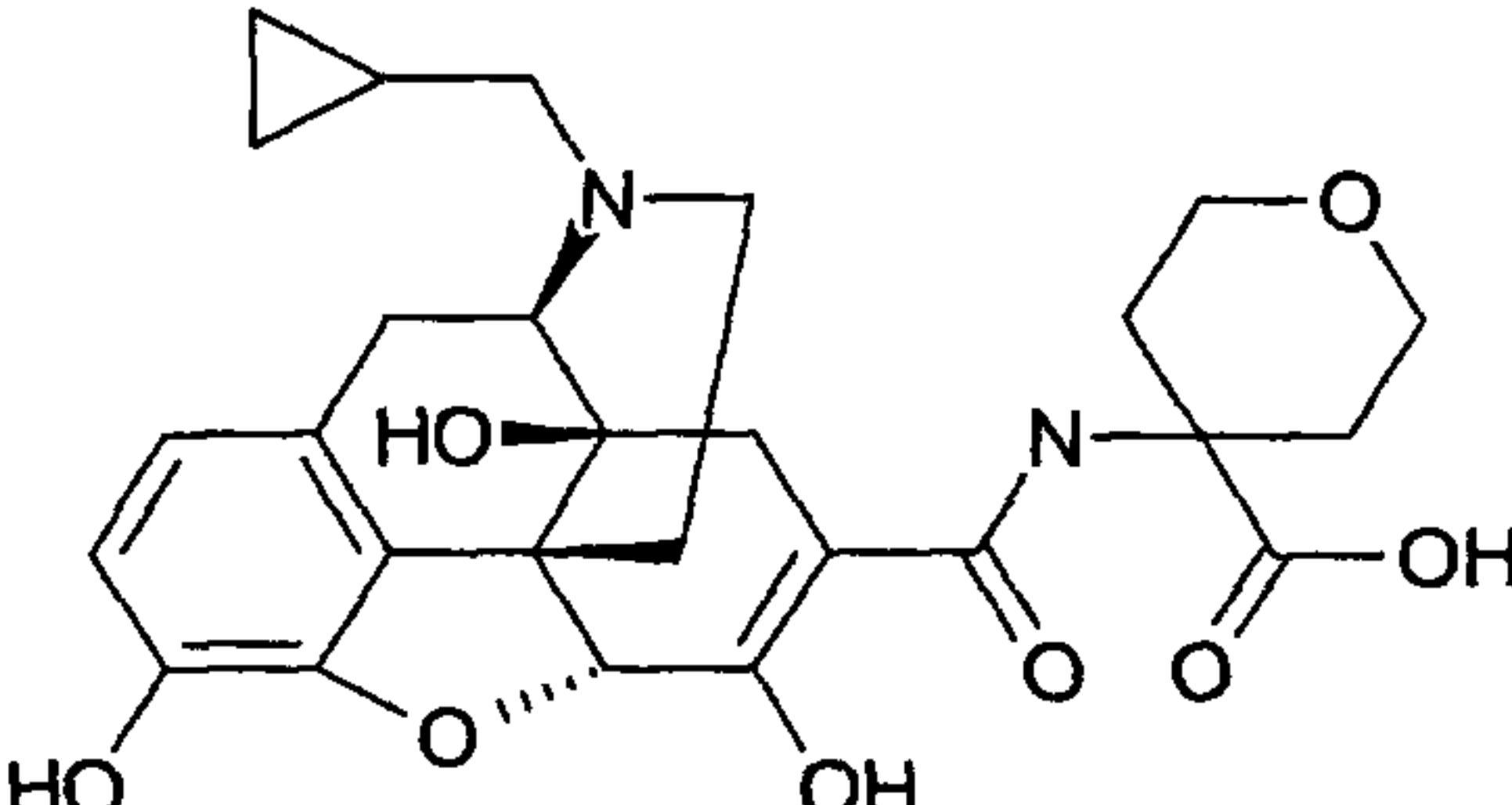
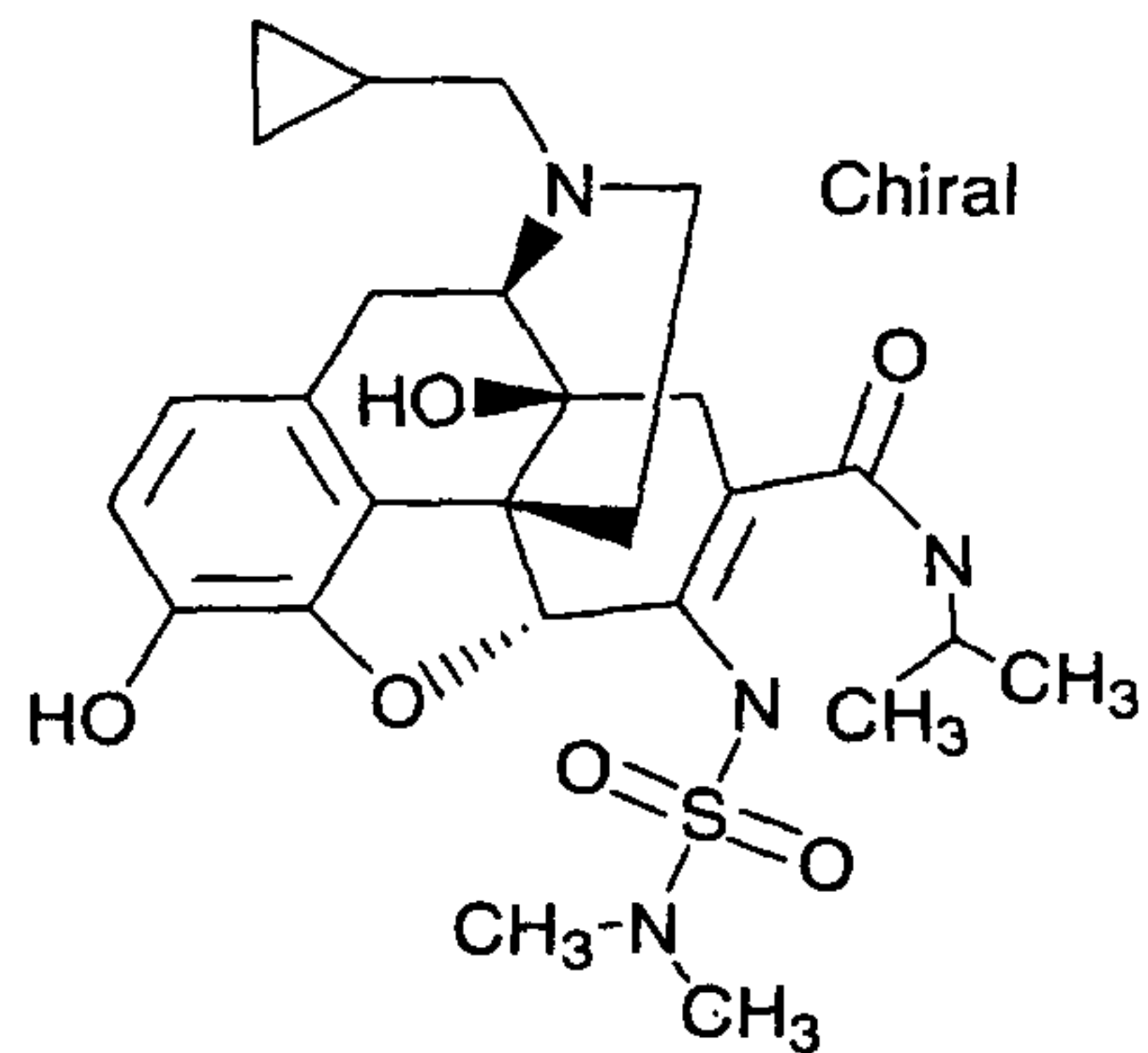
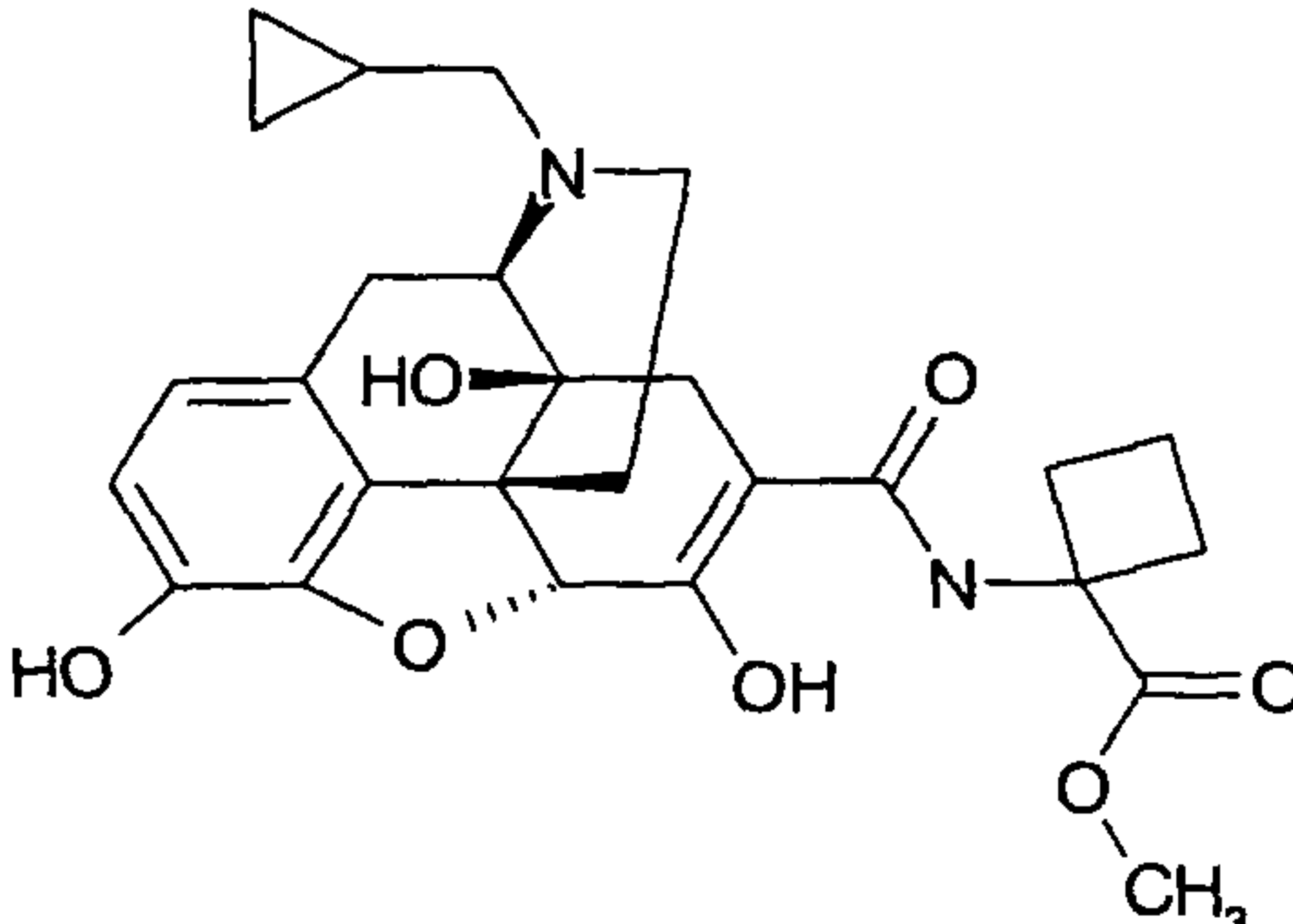
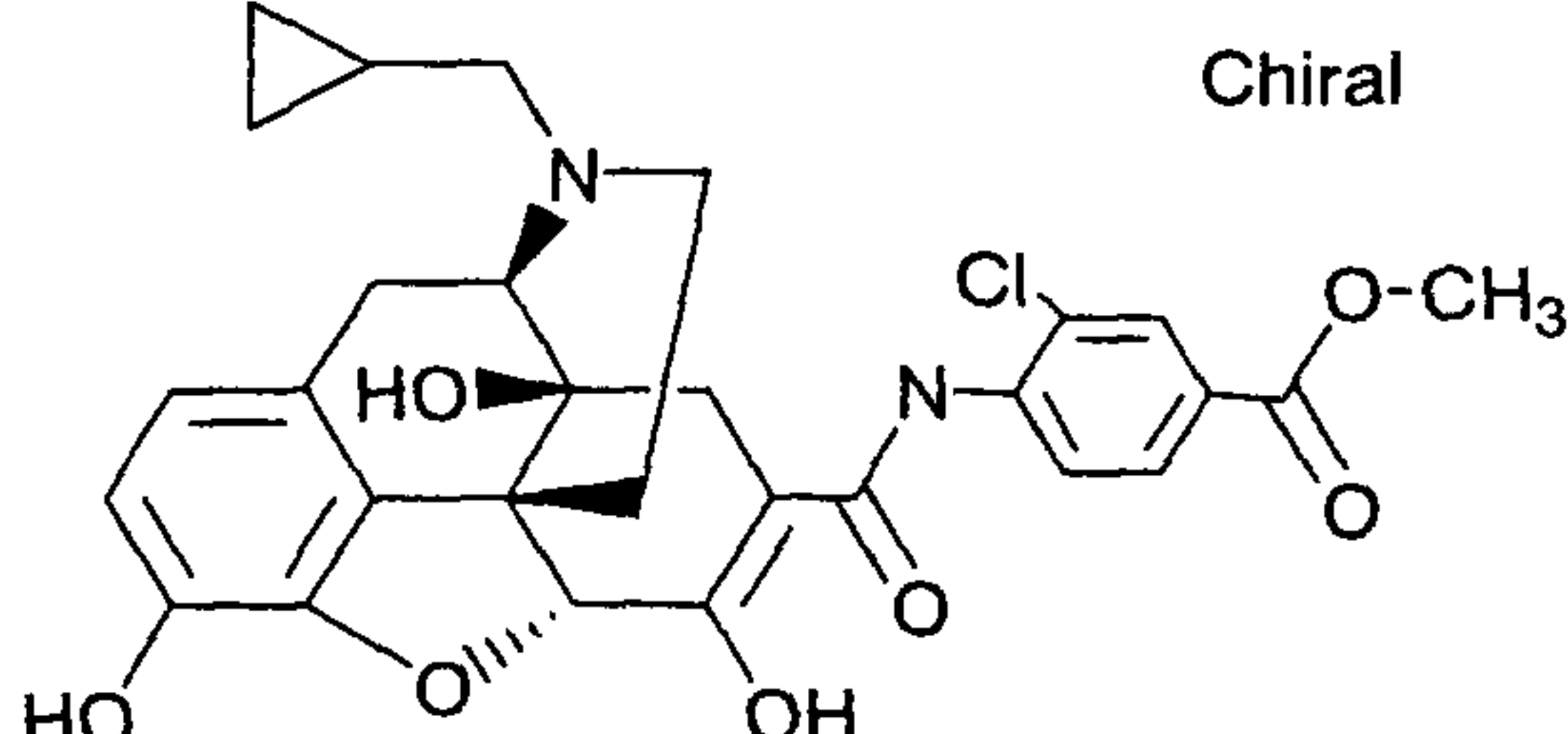
[0095]

[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	
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, 2H), 0.46-0.55 (m, 2H), 0.88 (m, 1H), 1.43 (d, J = 12.4 Hz, 1H), 1.65-2.65 (m, 12H), 2.97-3.70 (m, 6H), 3.59 (s, 3H), 4.74 (s 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 7.68 (brs, 1H), 9.16 (brs, 1H), 13.6 (brs, 1H)

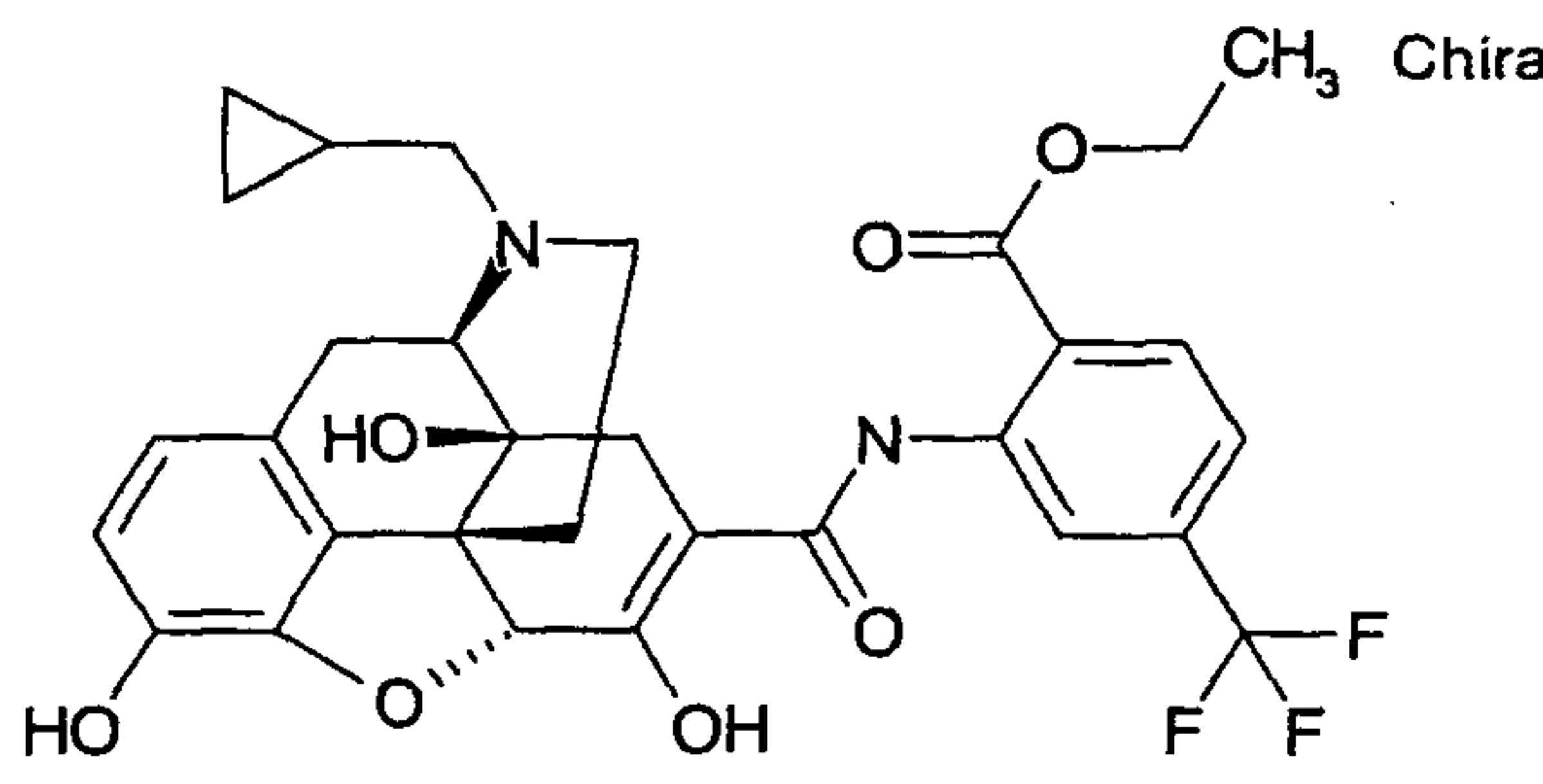
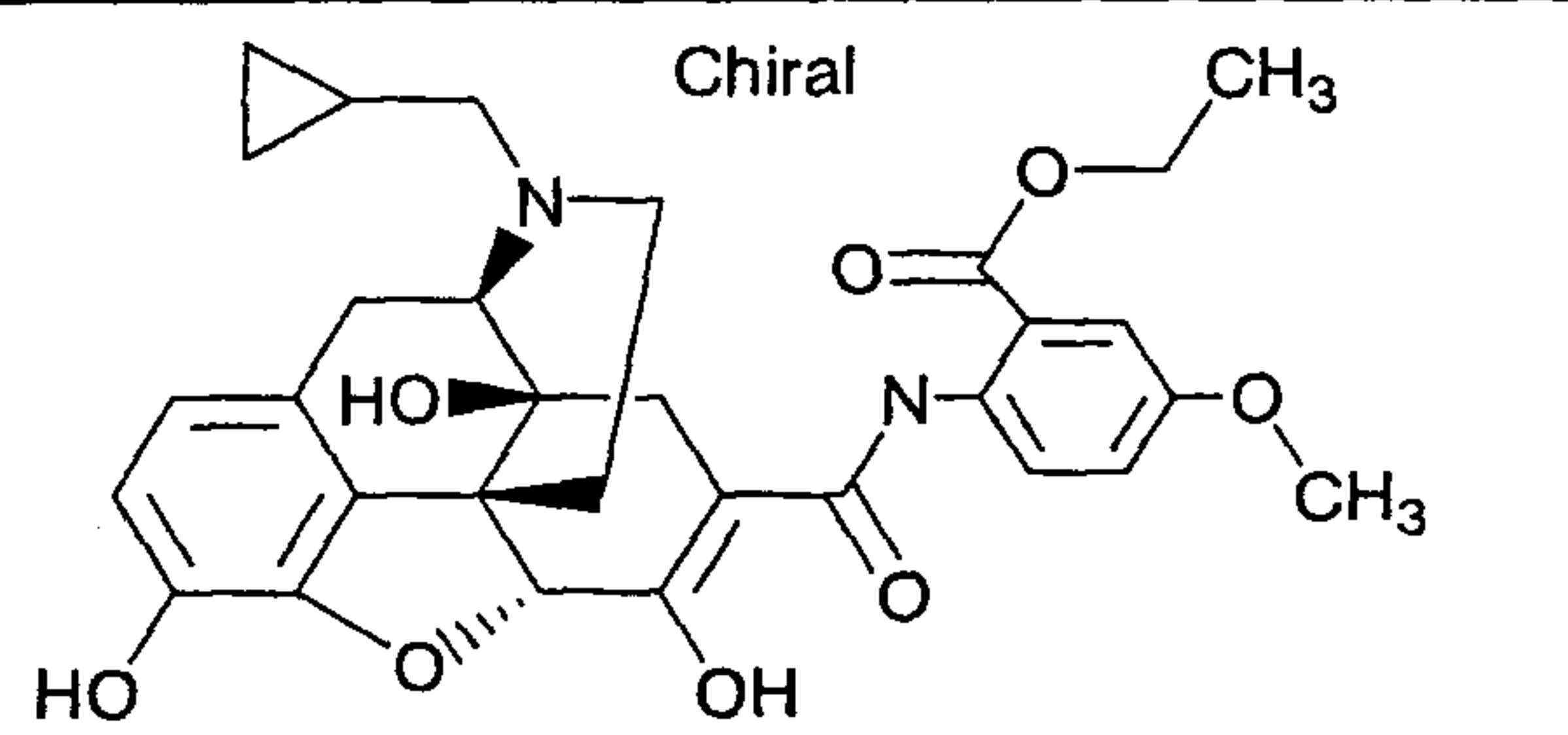
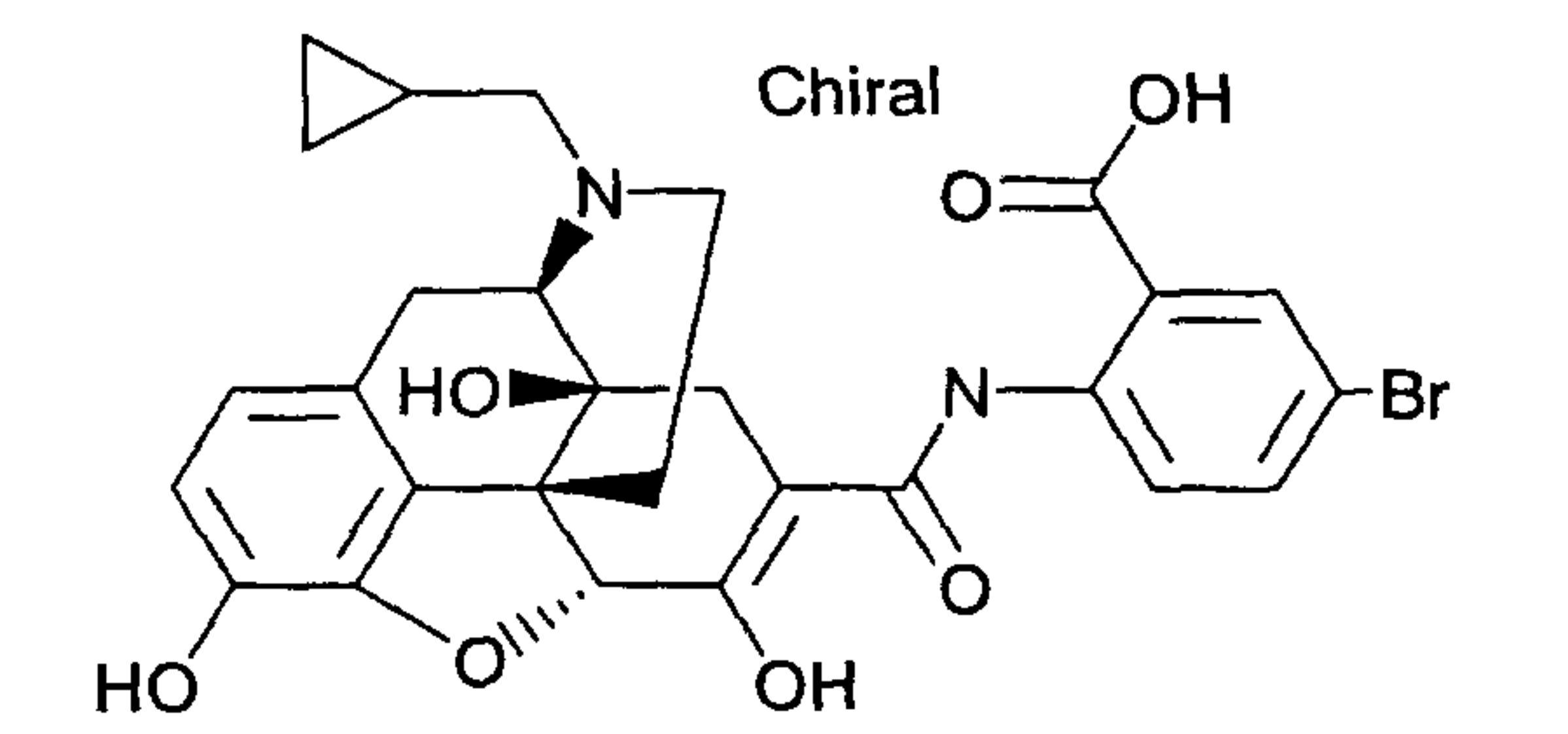
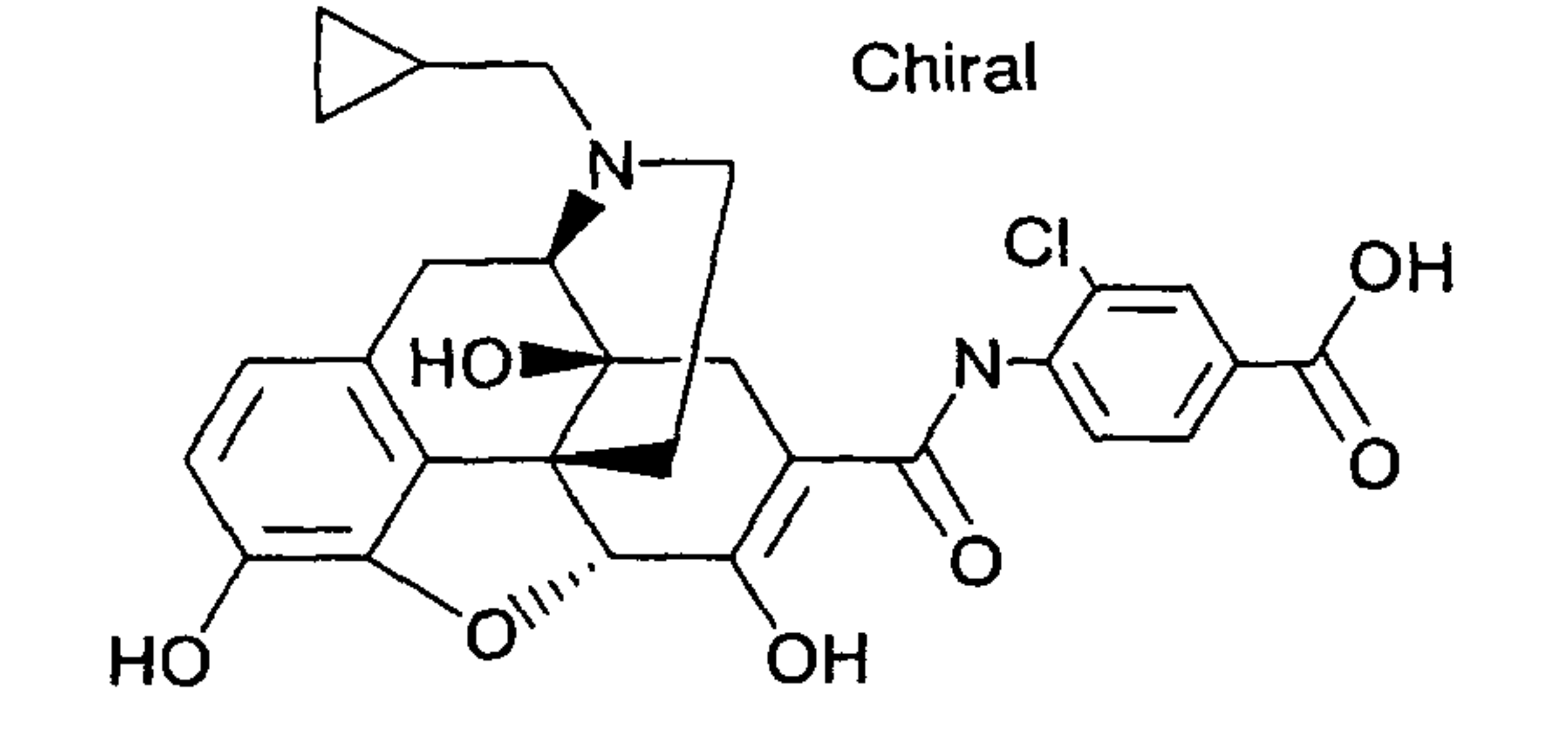
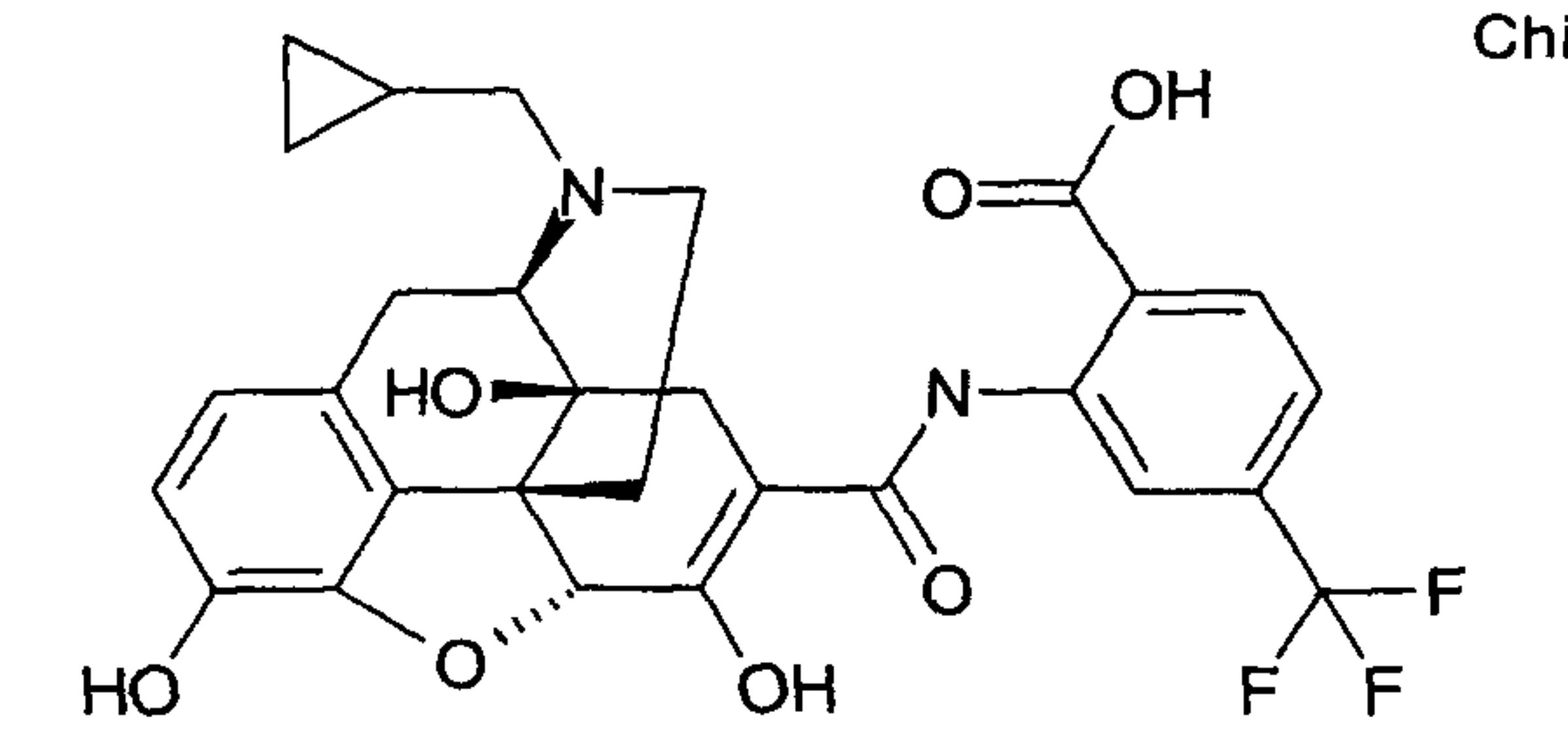
[0096]

[Table 51]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d6-DMSO) δ)
I-197	Chiral 		0.20–0.40 (m, 2H), 0.46–0.65 (m, 2H), 0.97 (m, 1H), 1.54 (d, J = 6.8 Hz, 1H), 1.80–2.10 (m, 3H), 2.31–3.69 (m, 15H), 4.83 (s, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 7.56 (brs, 1H), 9.29 (brs, 1H), 13.6 (brs, 1H)
I-198	Chiral 	m/z 533 [M+H] ⁺ 0.95 min	0.11–0.13 (m, 2H), 0.46–0.52 (m, 2H), 0.86 (m, 1H), 1.03 (d, J = 6.3 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 1.46 (brd, J = 8.4 Hz, 1H), 1.94 (d, J = 17.7 Hz, 1H), 2.71–2.60 (m, 7H), 2.81 (s, 6H), 3.04 (d, J = 17.1 Hz, 1H), 3.18 (brs, 1H), 3.95 (q, J = 5.4 Hz, 1H), 4.77 (brs, 1H), 5.45 (s, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 7.5 Hz, 1H), 7.64 (brs, 1H), 9.14 (brs, 1H), 12.2 (brs, 1H)
I-199	Chiral 	m/z 497 [M+H] ⁺ 0.97 min	0.13–0.15 (m, 2H), 0.48–0.52 (m, 2H), 0.86 (m, 1H), 1.41 (d, J = 11.4 Hz, 1H), 1.85 (t, J = 7.8 Hz, 2H), 1.93 (d, J = 16.5 Hz, 1H), 2.07–2.62 (m, 11H), 3.05 (d, J = 18.3 Hz, 1H), 3.21 (d, J = 6.0 Hz, 1H), 3.59 (s, 3H), 4.72 (s, 1H), 4.77 (brs, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 8.26 (brs, 1H), 9.15 (brs, 1H), 14.1 (brs, 1H)
I-200	Chiral 	m/z 553 [M+H] ⁺ 0.47 min	

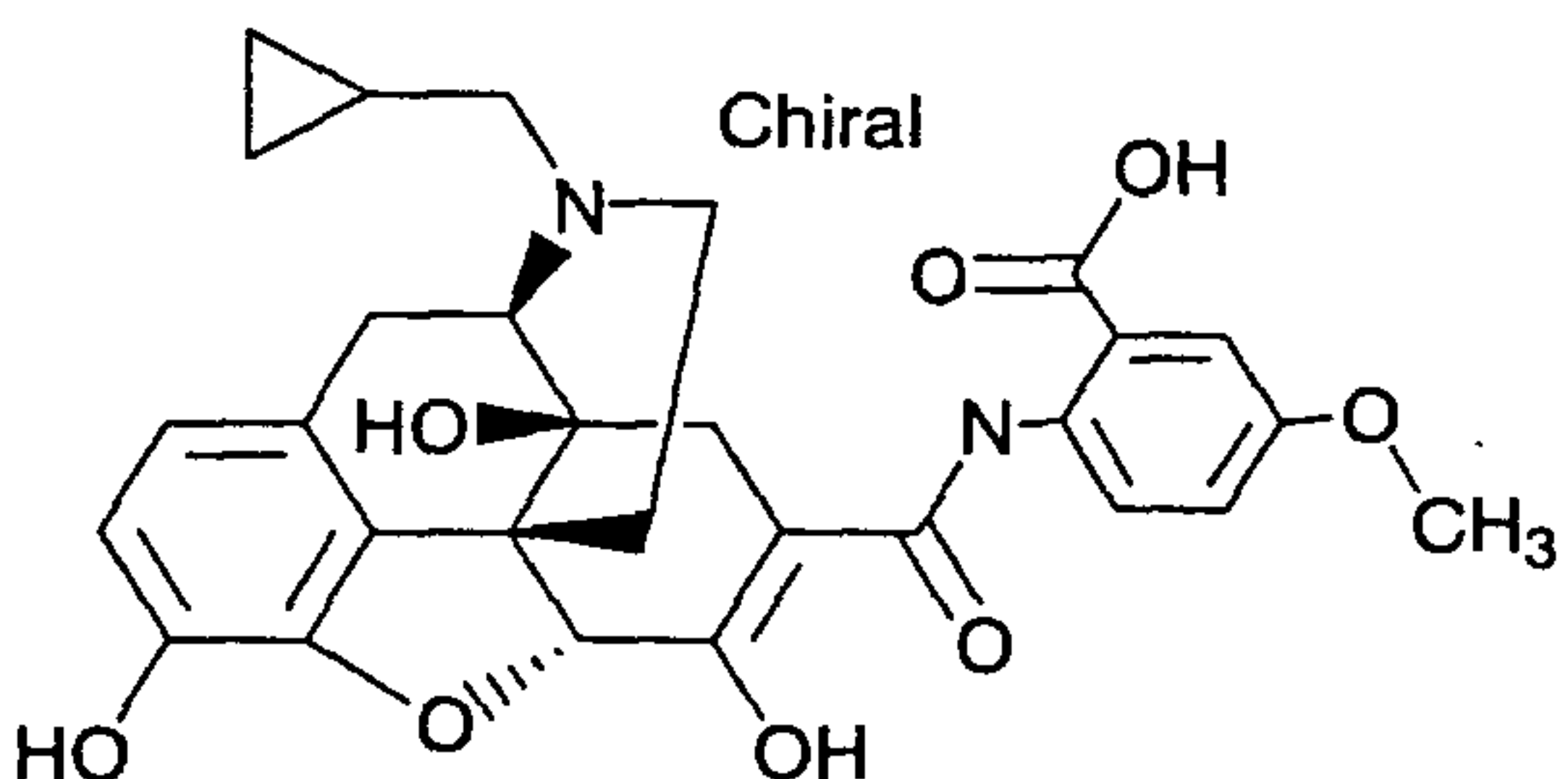
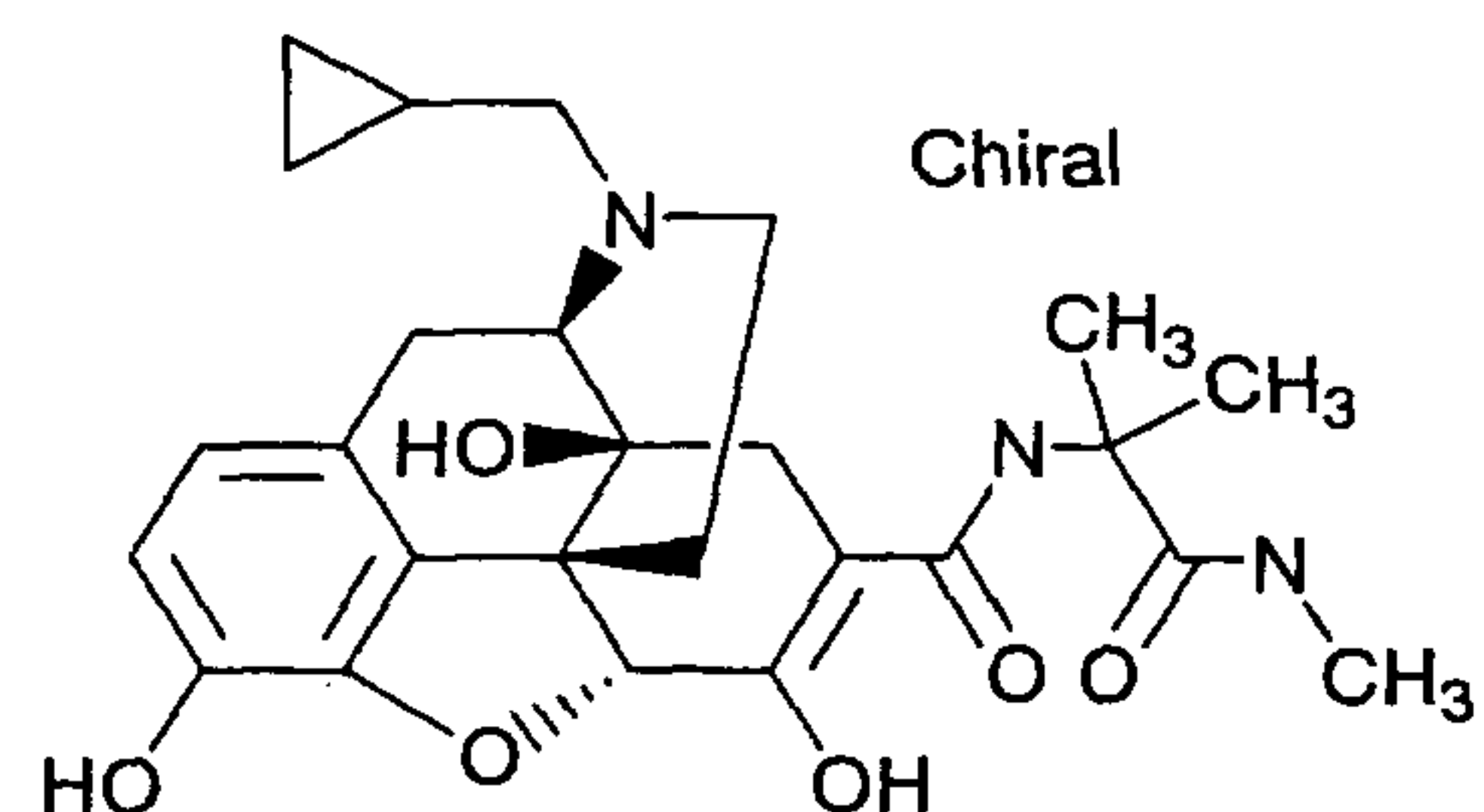
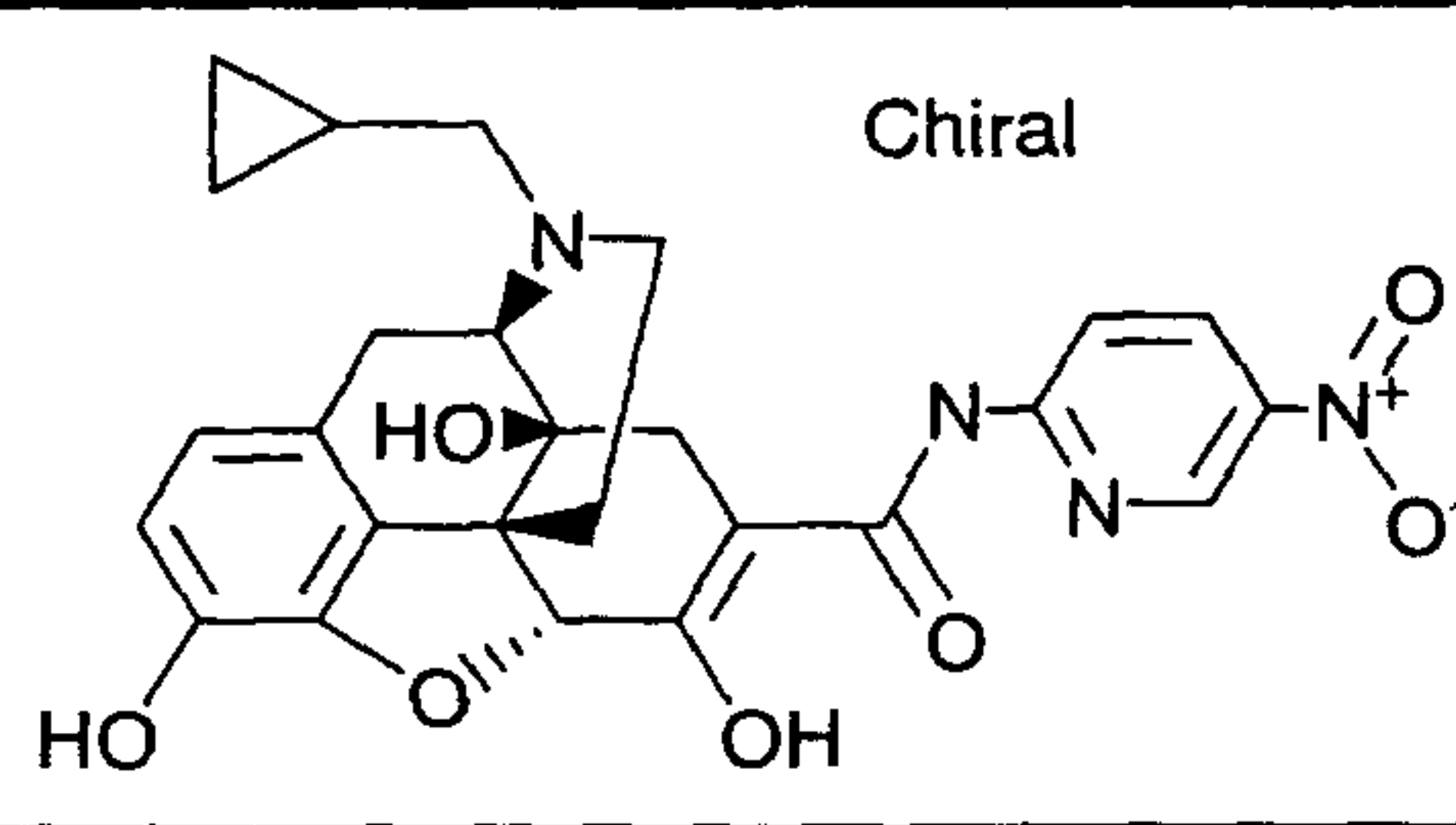
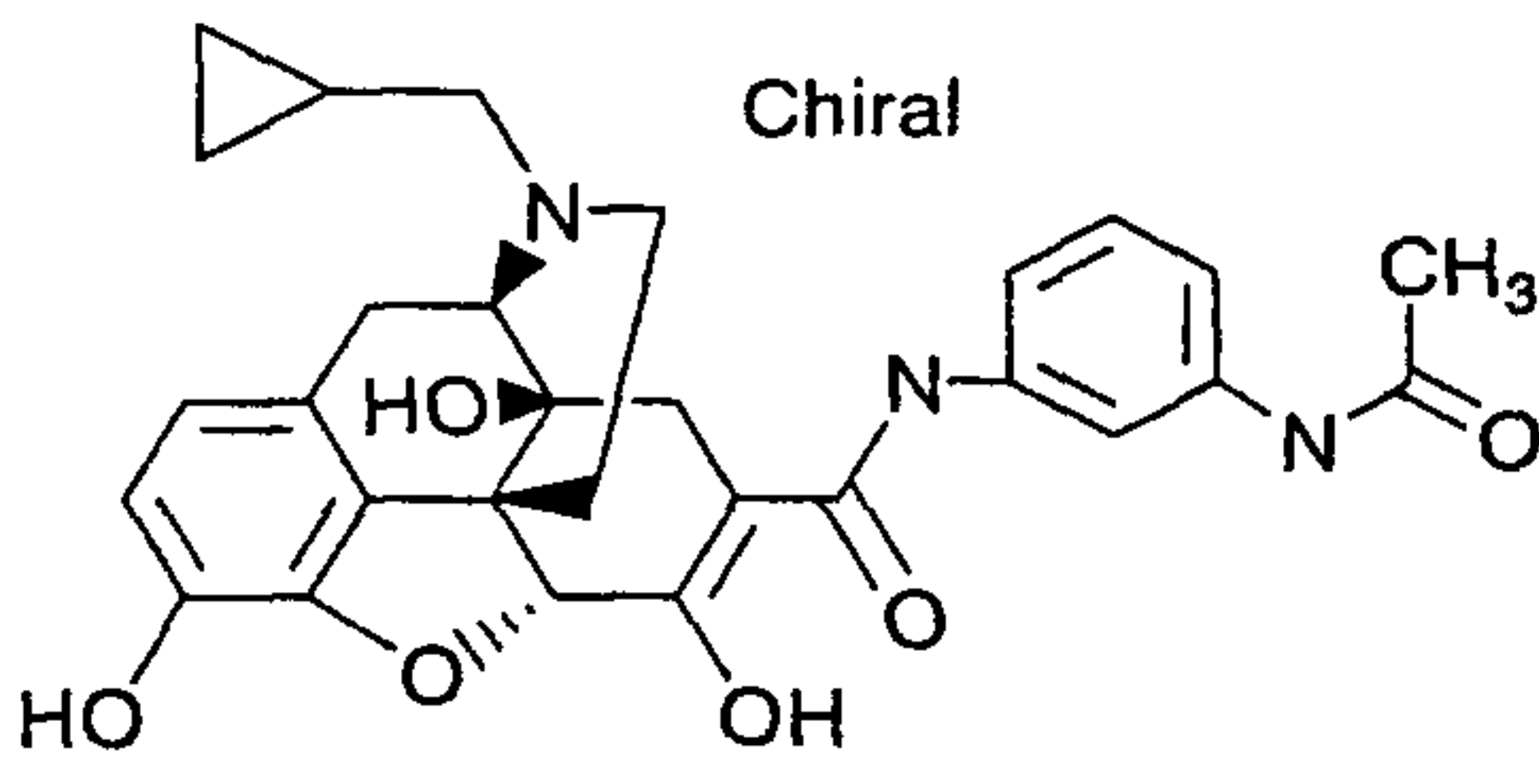
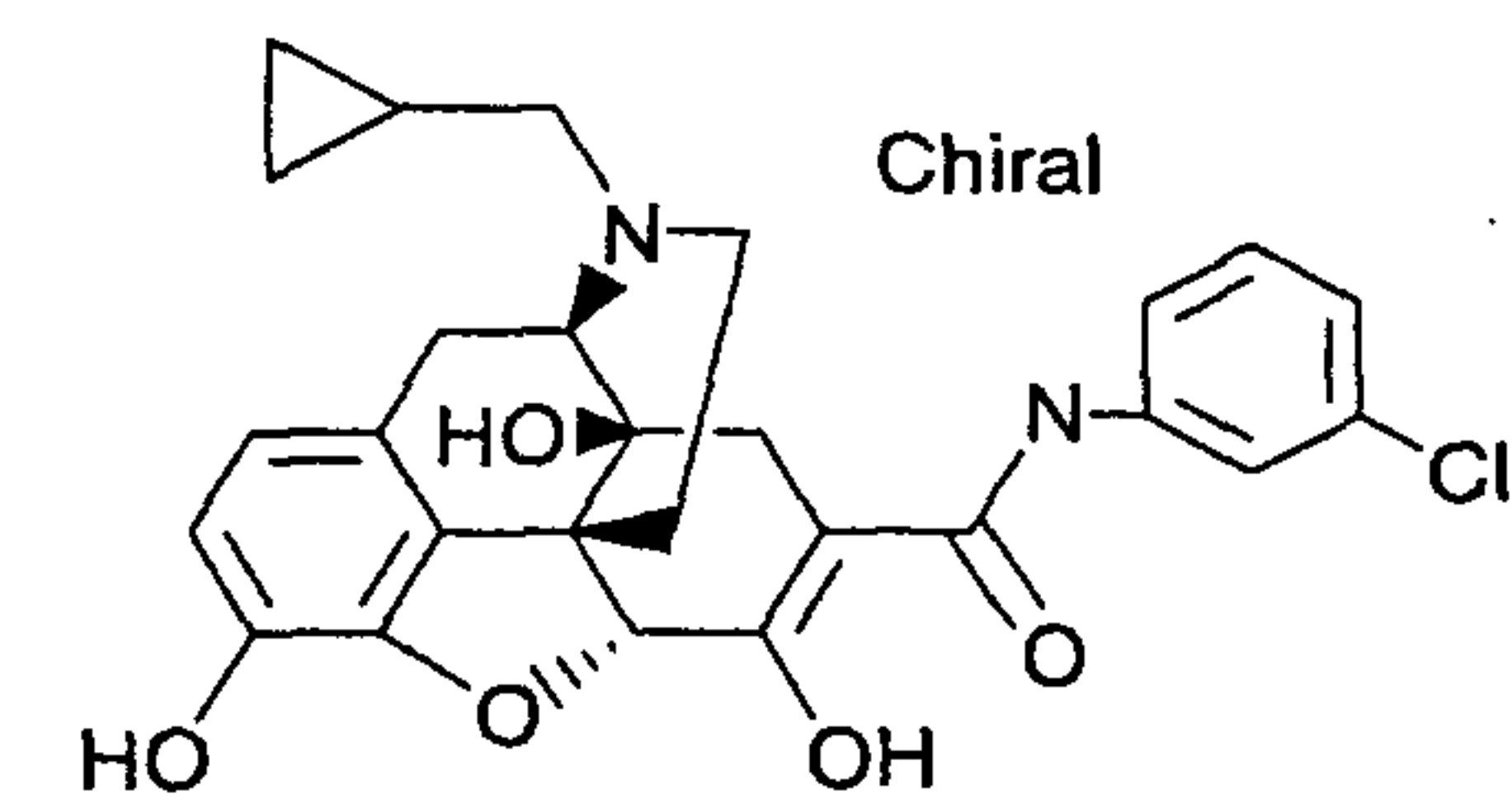
[0097]

[Table 52]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-201	 Chiral	m/z 601 [M+H] ⁺ 1.01 min	
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	

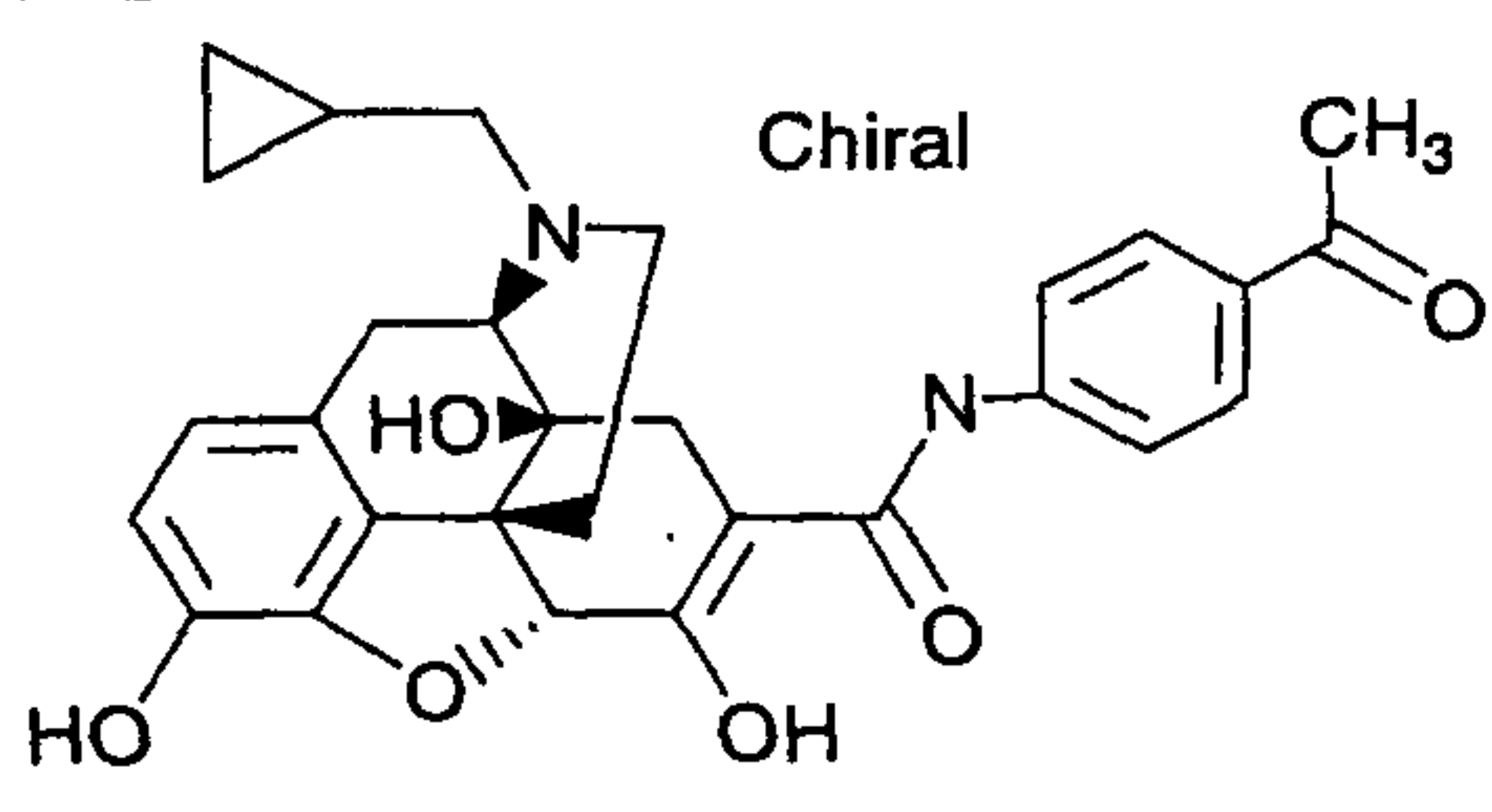
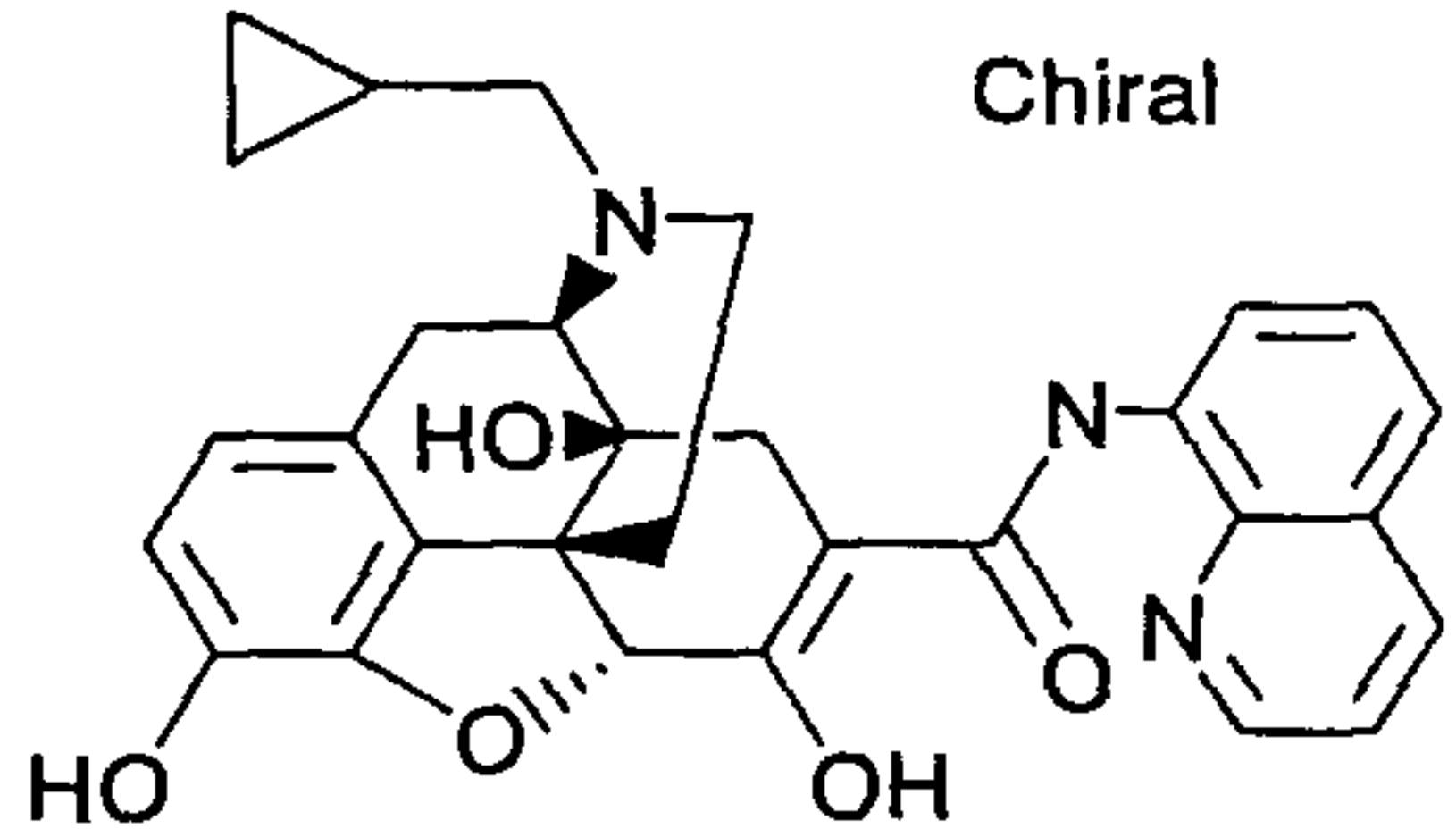
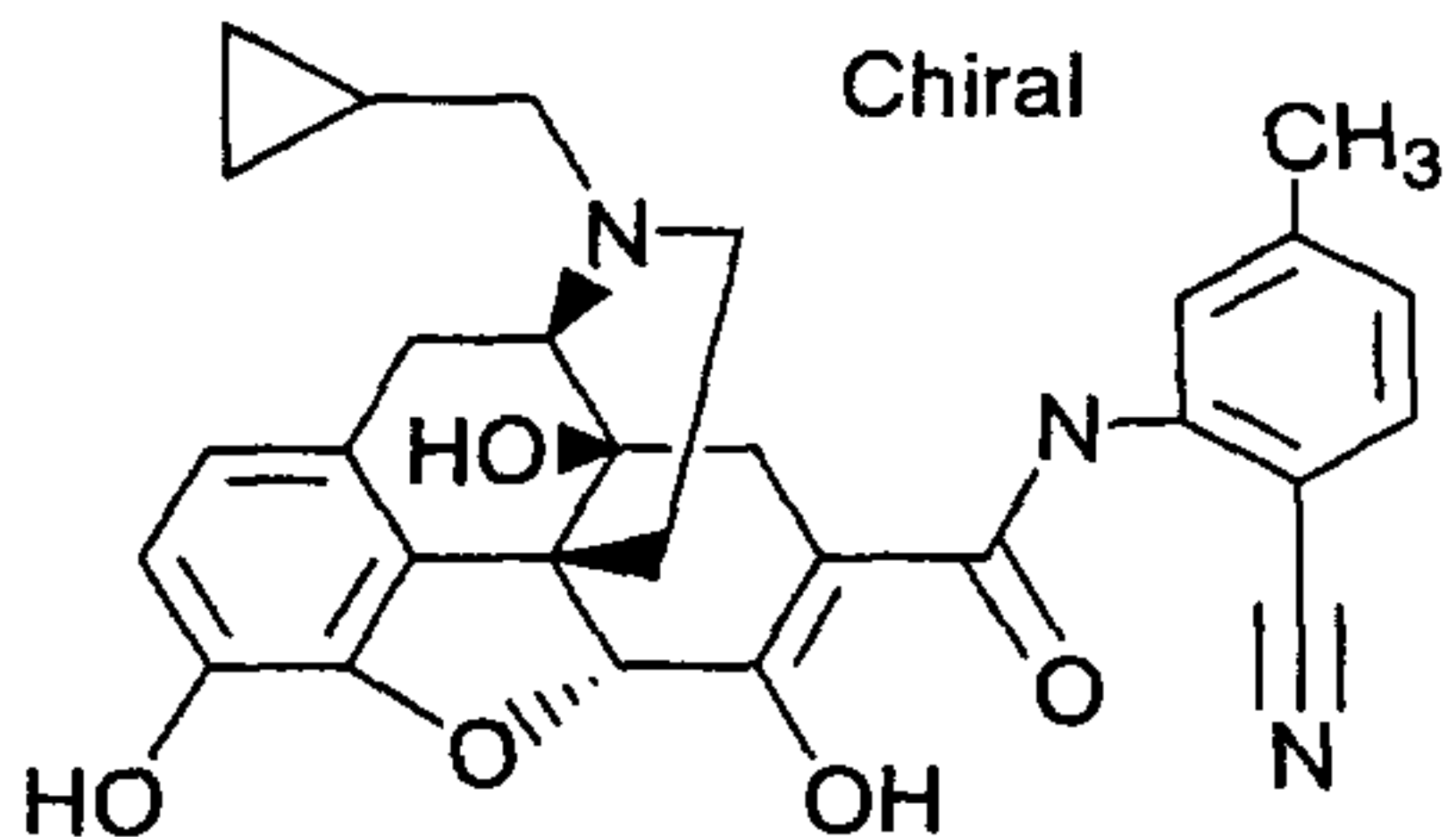
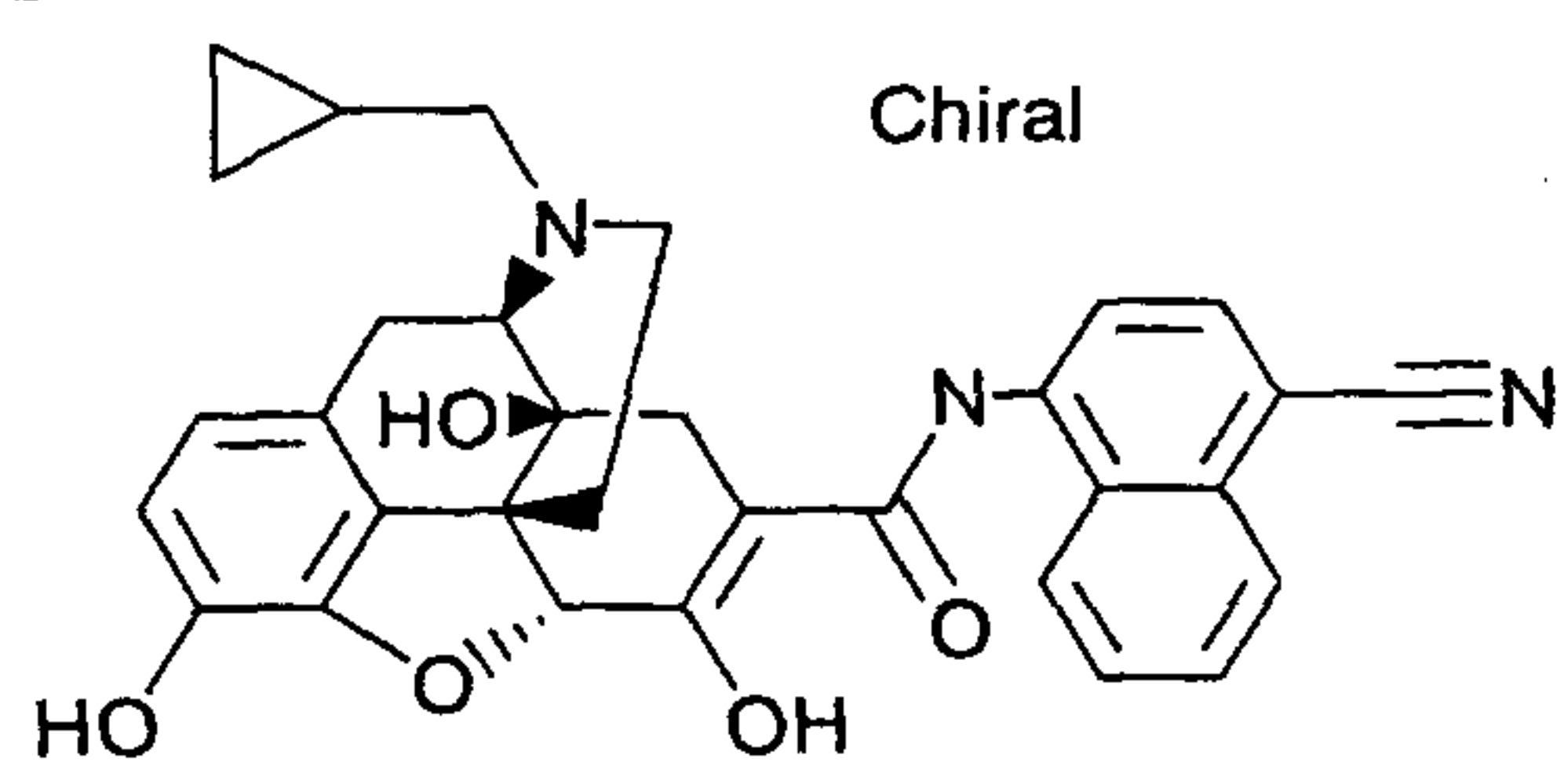
[0098]

[Table 53]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -DMSO) δ)
I-206		m/z 535 [M+H] ⁺ 0.41 min	
I-207		m/z 484 [M+H] ⁺ 0.32 min	
I-208		m/z 507 [M+H] ⁺ 1.05 min	
I-209		m/z 518 [M+H] ⁺ 1.14 min**	
I-210		m/z 495 [M+H] ⁺ 1.64 min**	

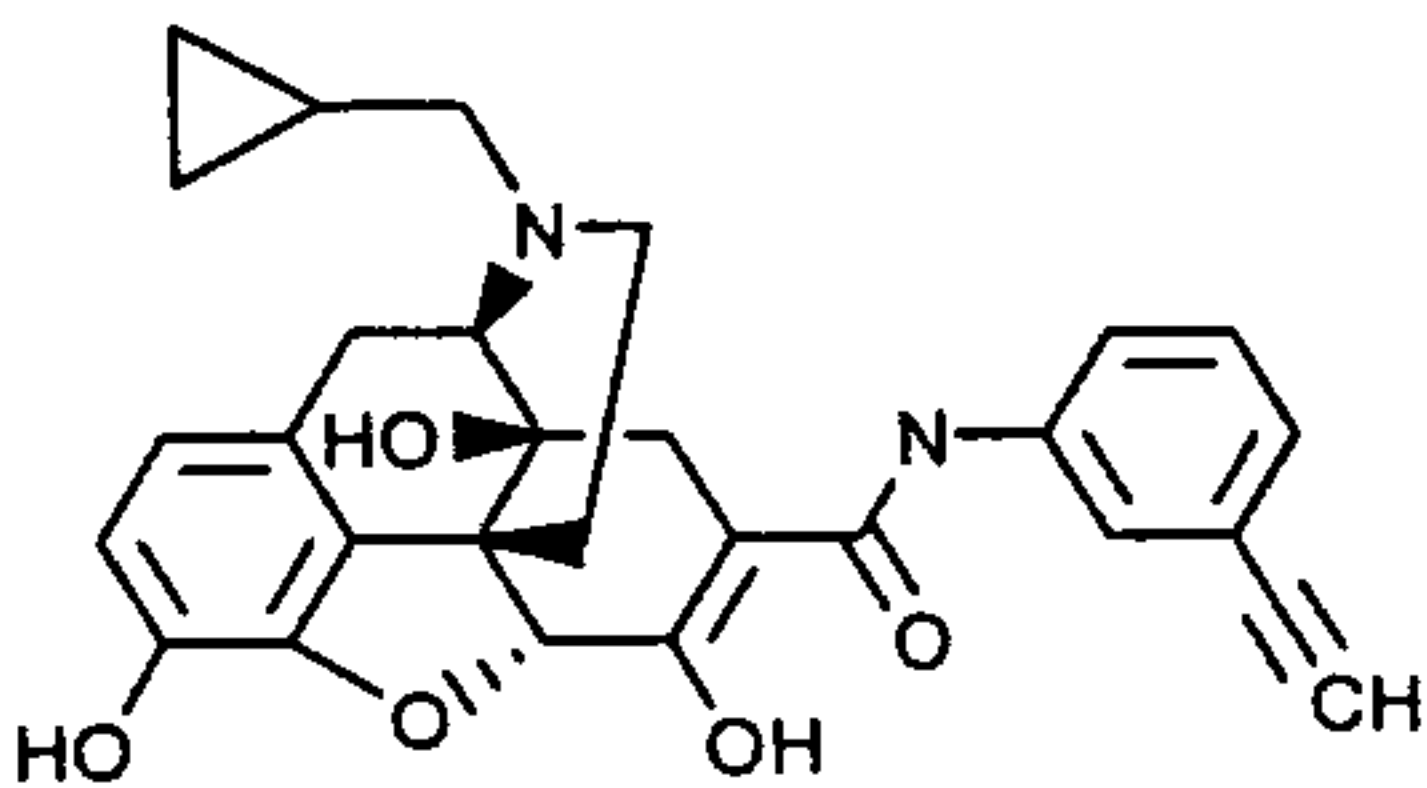
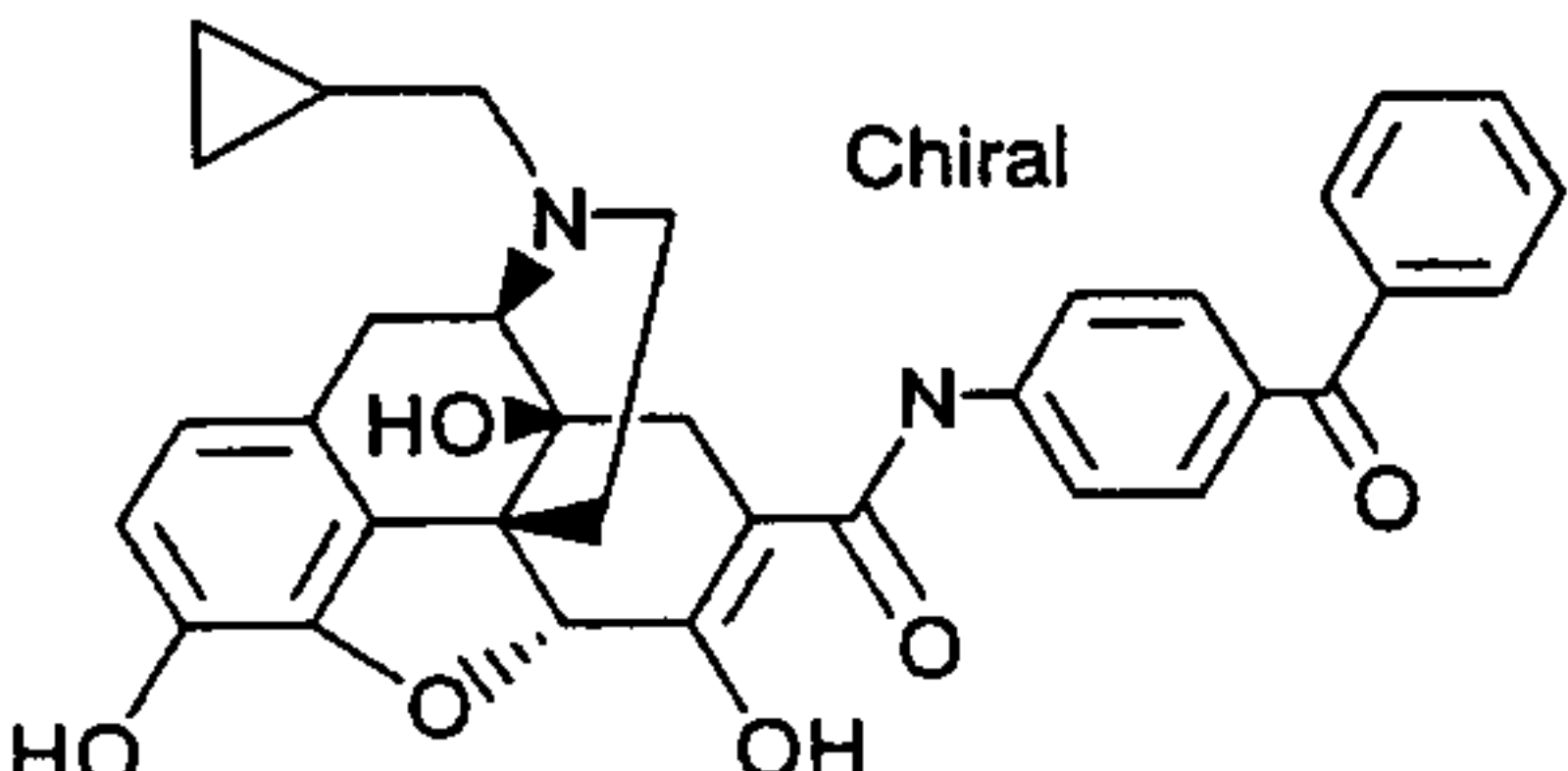
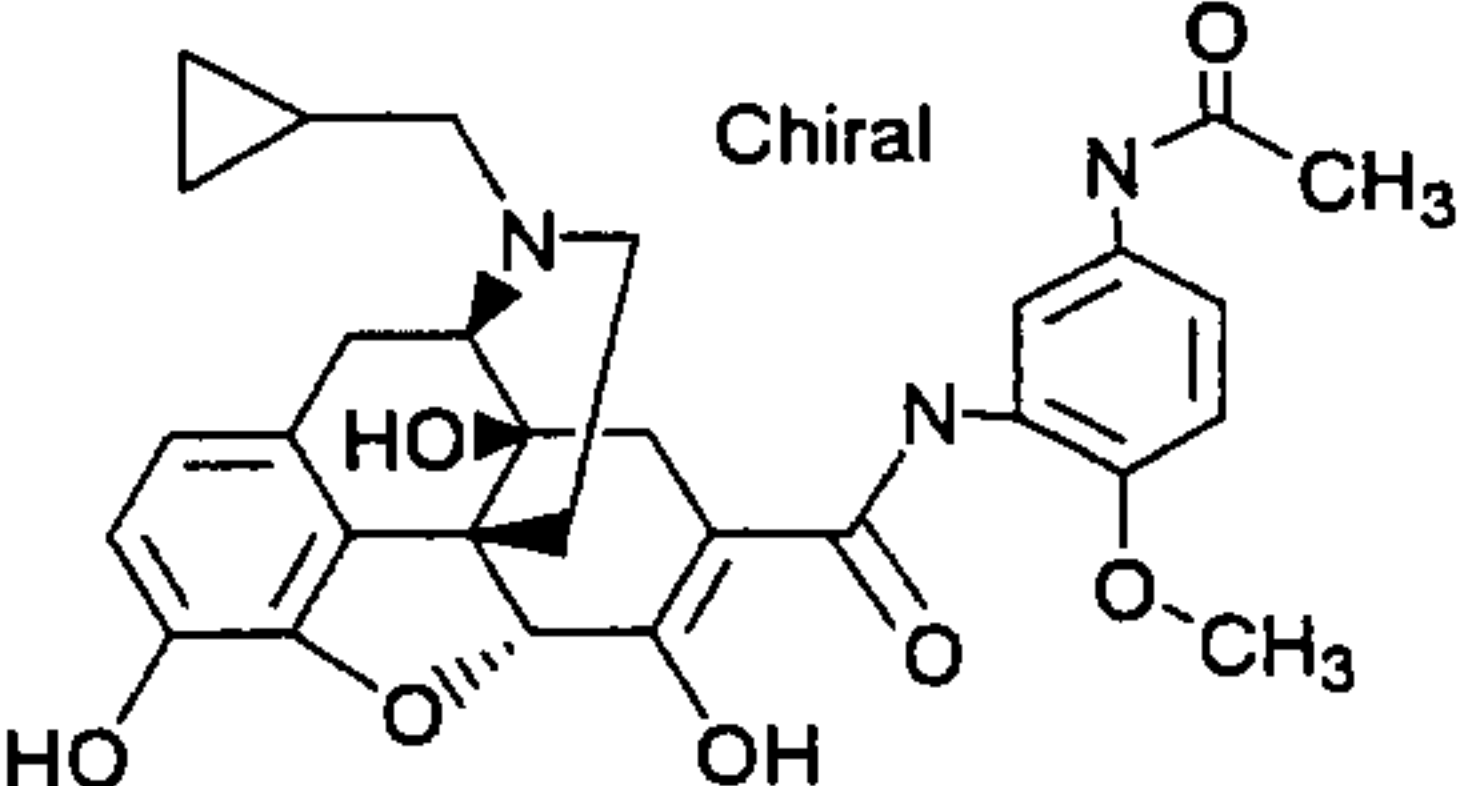
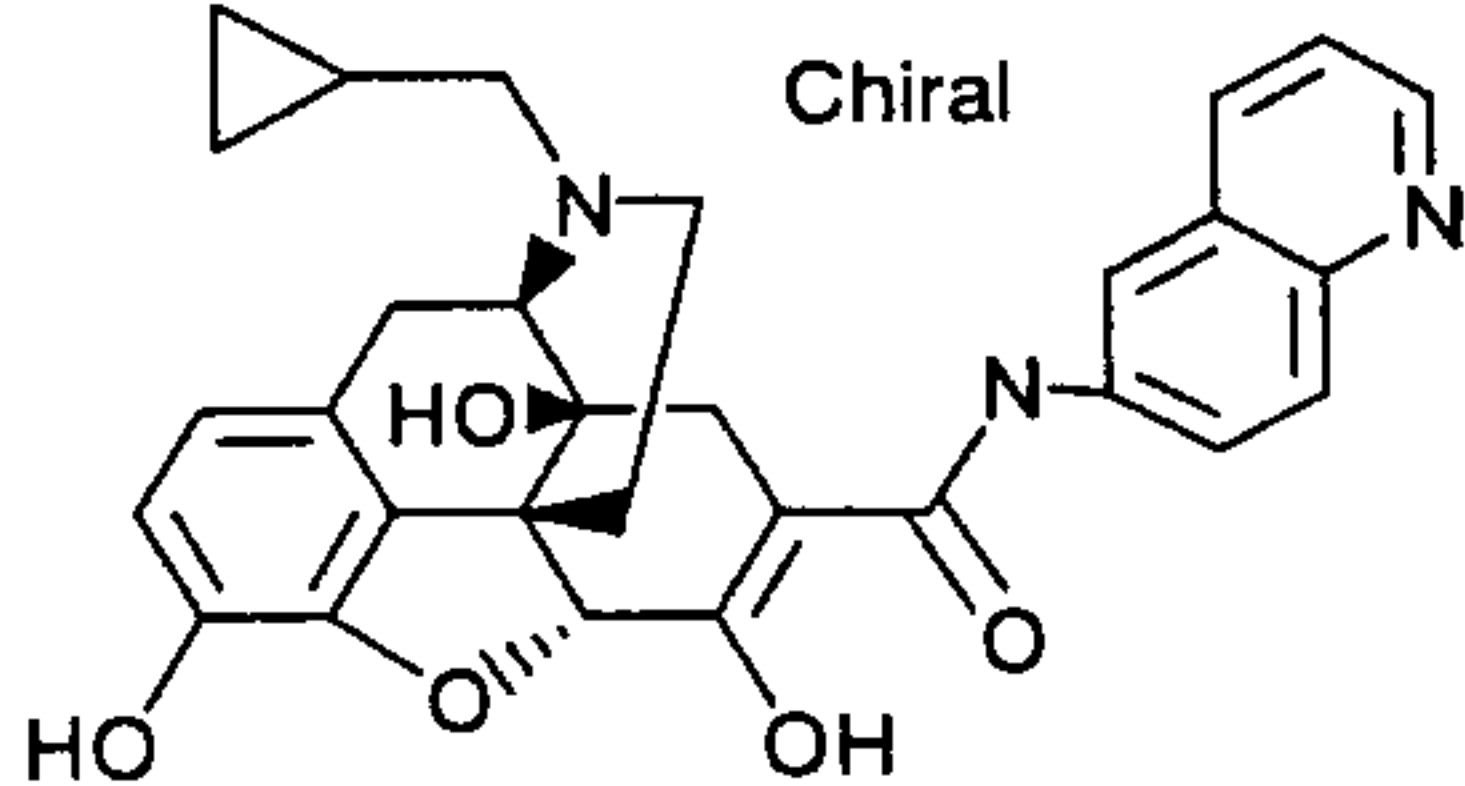
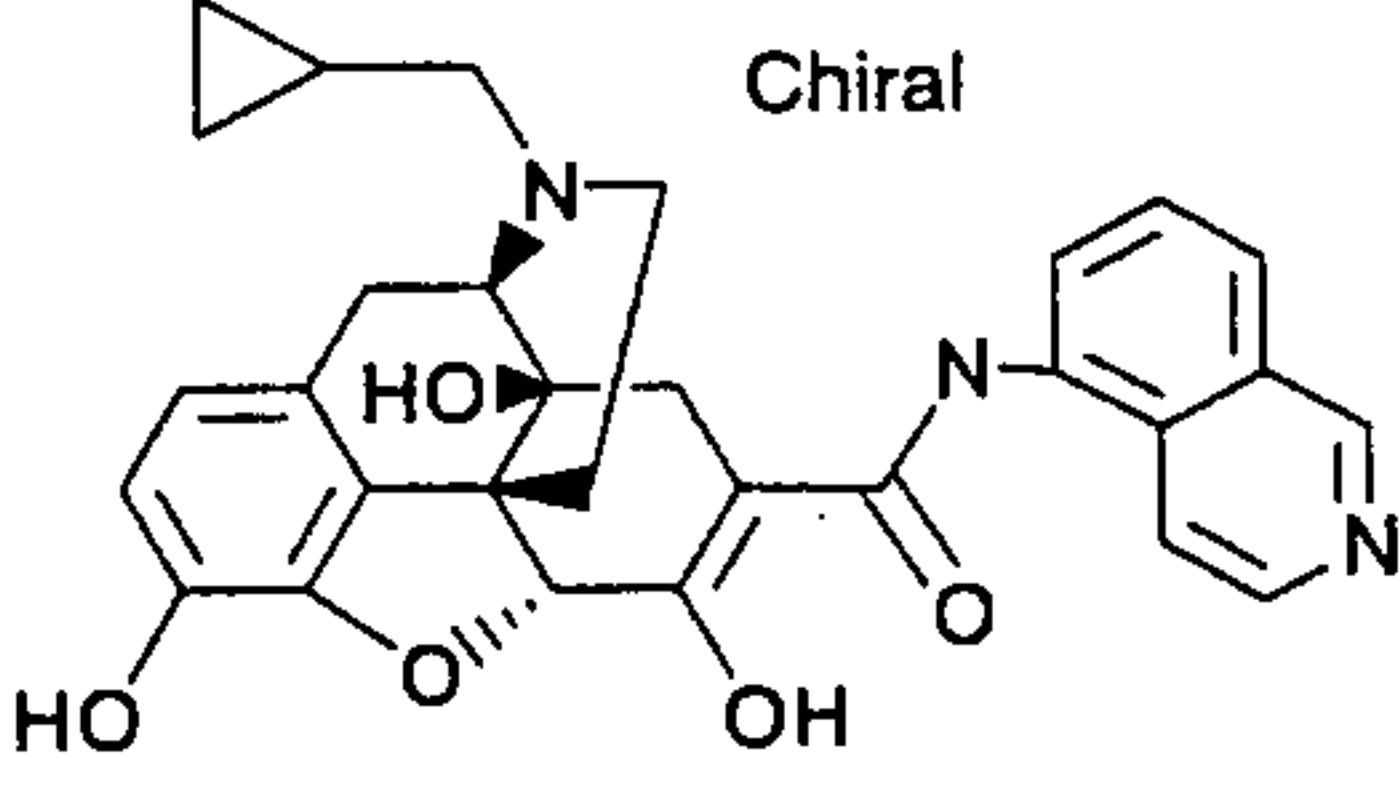
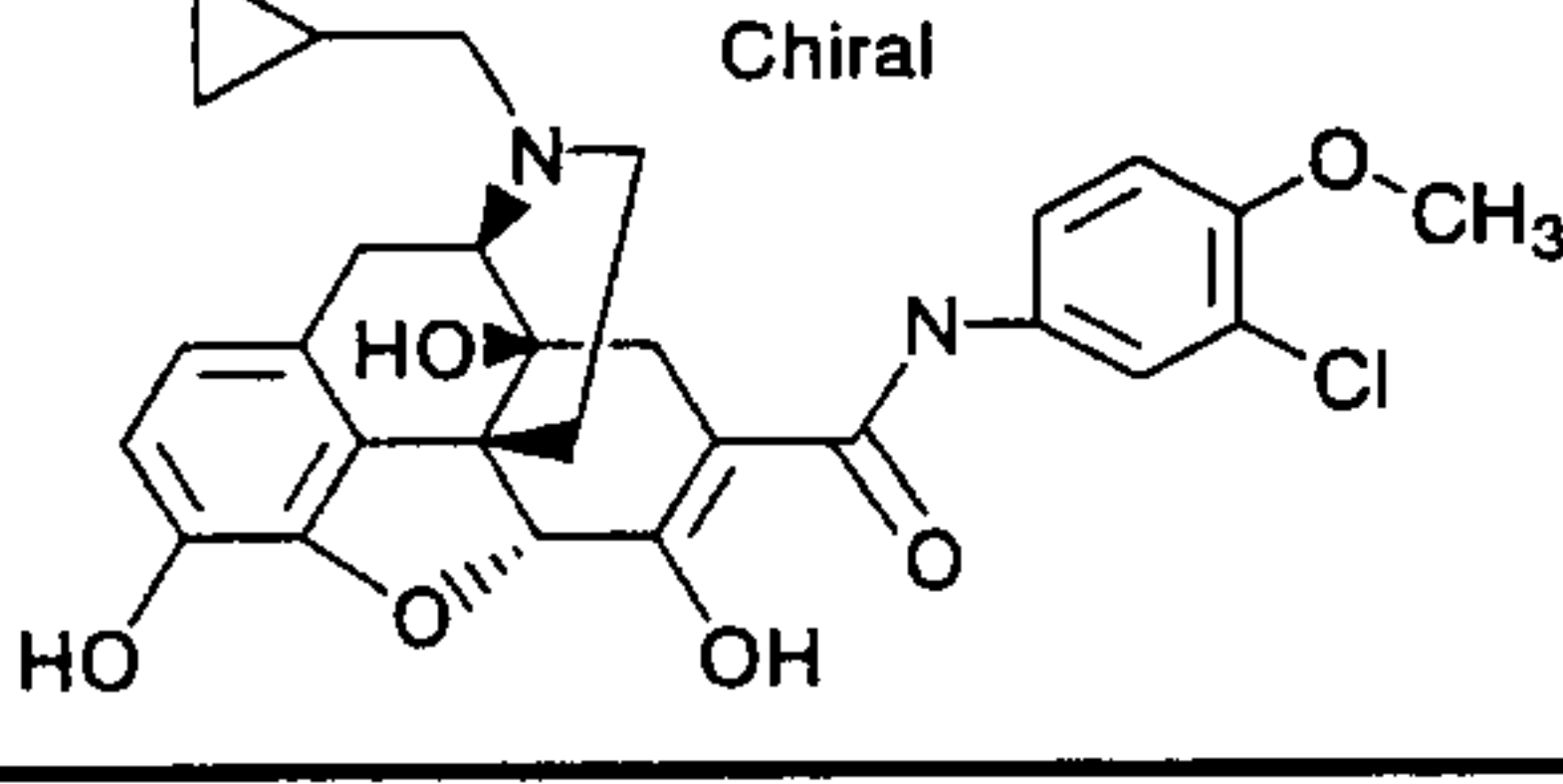
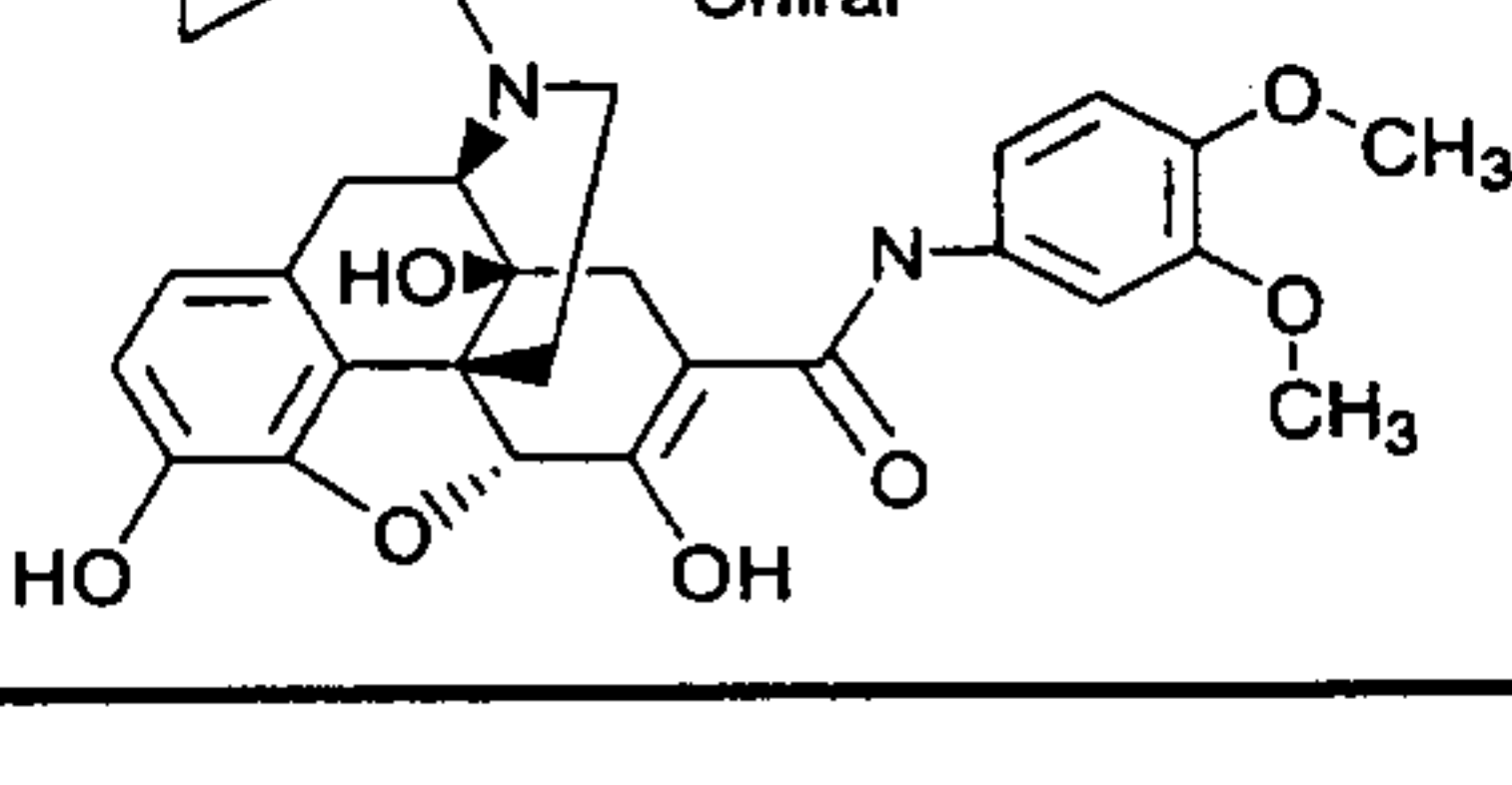
[0099]

[Table 54]

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

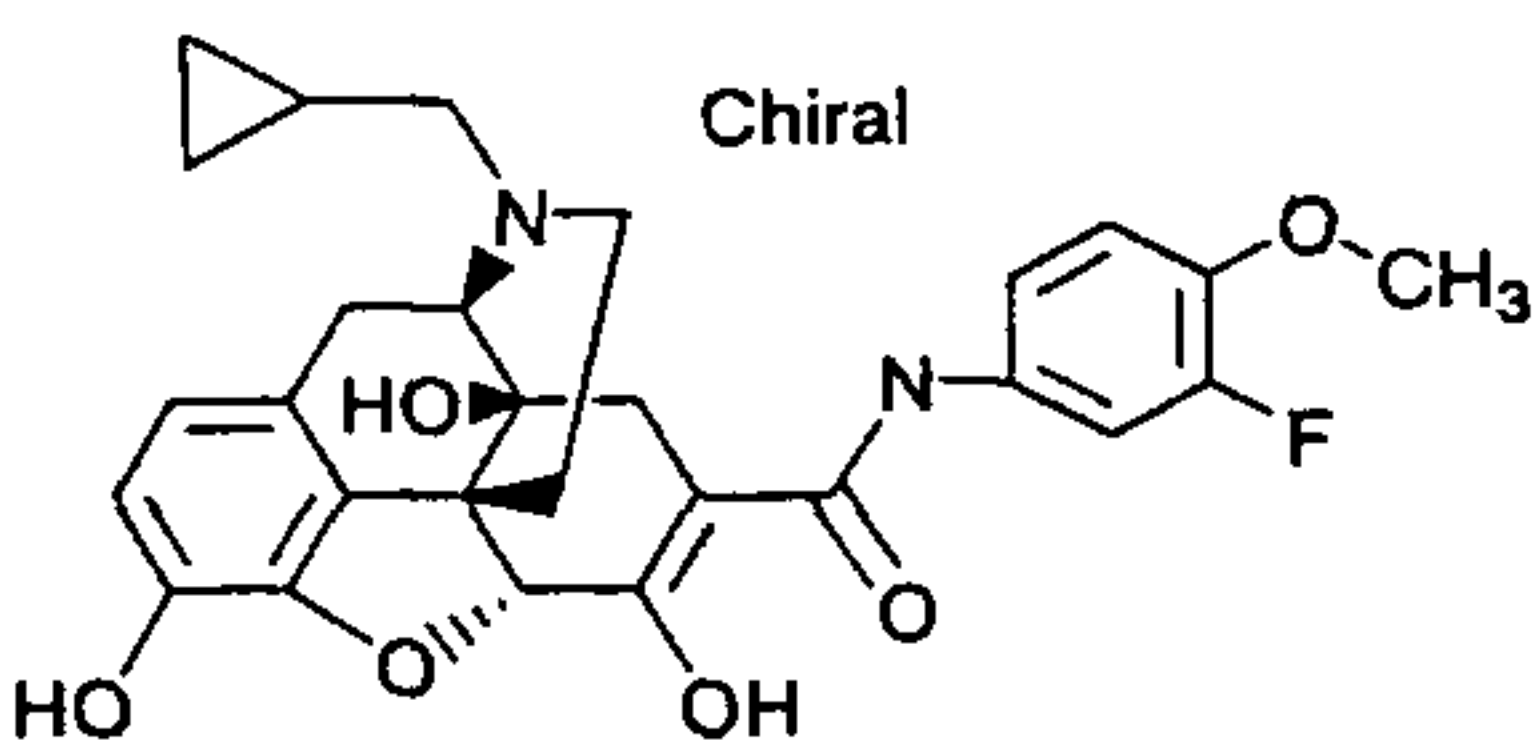
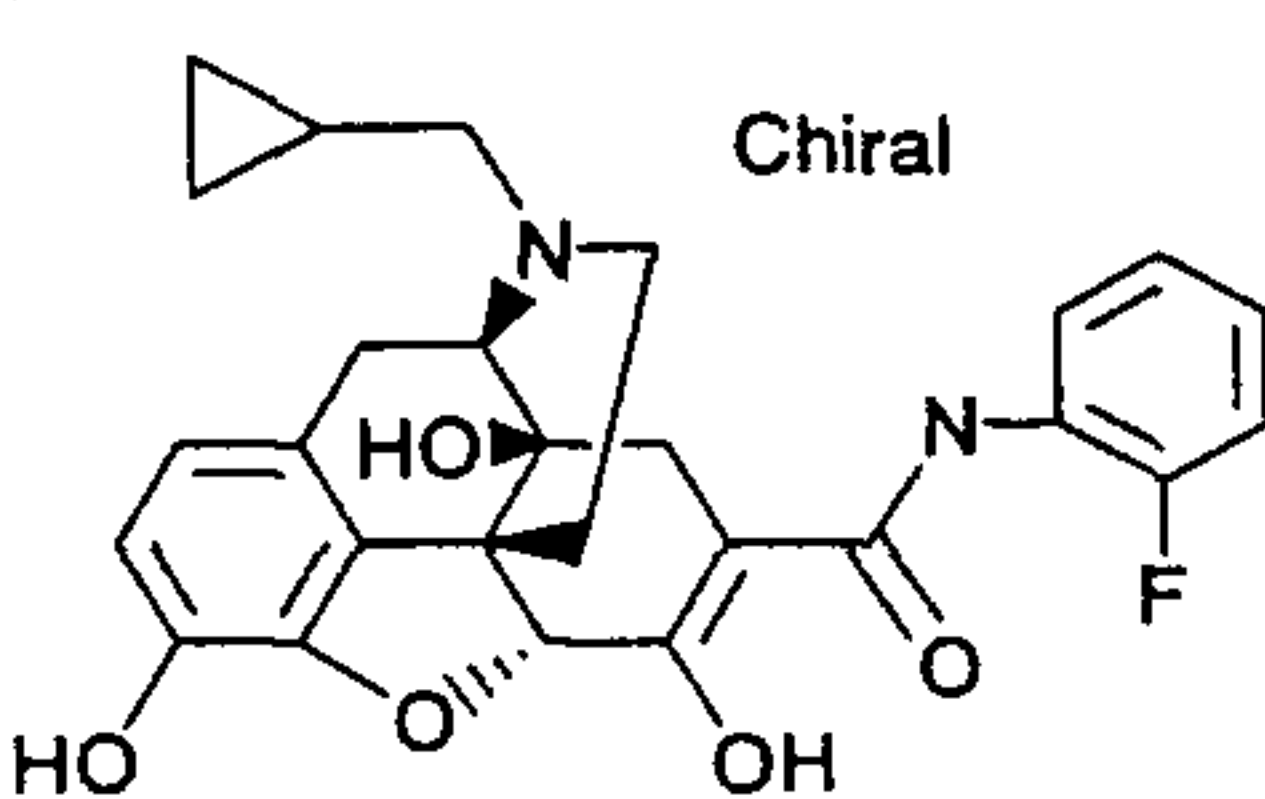
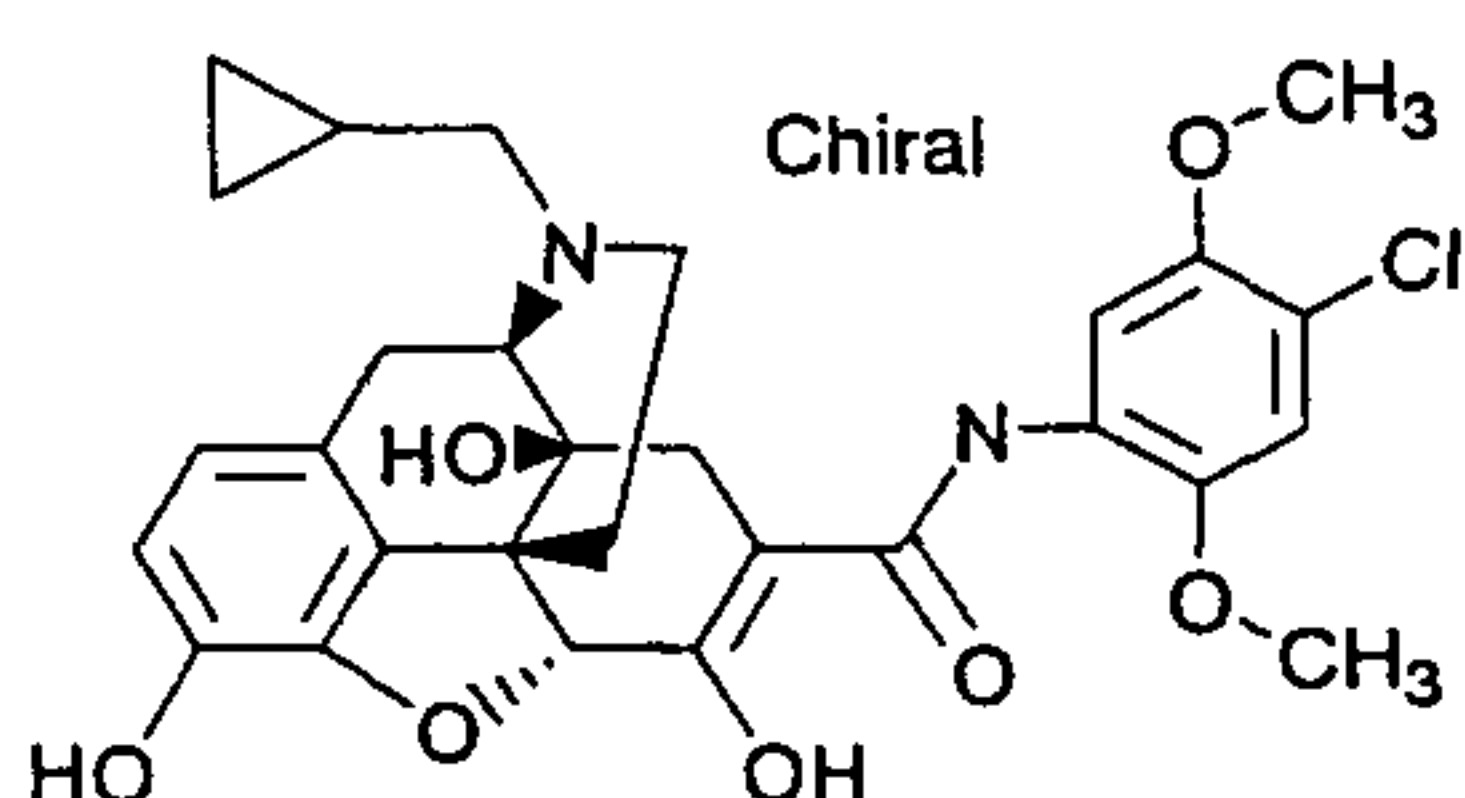
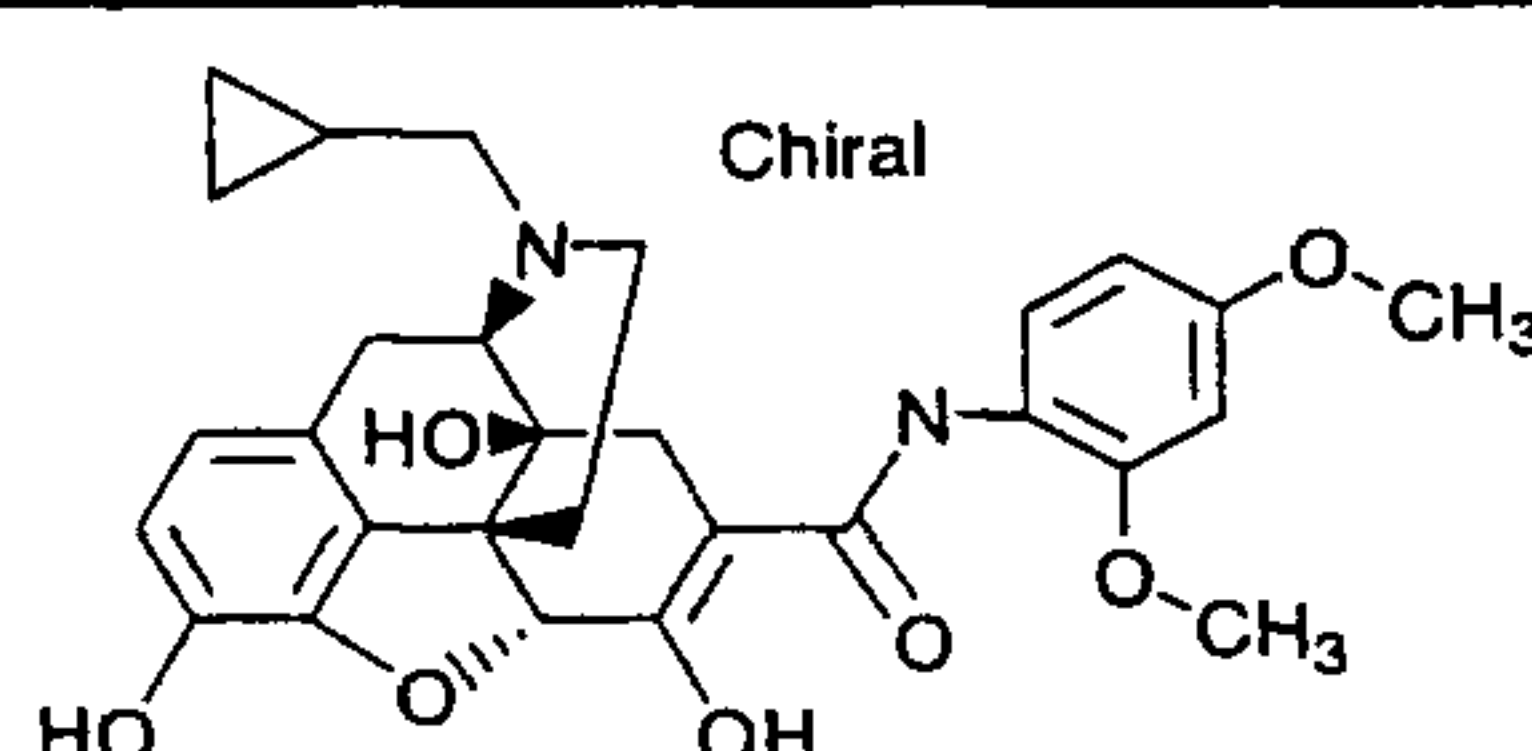
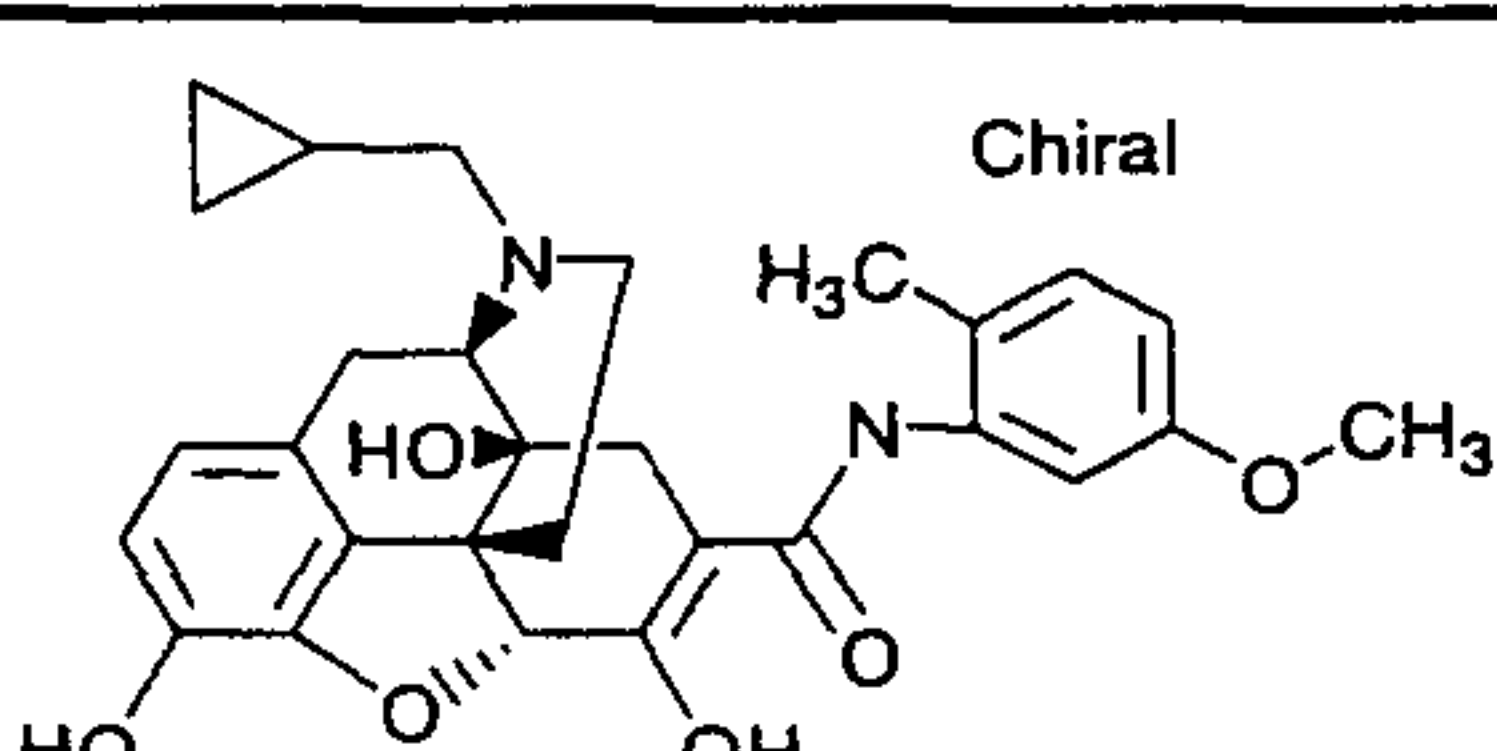
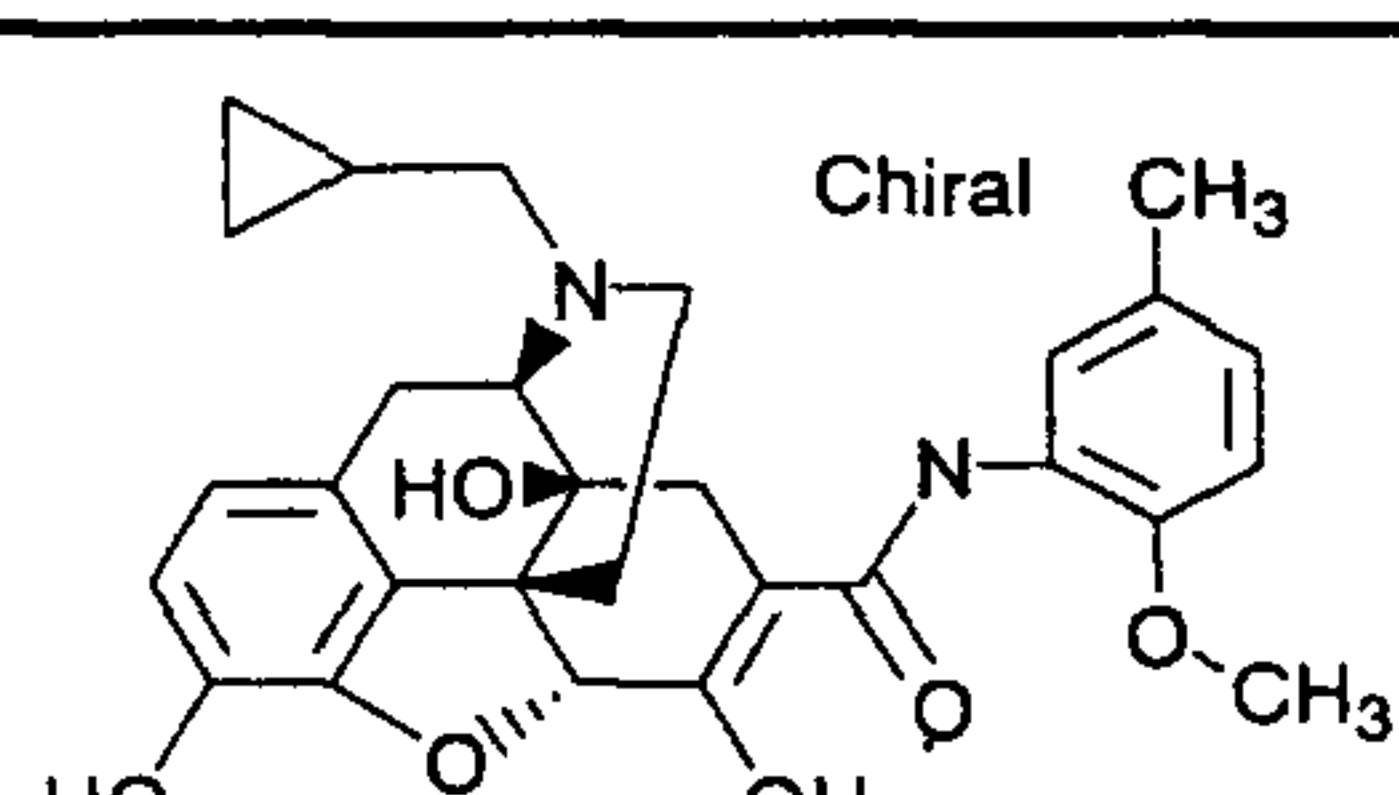
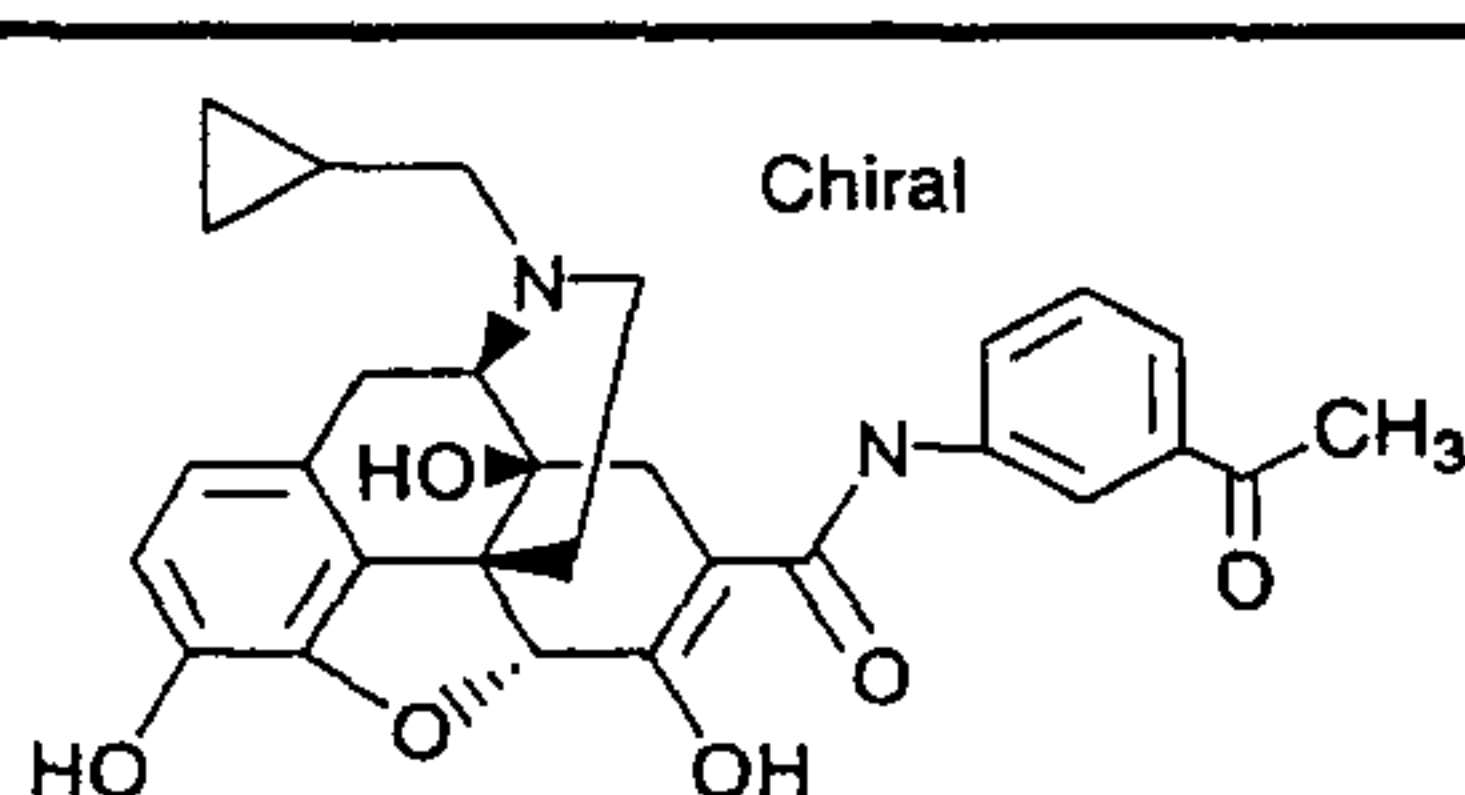
[0100]

[Table 55]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (1H-NMR (d6-DMSO) δ)
I-215		m/z 485 [M+H] ⁺ 1.60 min**	
I-216		m/z 565 [M+H] ⁺ 1.82 min**	
I-217		m/z 548 [M+H] ⁺ 1.17 min**	
I-218		m/z 512 [M+H] ⁺ 0.95 min**	
I-219		m/z 512 [M+H] ⁺ 1.66 min **	
I-220		m/z 525 [M+H] ⁺ 1.60 min**	
I-221		m/z 521 [M+H] ⁺ 1.35 min **	

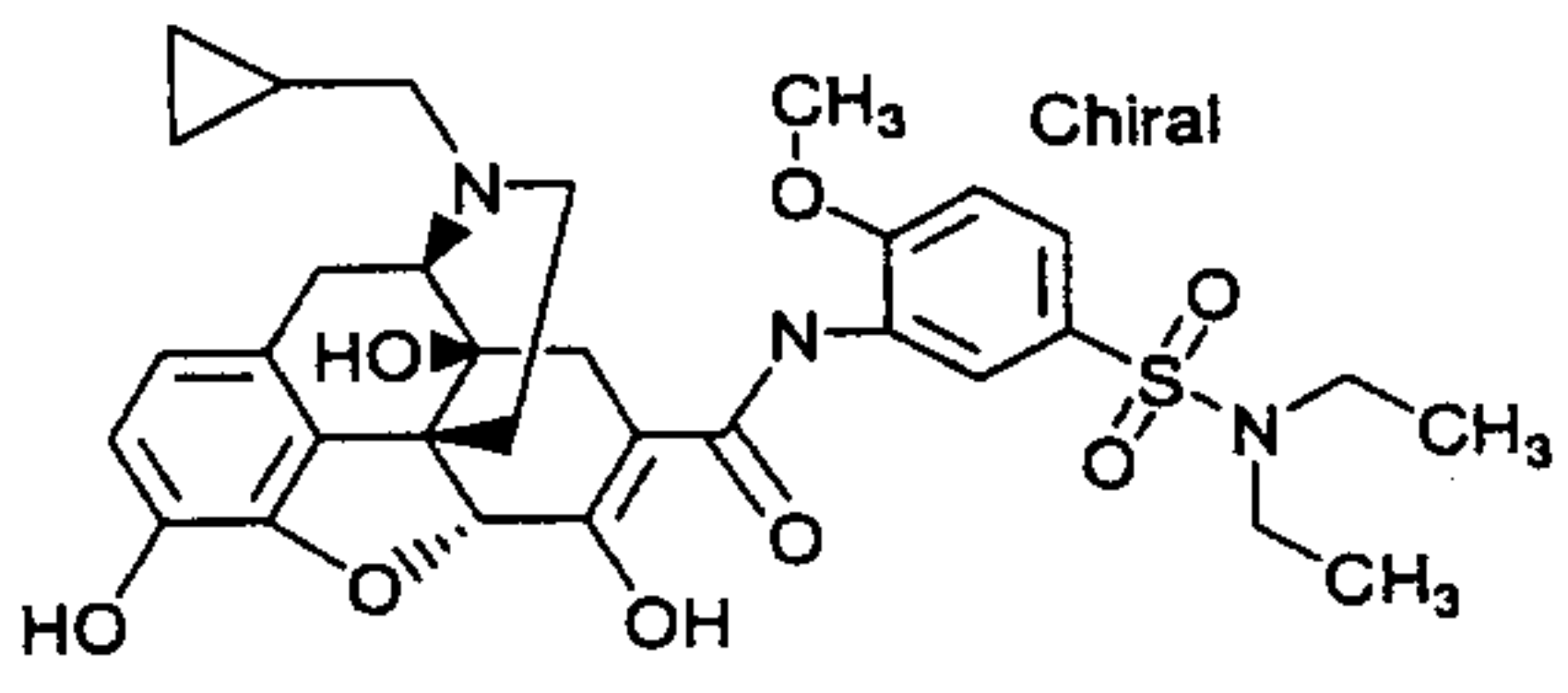
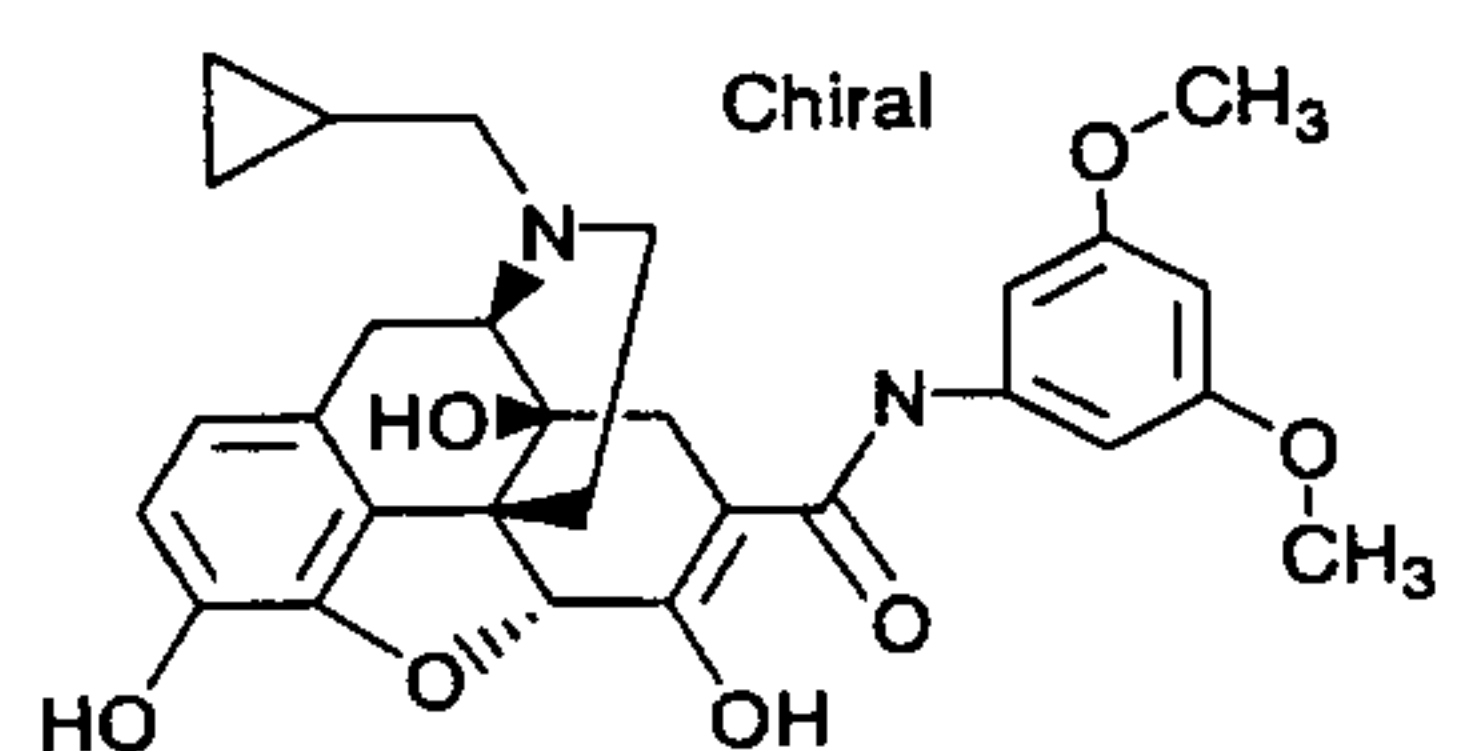
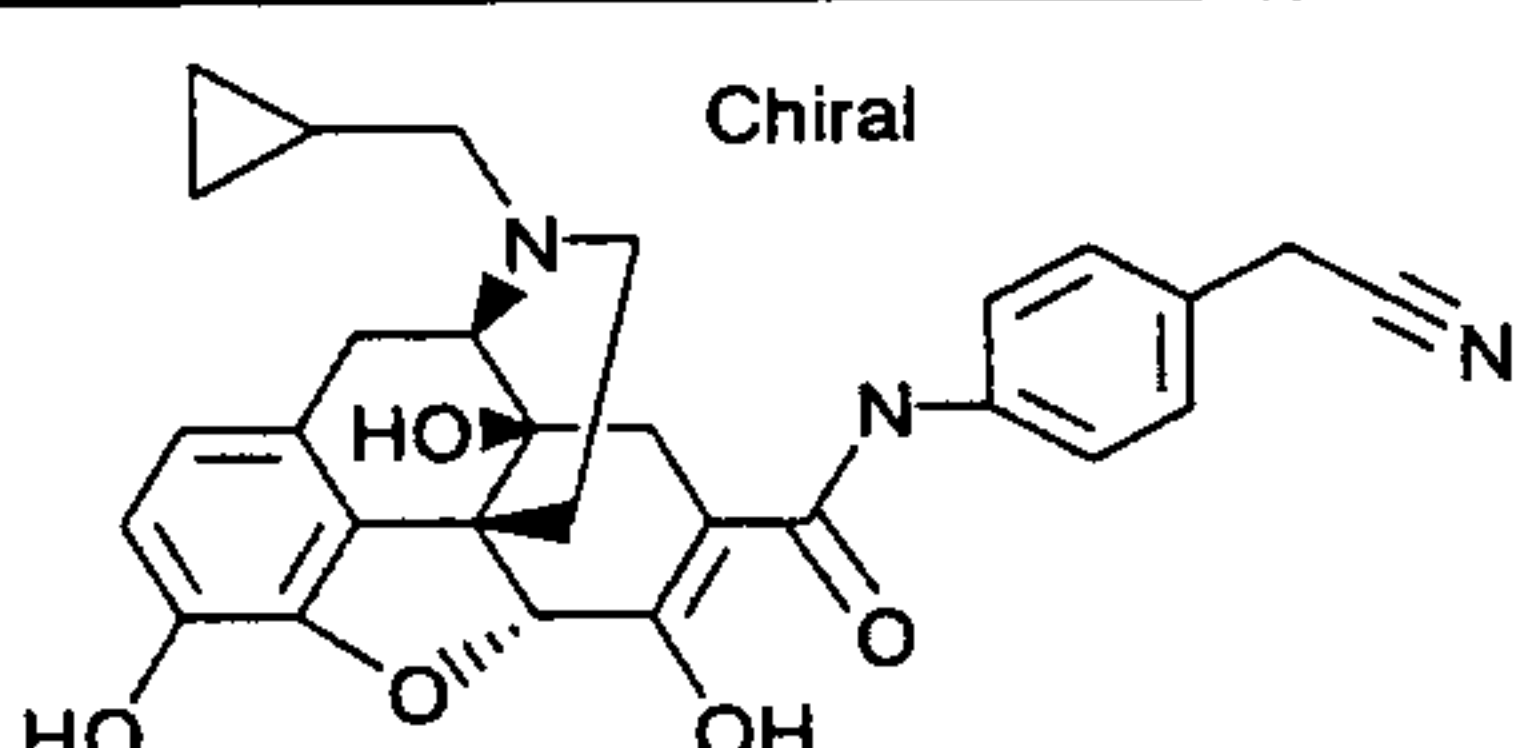
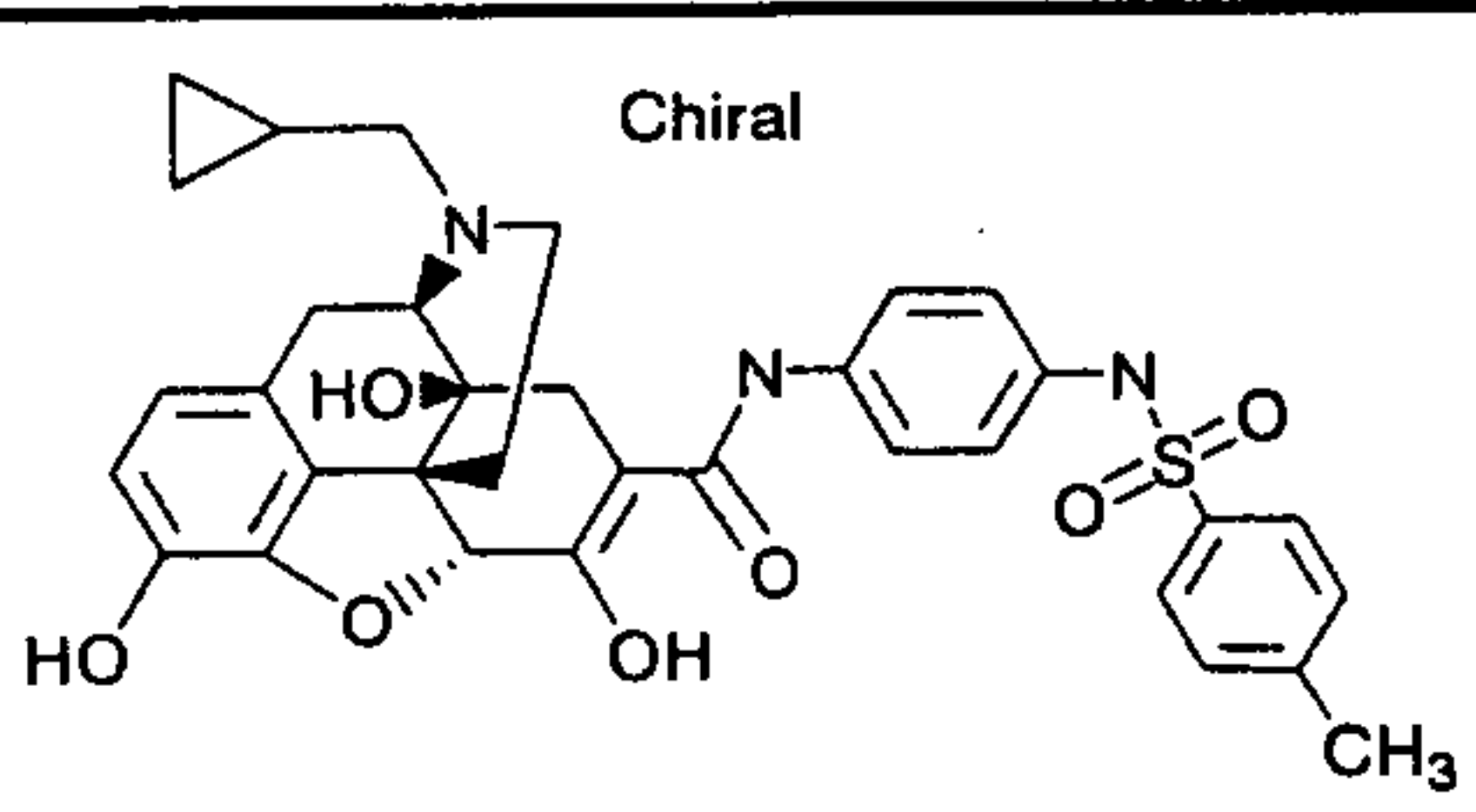
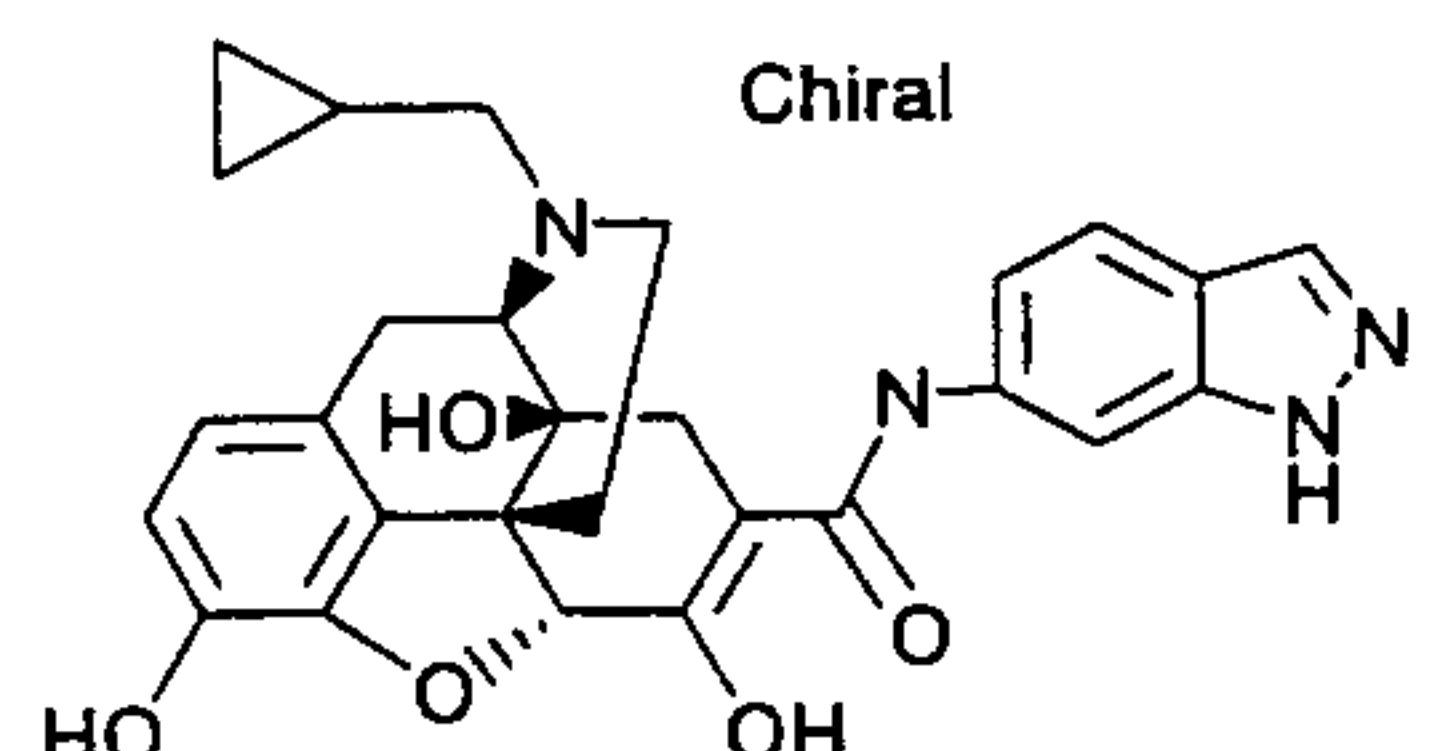
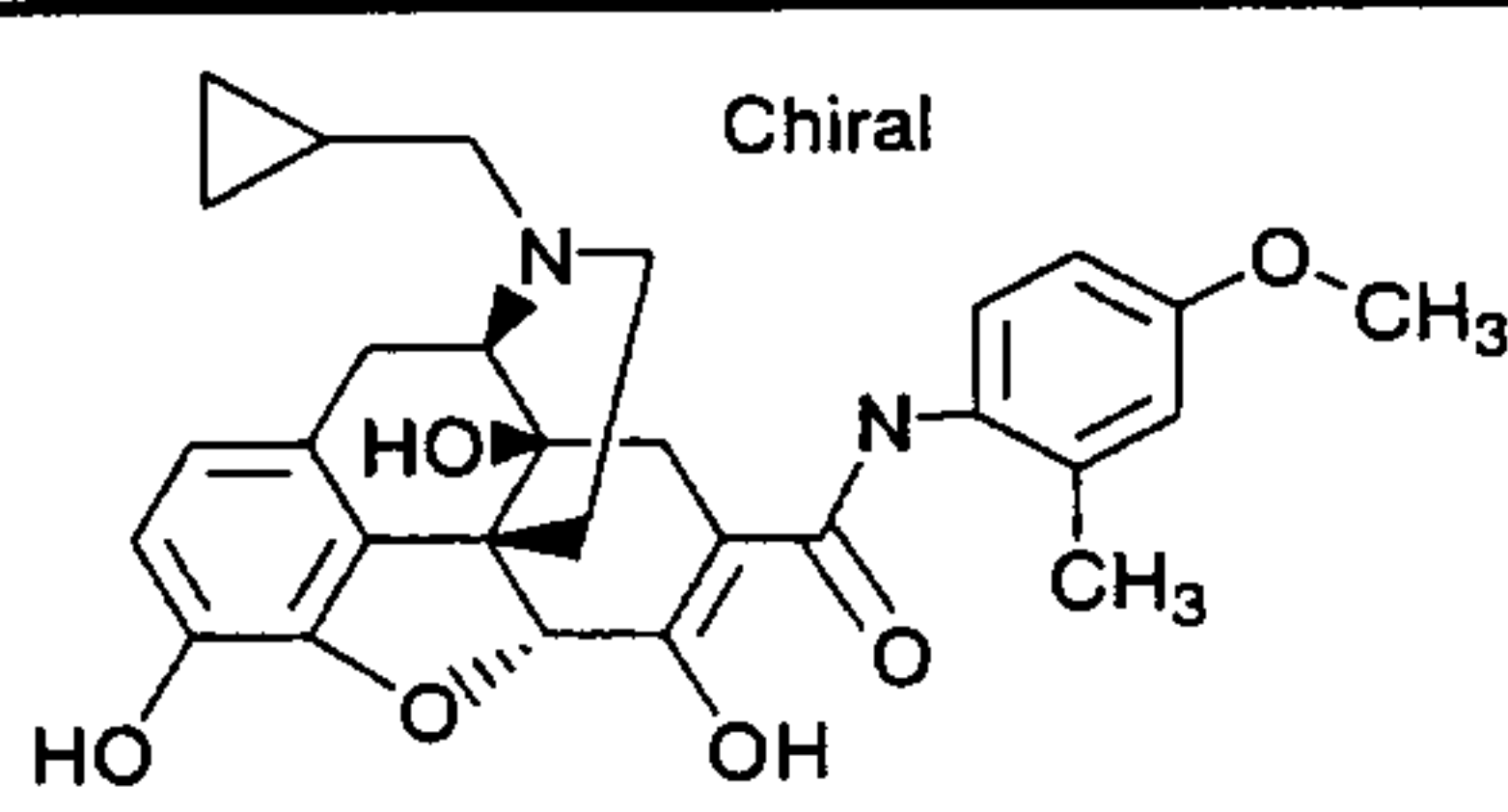
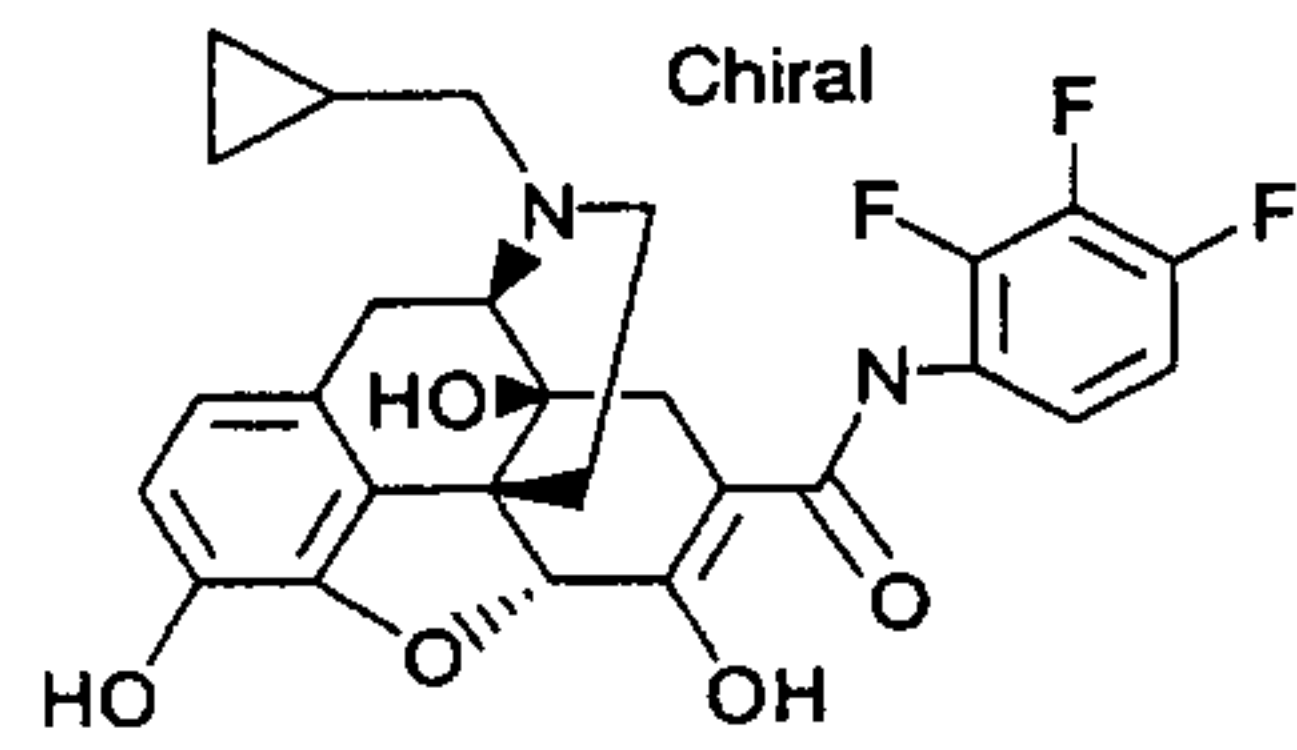
[0101]

[Table 56]

Compound No.	Chemical structure	LC/MS [†]	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 **	
I-227	 Chiral	m/z 505 [M+H] ⁺ 1.64 min **	
I-228	 Chiral	m/z 503 [M+H] ⁺ 1.38 min **	

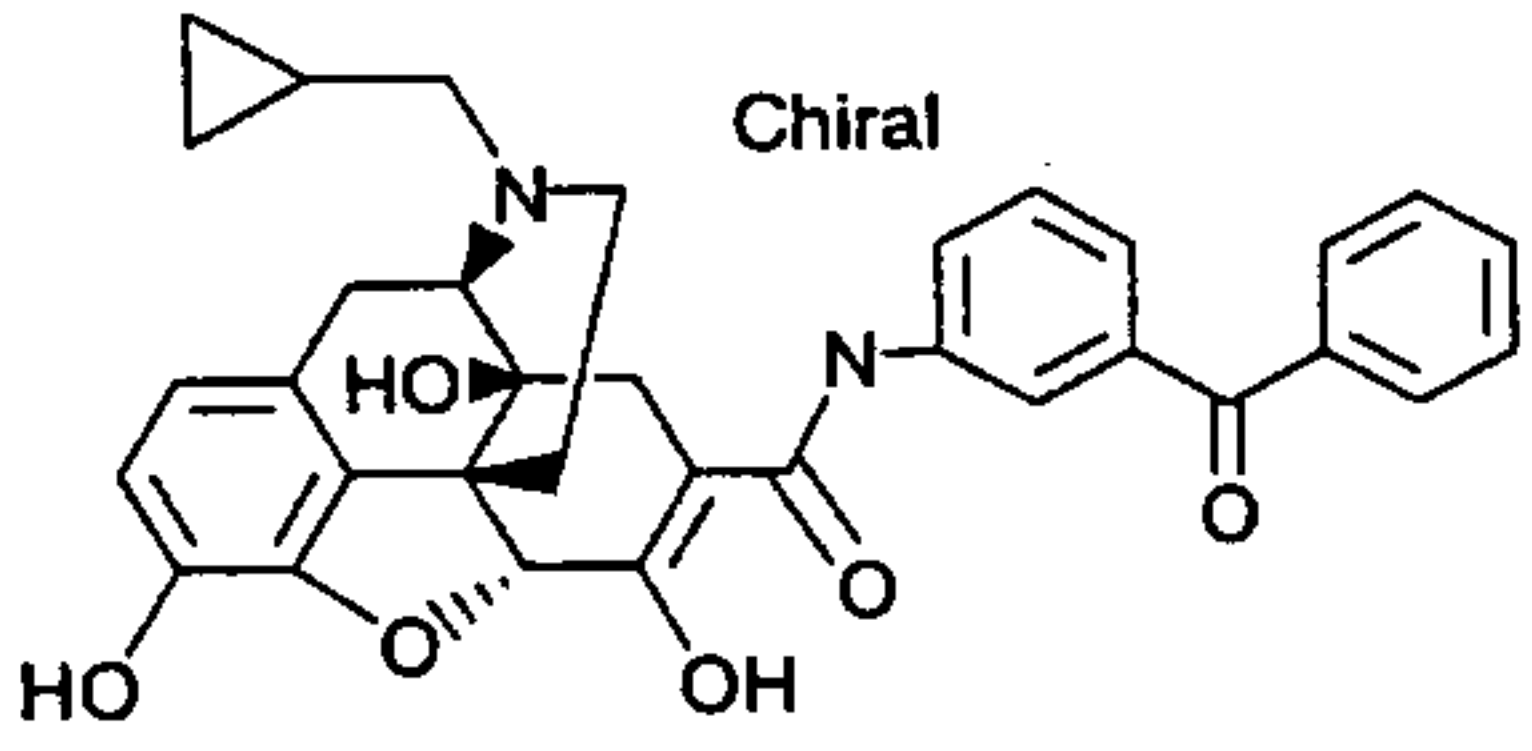
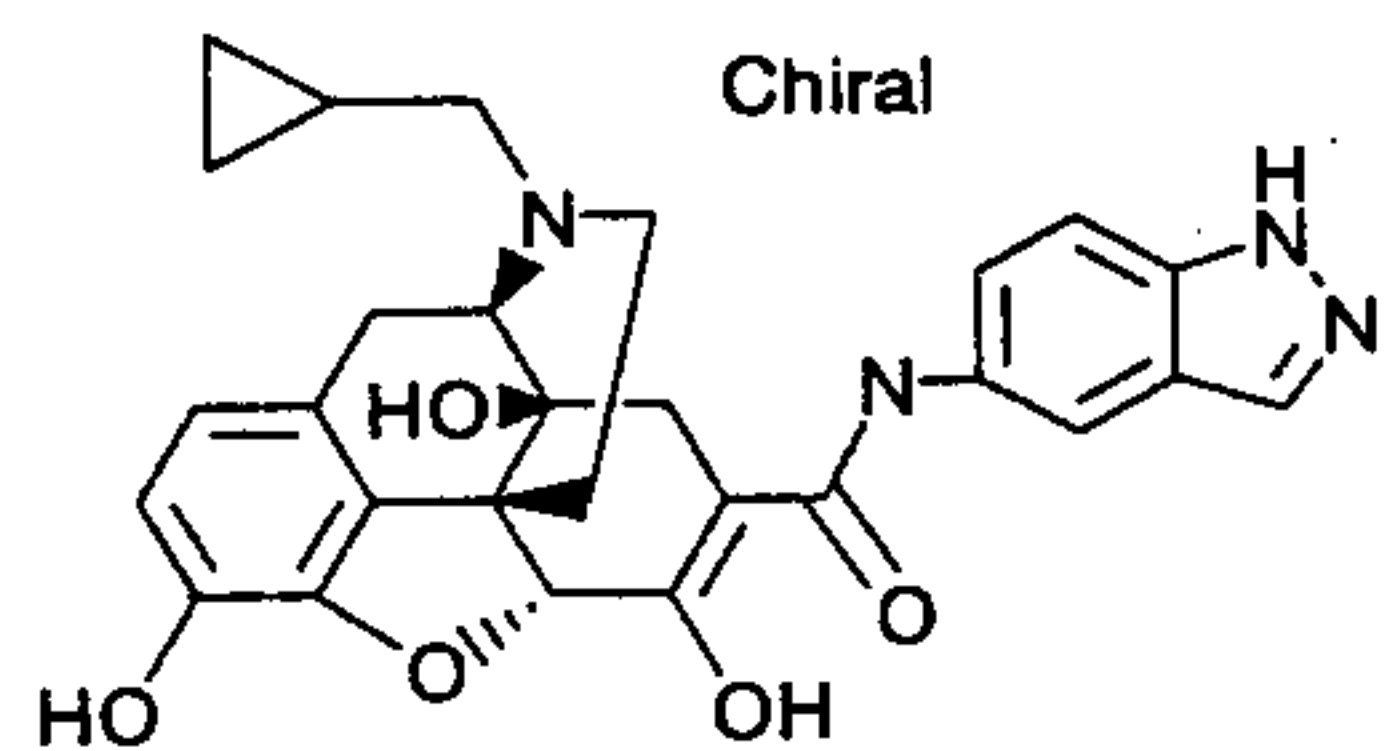
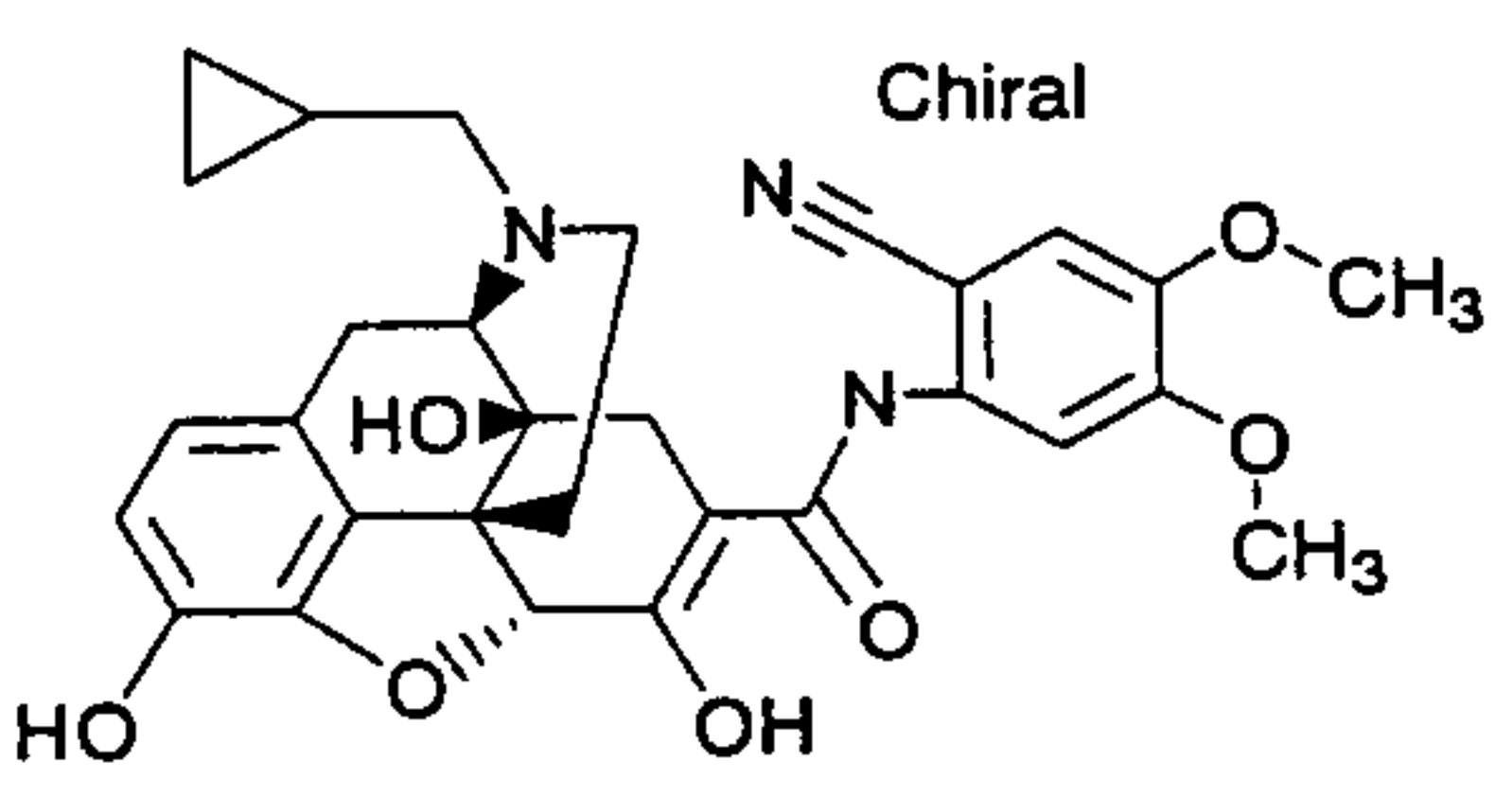
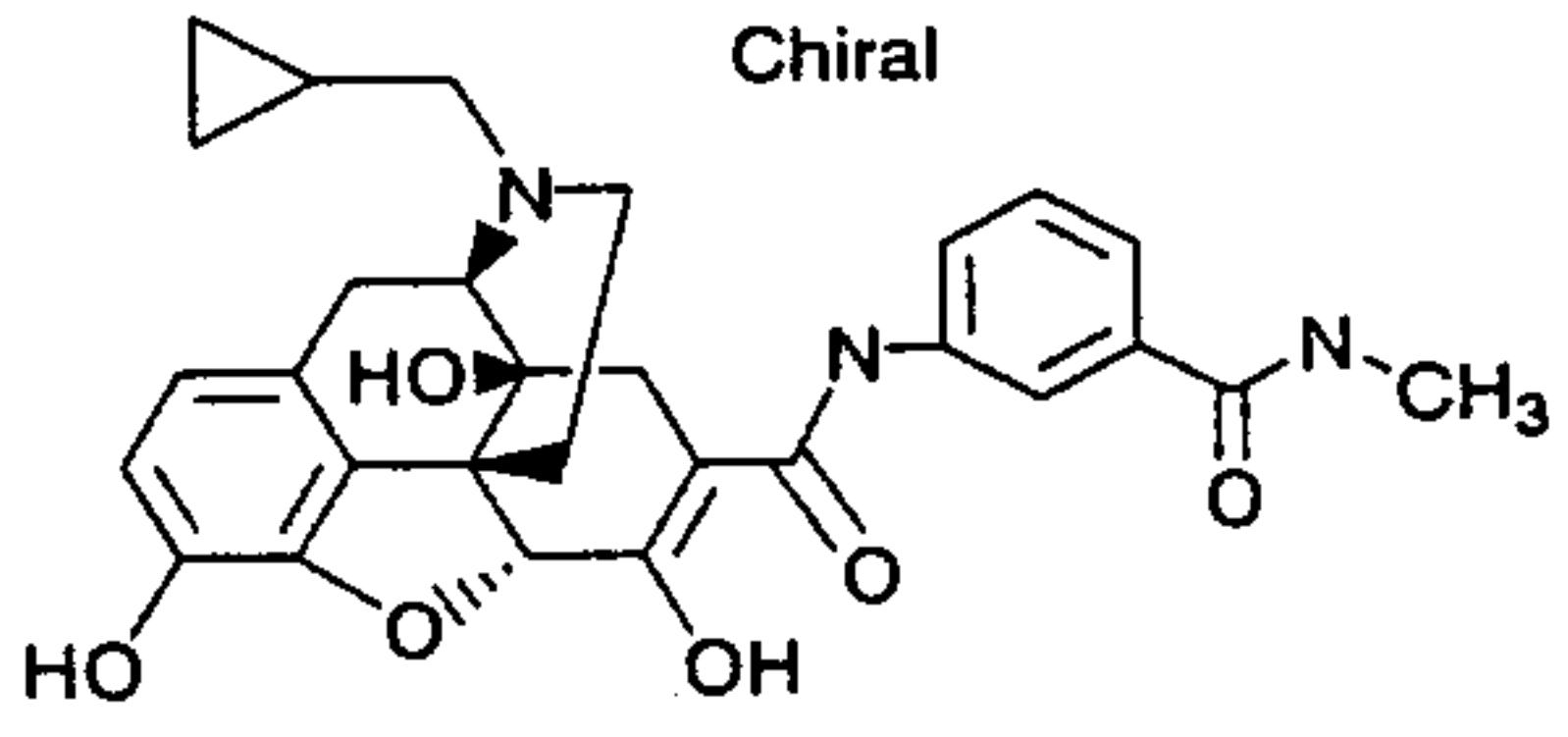
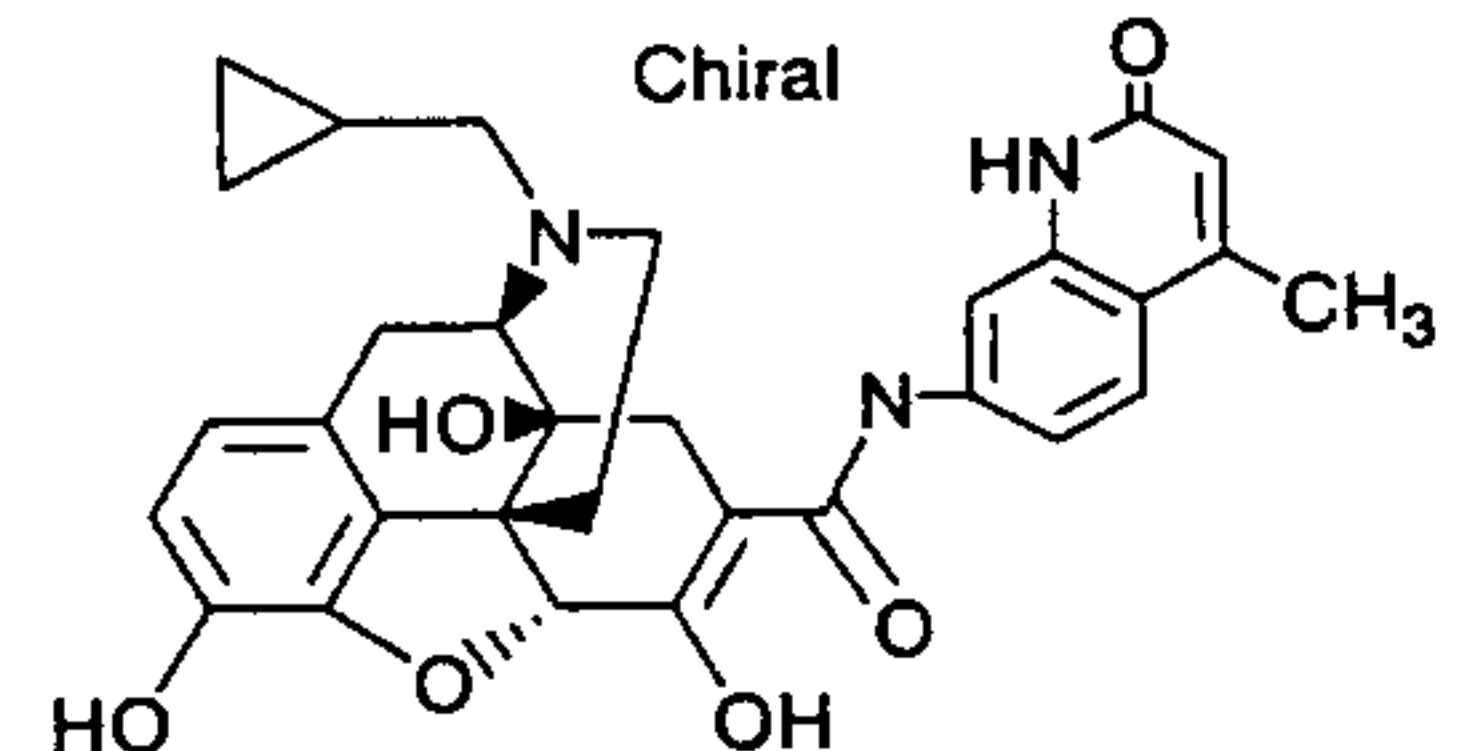
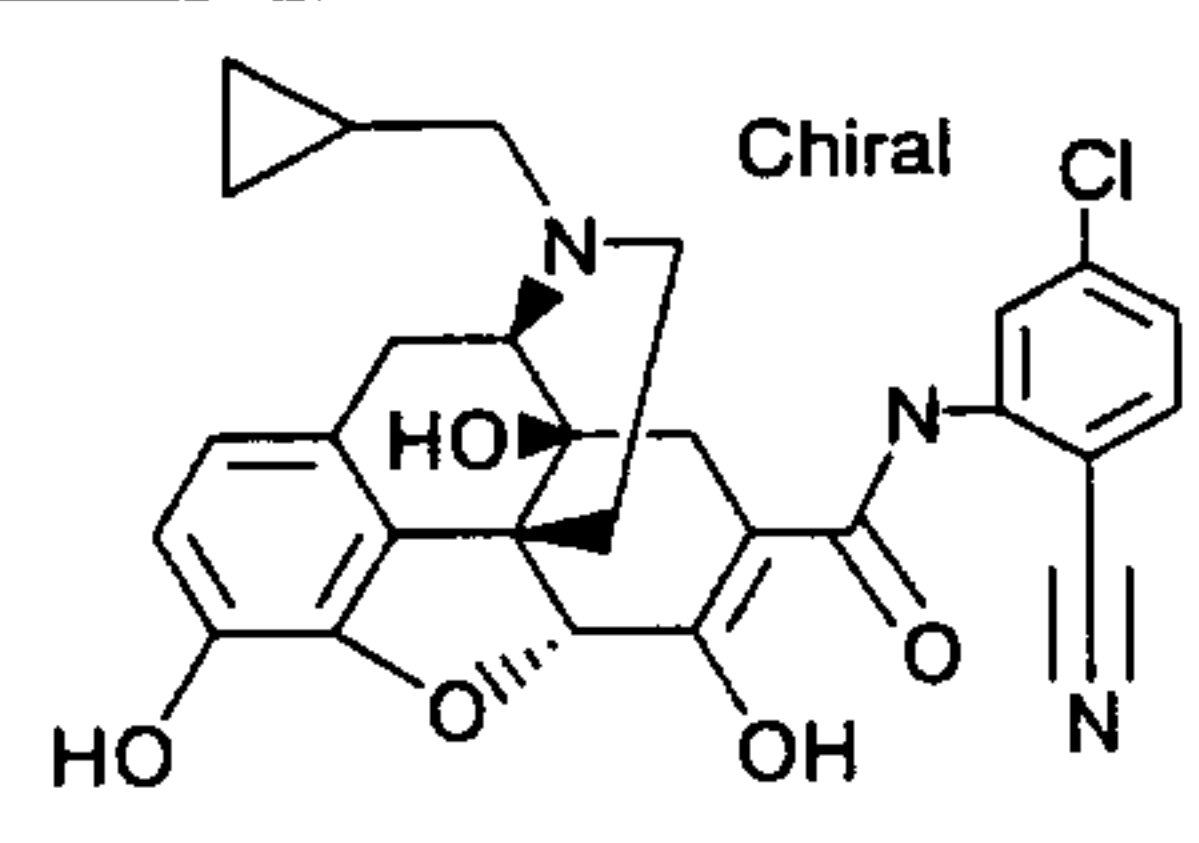
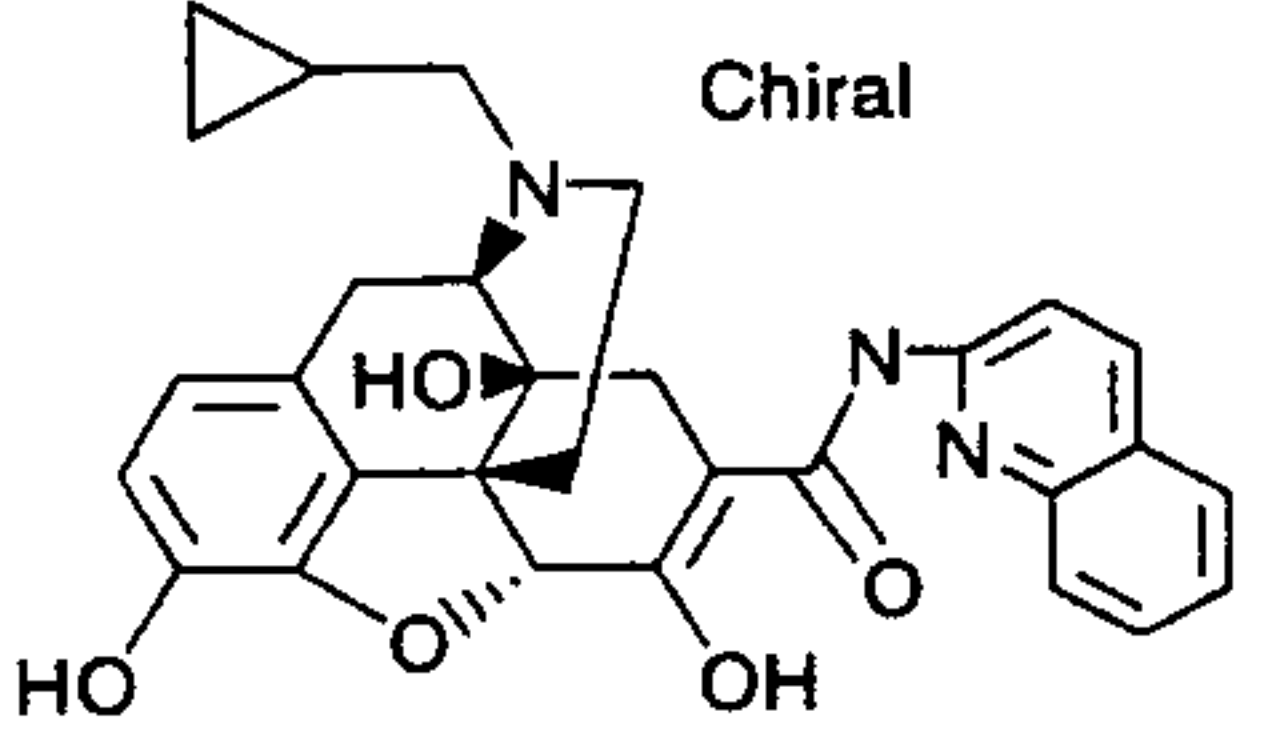
[0102]

[Table 57]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (1H-NMR (d6-DMSO) δ)
I-229		m/z 626 [M+H] ⁺ 1.74 min**	
I-230		m/z 521 [M+H] ⁺ 1.56 min**	
I-231		m/z 500 [M+H] ⁺ 1.40 min **	
I-232		m/z 630 [M+H] ⁺ 1.72 min**	
I-233		m/z 501 [M+H] ⁺ 1.25 min**	
I-234		m/z 505 [M+H] ⁺ 1.46 min**	
I-235		m/z 515 [M+H] ⁺ 1.56 min**	

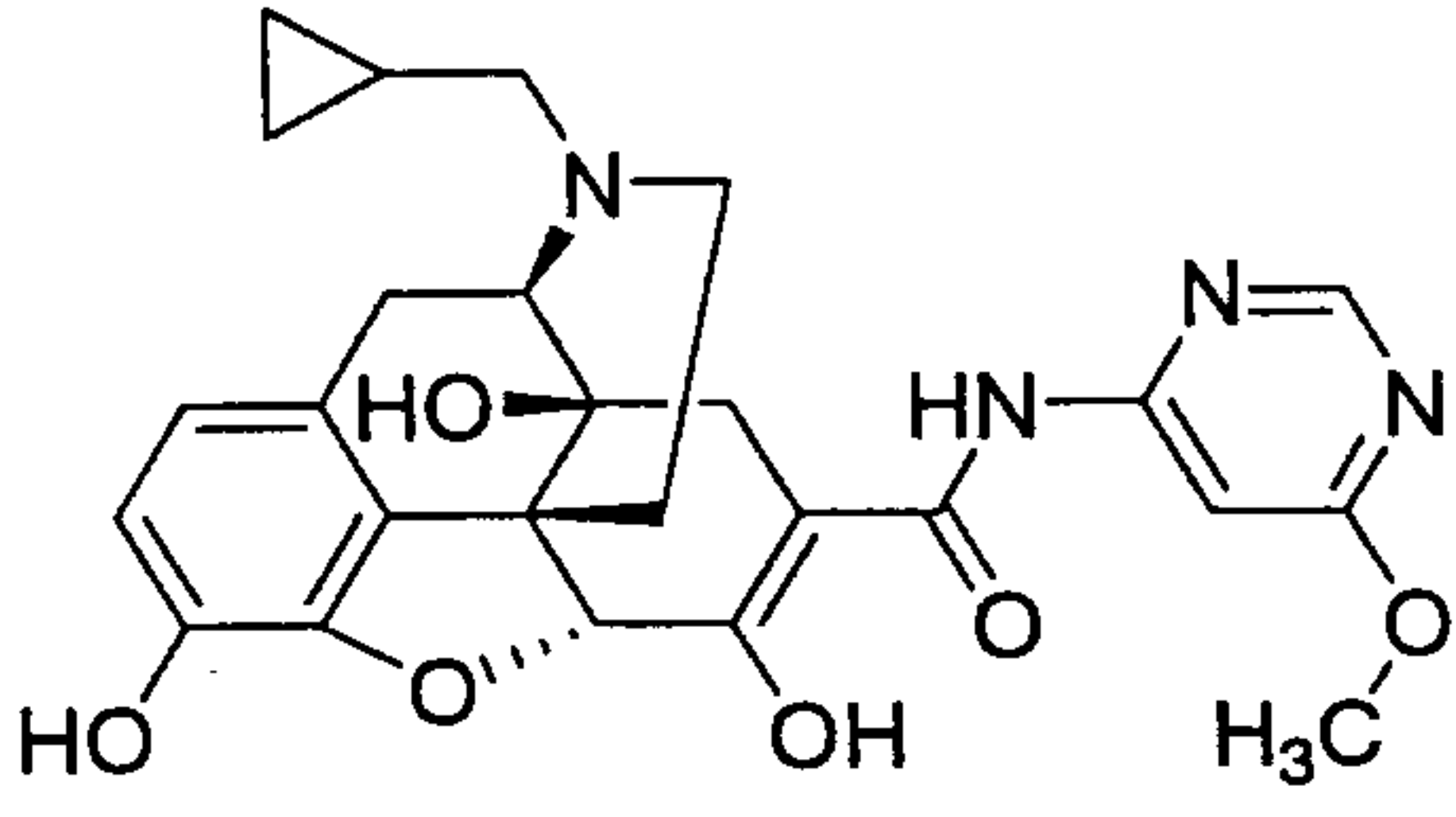
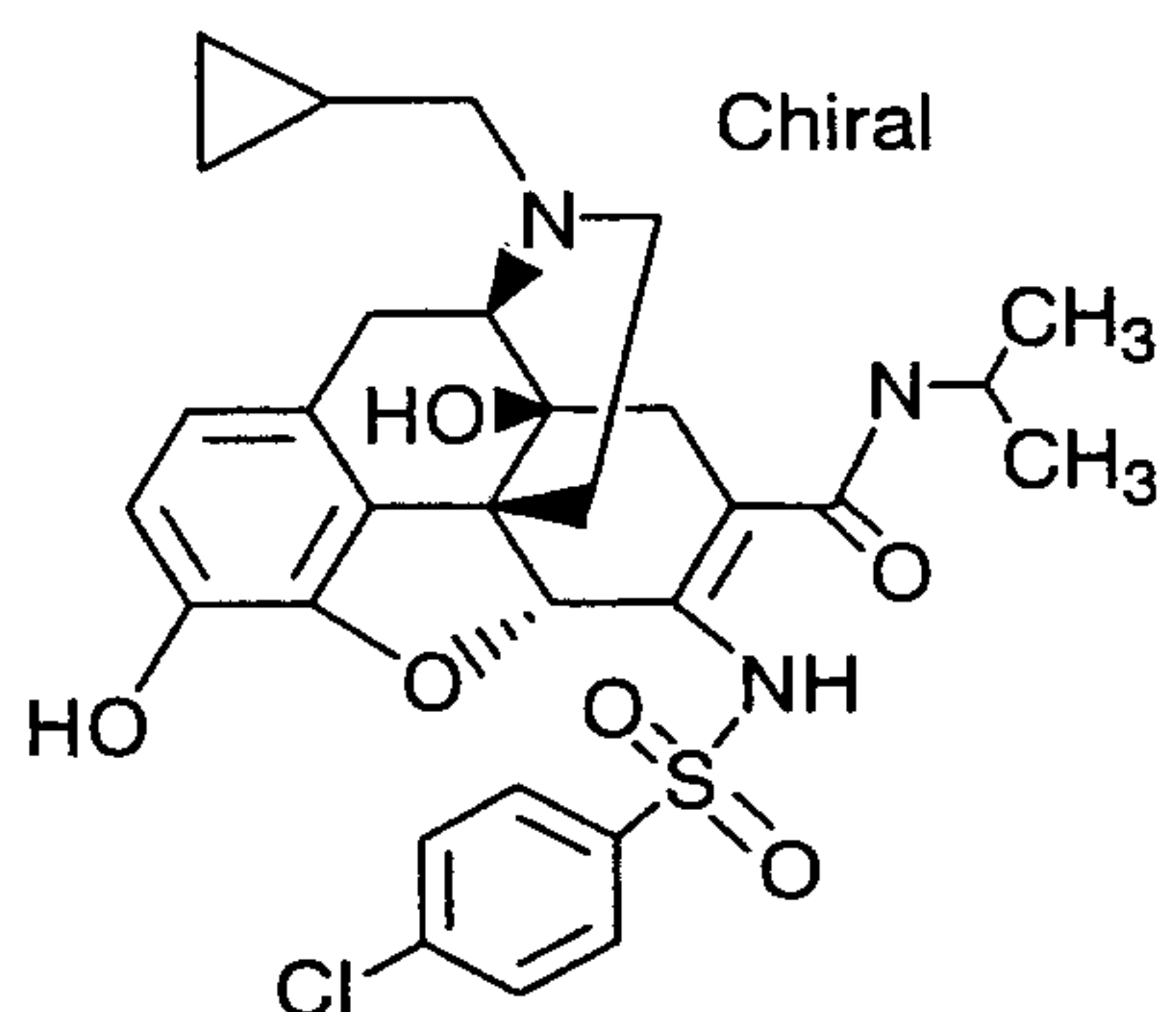
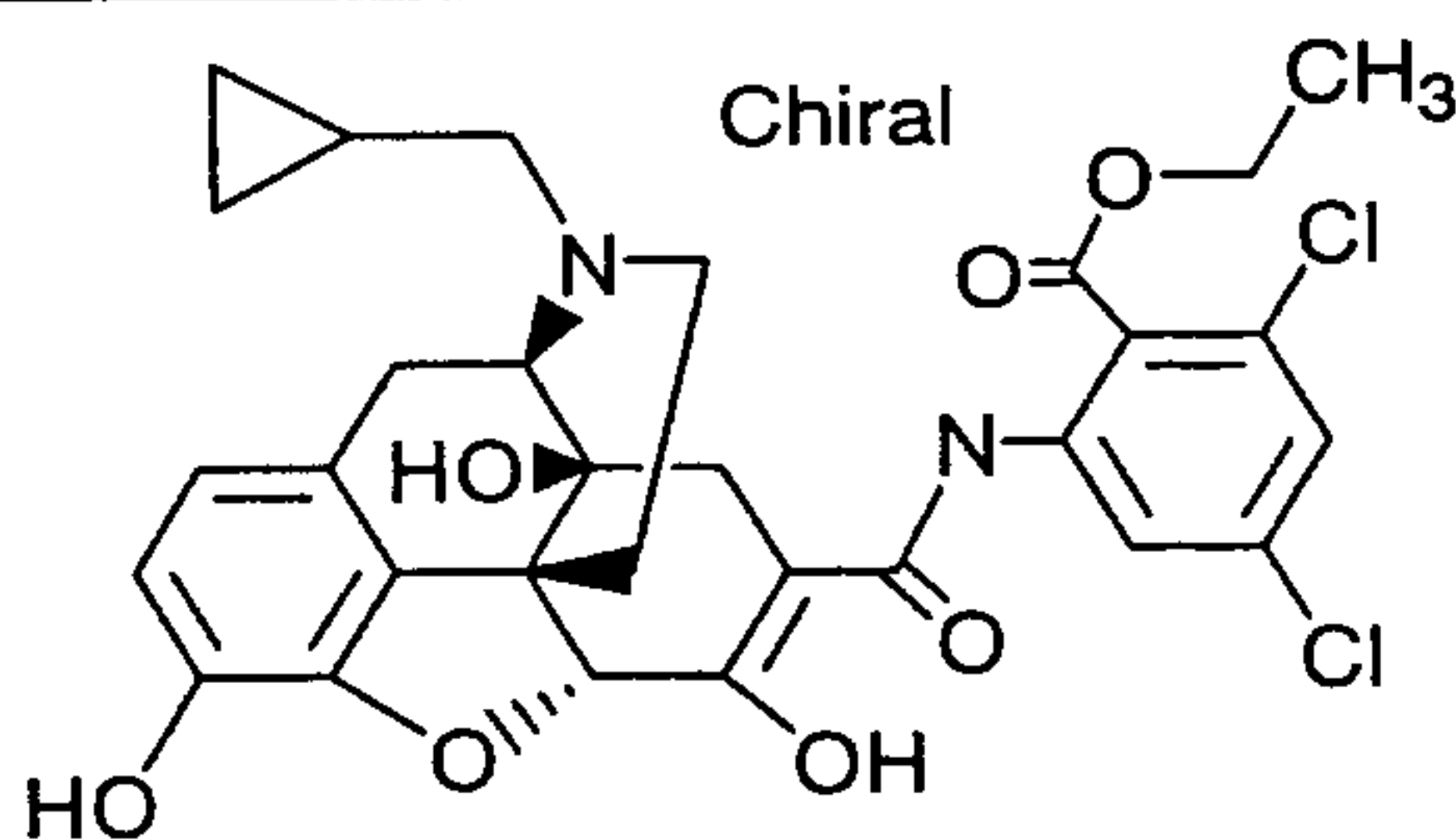
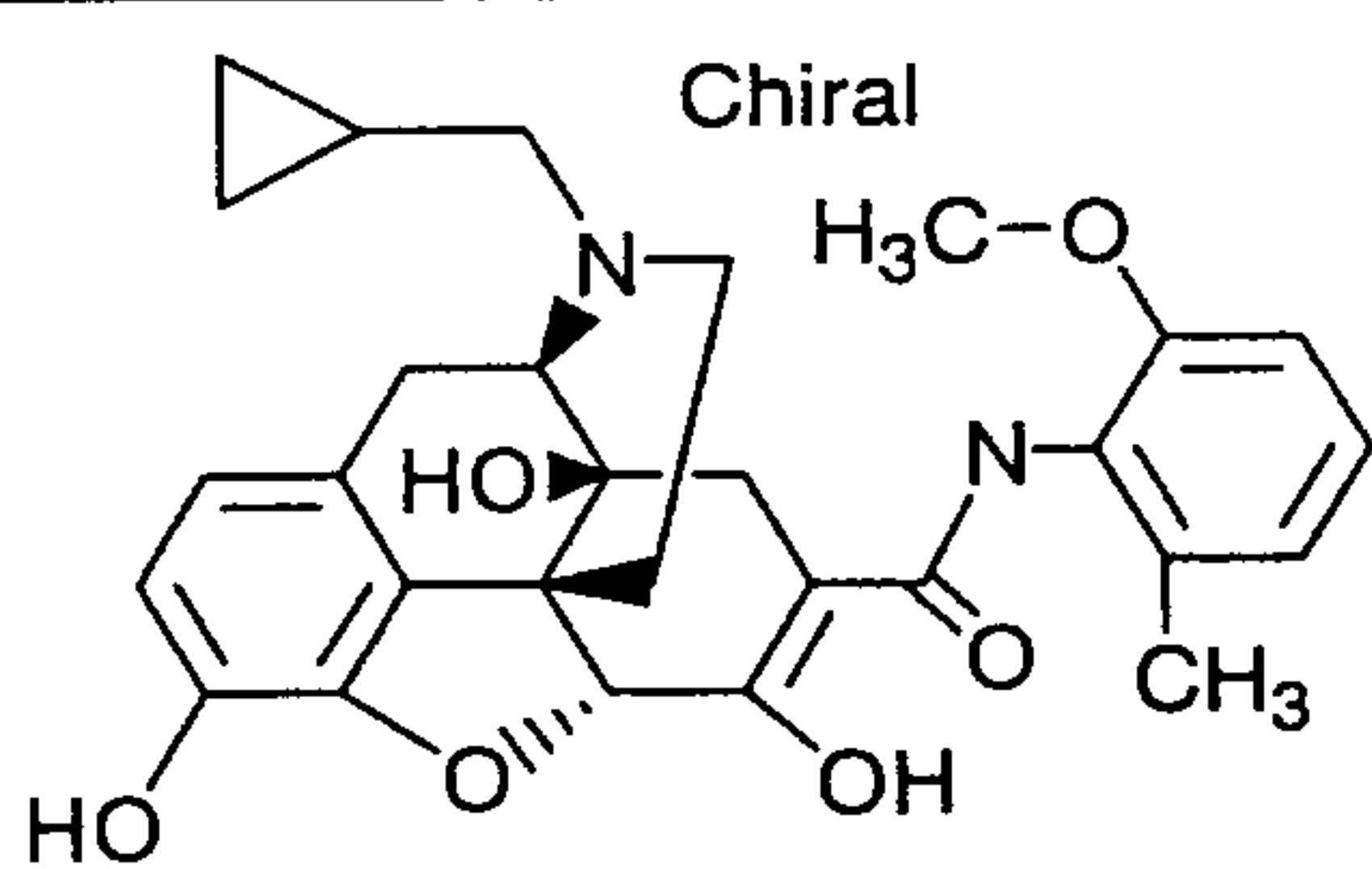
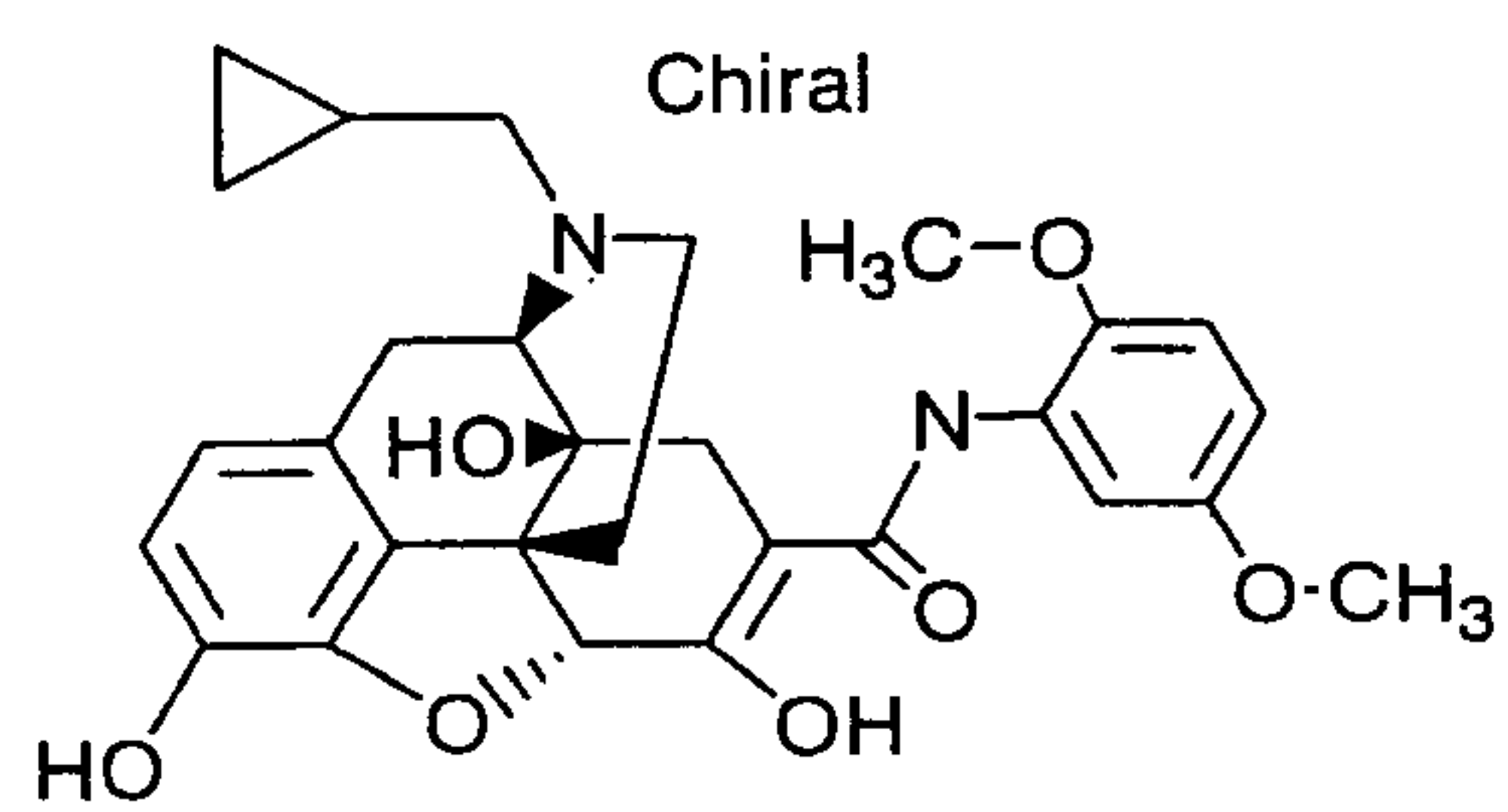
[0103]

[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**	
I-237	 Chiral	m/z 501 [M+H] ⁺ 1.17 min**	
I-238	 Chiral	m/z 546 [M+H] ⁺ 1.29 min **	
I-239	 Chiral	m/z 518 [M+H] ⁺ 1.21 min **	
I-240	 Chiral	m/z 542 [M+H] ⁺ 1.31 min**	
I-241	 Chiral	m/z 520 [M+H] ⁺ 1.50 min **	
I-242	 Chiral		

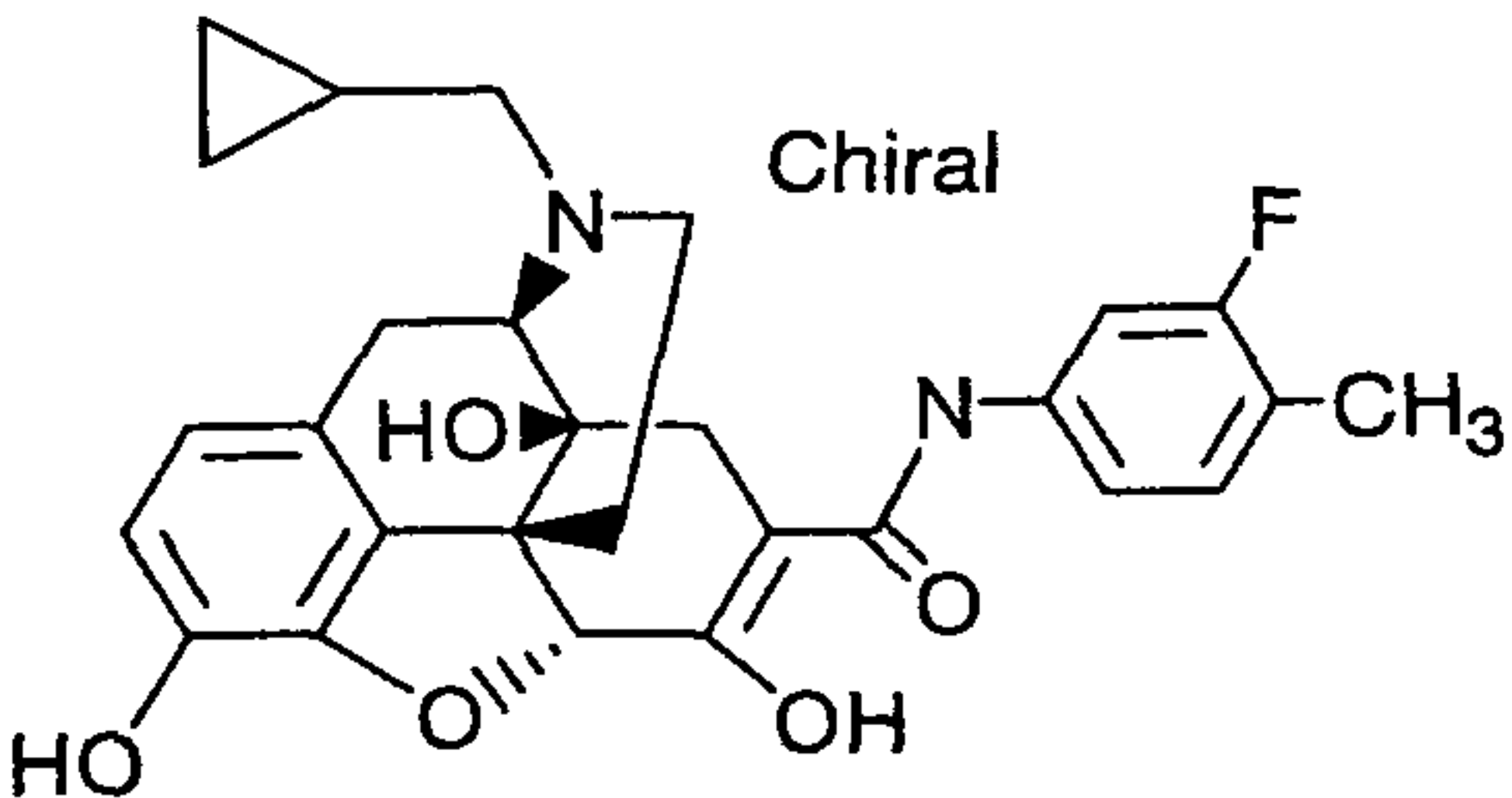
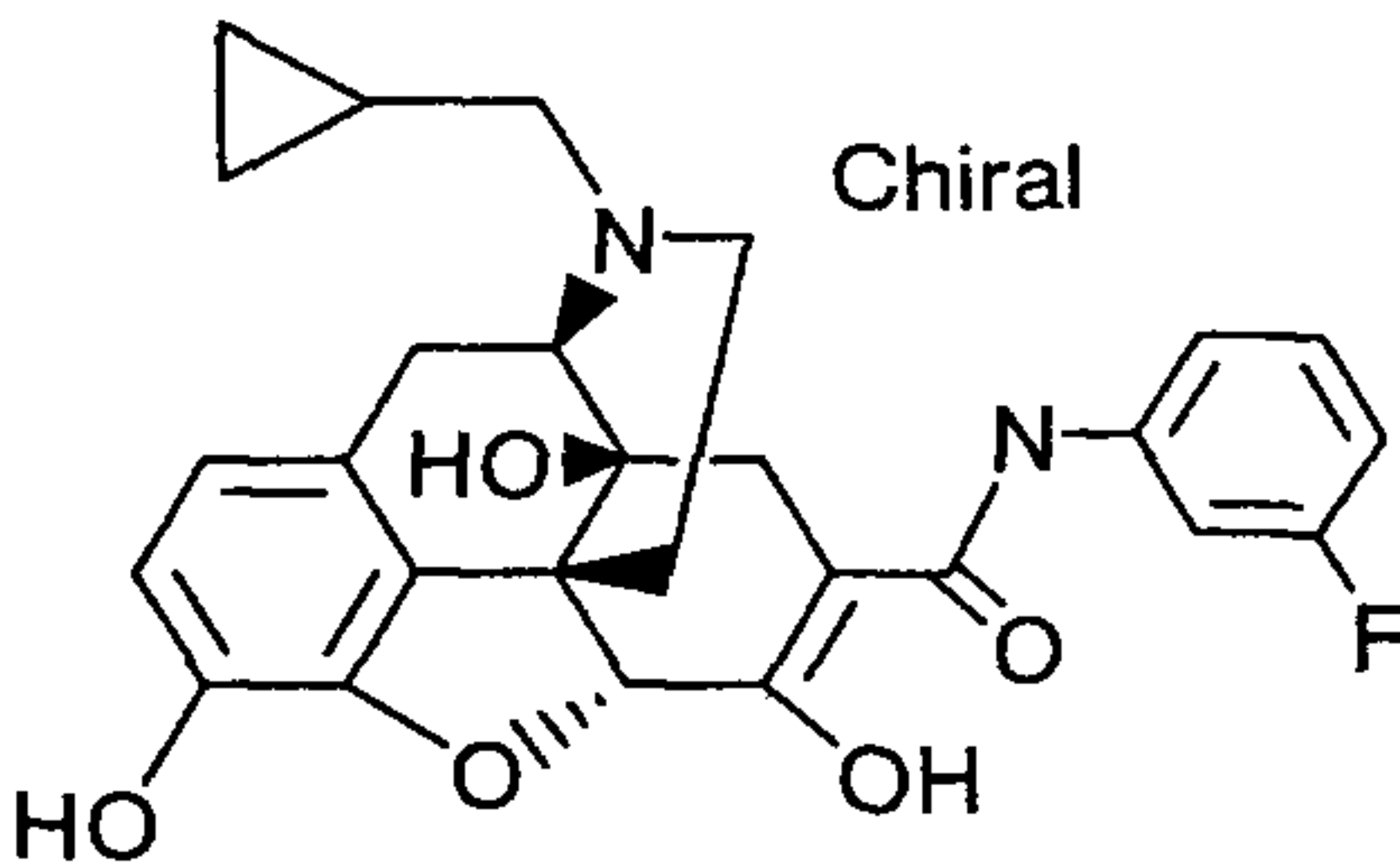
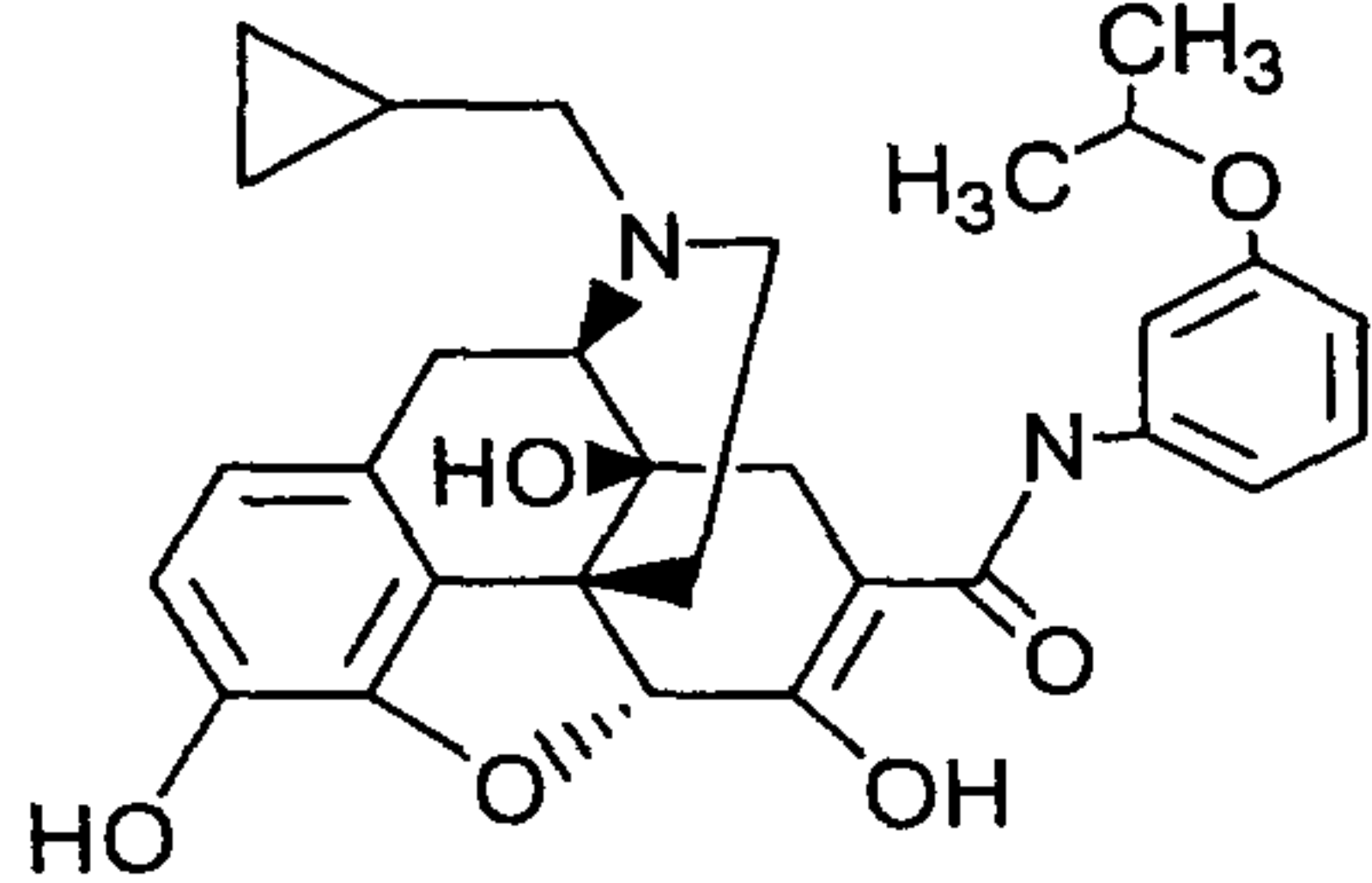
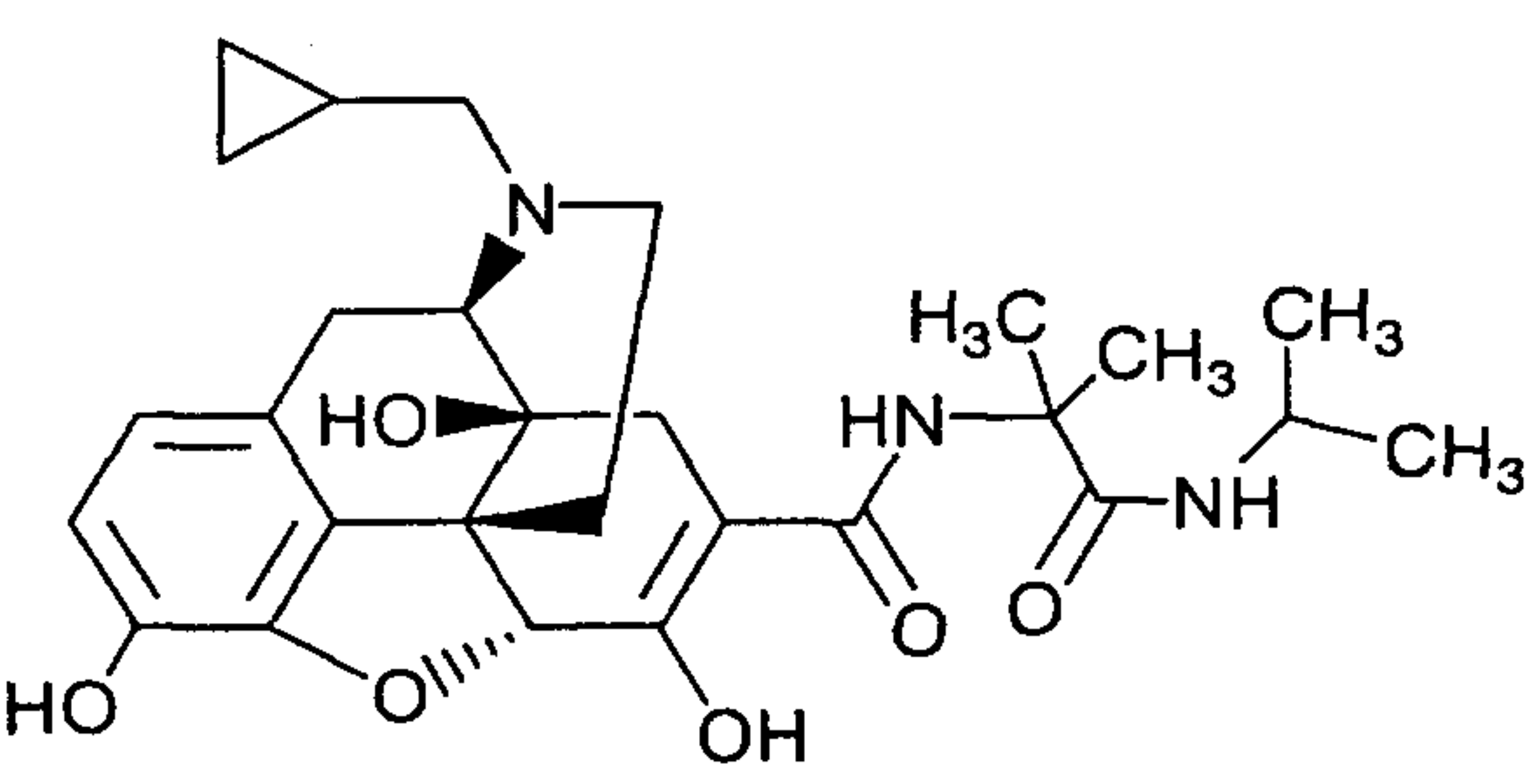
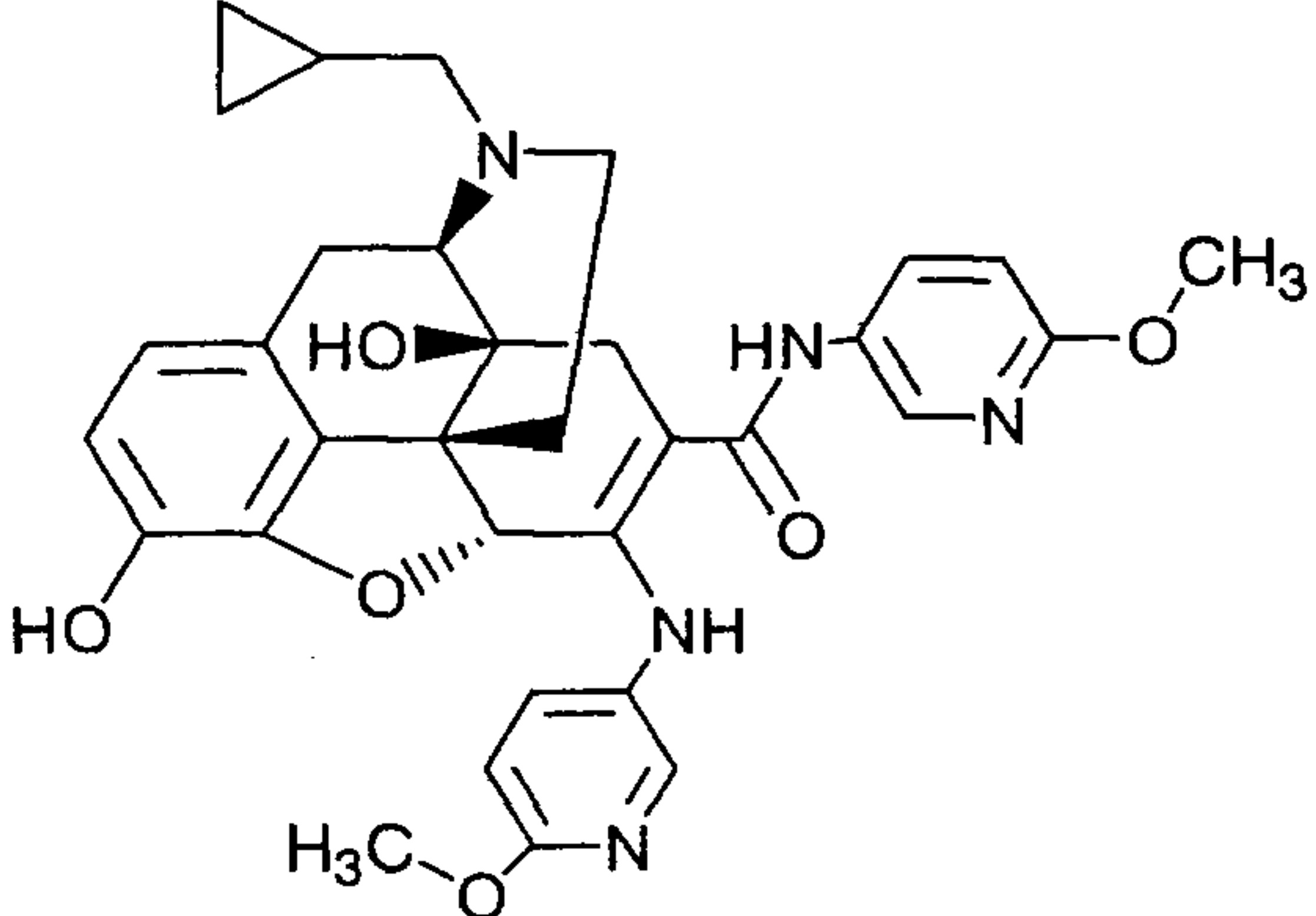
[0104]

[Table 59]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d6-DMSO) δ)
I-243		m/z 493 [M+H] ⁺ 1.05 min	
I-244		m/z 601 [M+H] ⁺ 1.02 min	0.11–0.13 (m, 2H), 0.48–0.51 (m, 2H), 0.87 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H), 1.48 (d, J = 11.1 Hz, 1H), 1.88 (d, J = 18.0 Hz, 1H), 2.10 (s, 3H), 2.18–2.57 (m, 7H), 3.04 (d, J = 16.8 Hz, 1H), 3.19 (brs, 1H), 3.78 (q, J = 6.9 Hz, 1H), 4.68 (brs, 1H), 5.43 (brs, 1H), 6.49 (d, J = 6.6 Hz, 1H), 6.51 (d, J = 6.6 Hz, 1H), 7.35–7.37 (m, 2H), 7.54 (brs, 1H), 7.85 (d, J = 6.9 Hz, 2H), 9.09 (brs, 1H), 12.4 (brs, 1H)
I-245		m/z 601 [M+H] ⁺ 0.76 min	
I-246		m/z 505 [M+H] ⁺ 1.38 min **	
I-247		m/z 521 [M+H] ⁺ 1.58 min**	

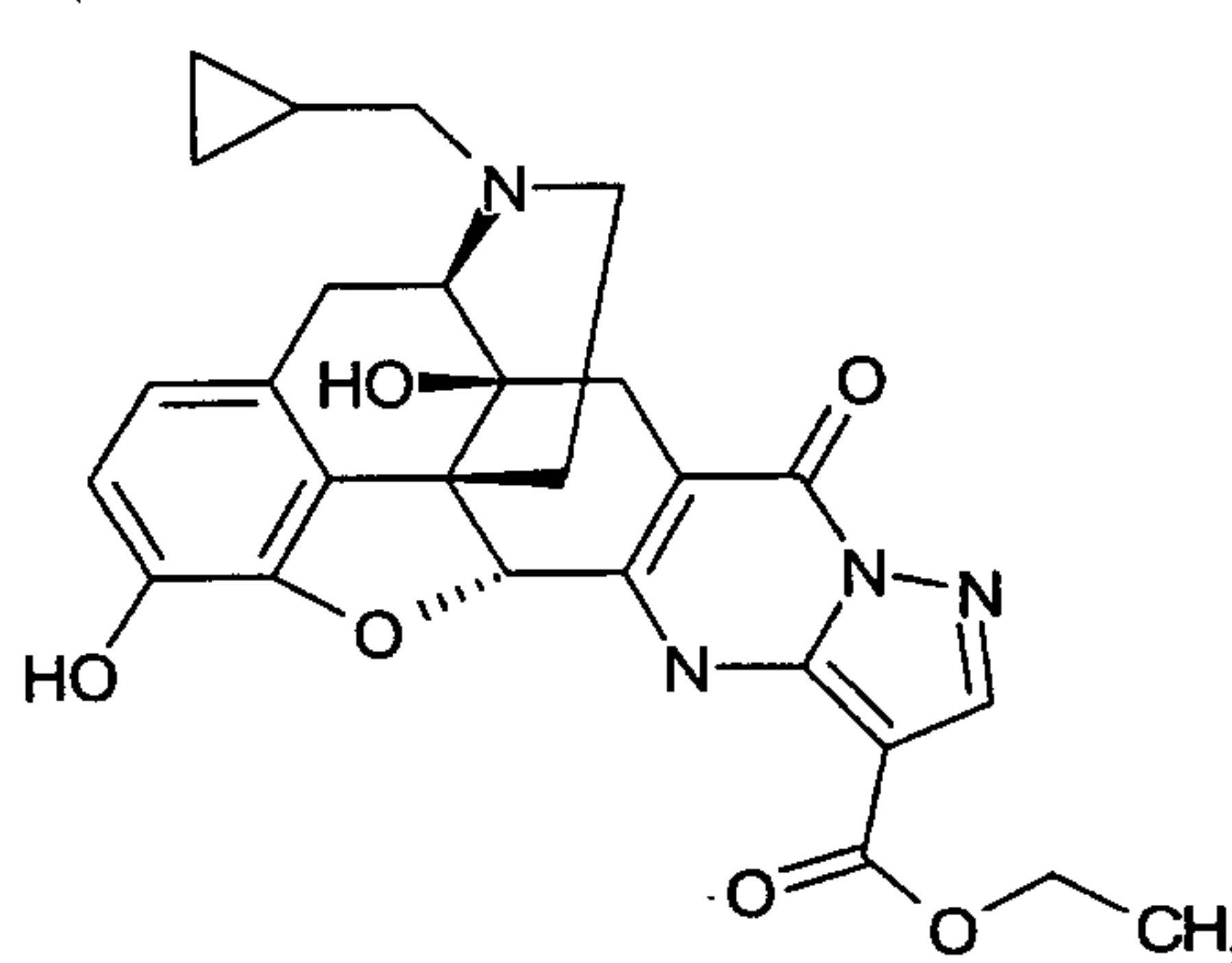
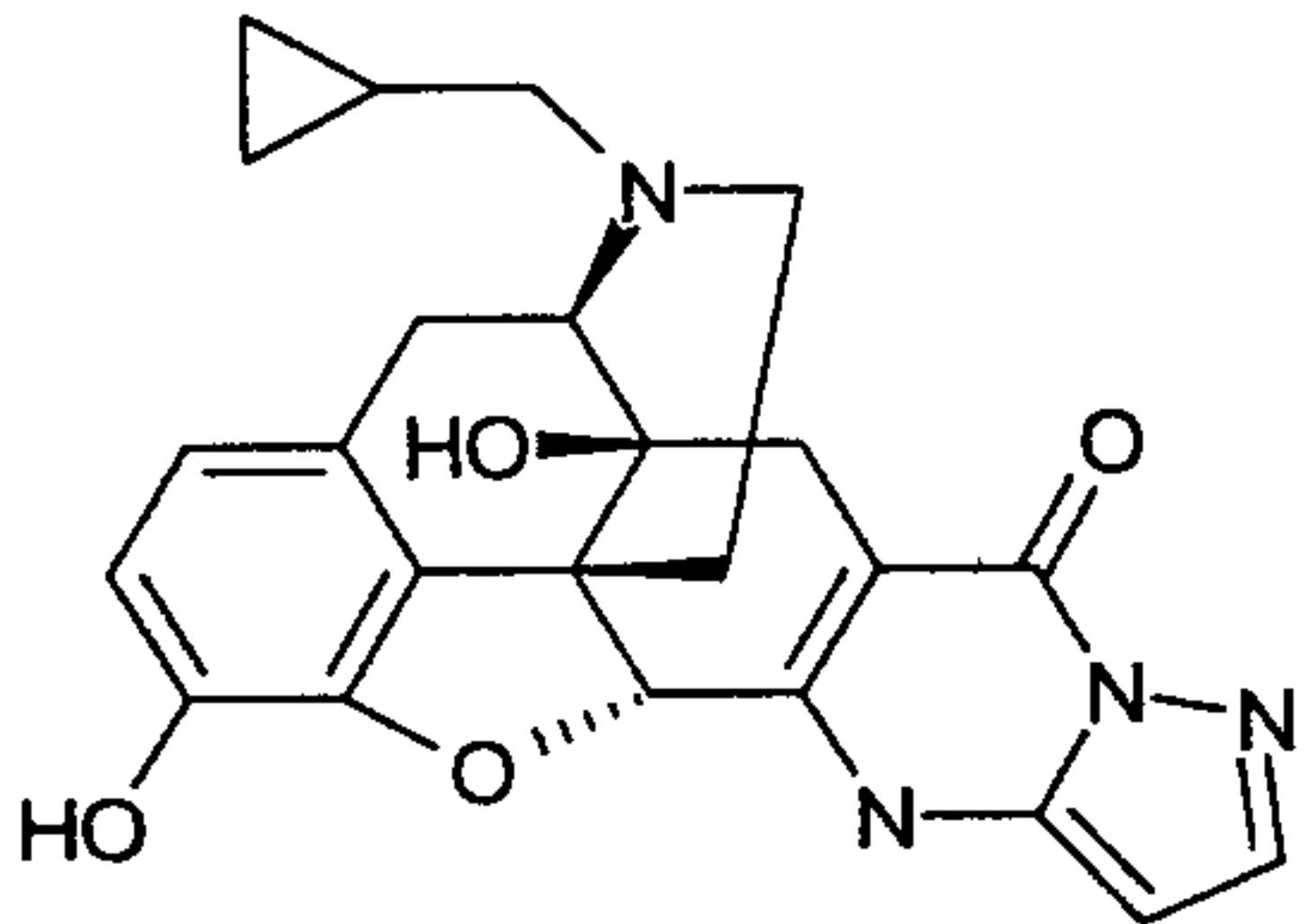
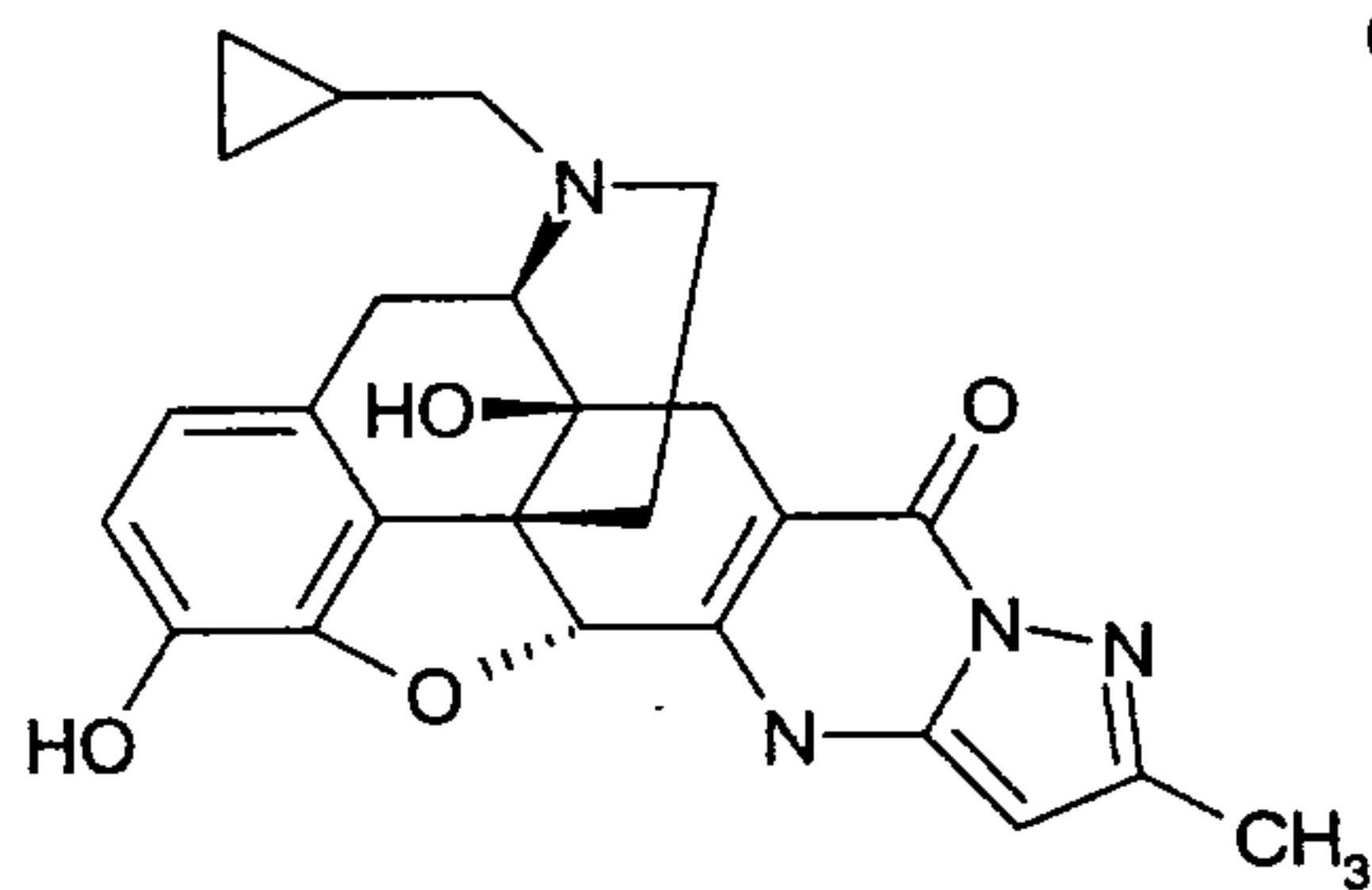
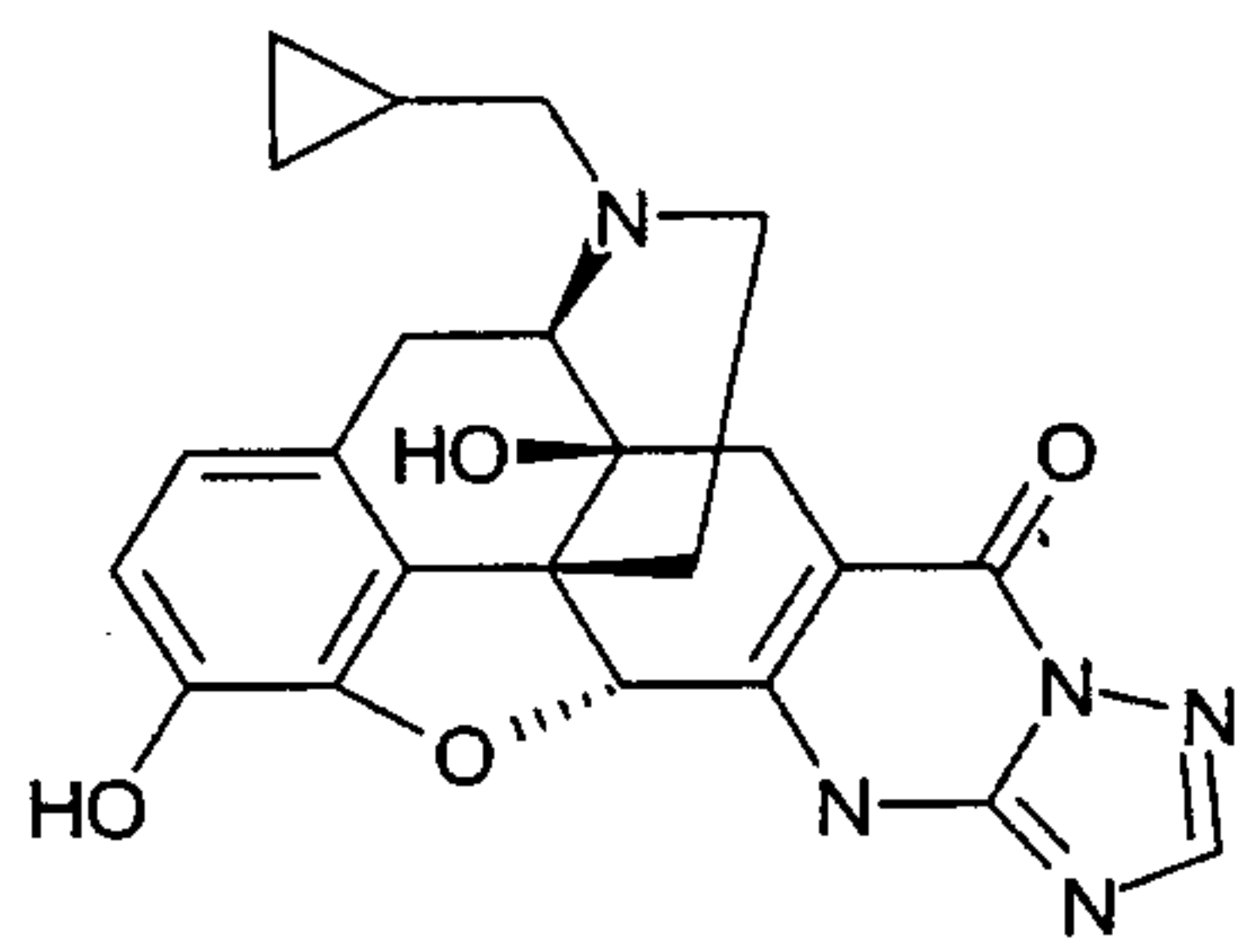
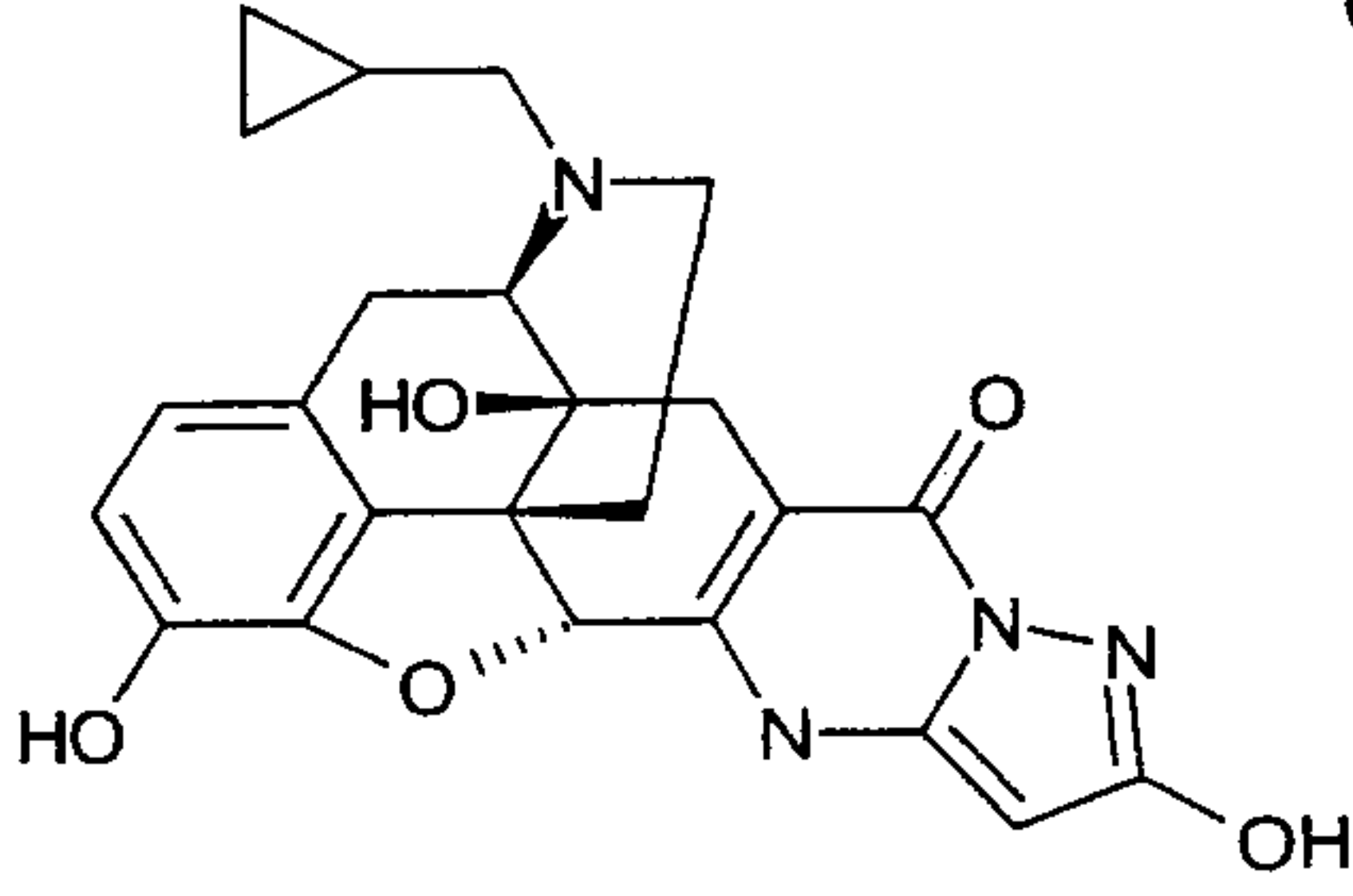
[0105]

[Table 60]

Compound No.	Chemical structure	LC/MS ^{*1}	NMR (¹ H-NMR (d ₆ -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 **	
I-251		m/z 512 [M+H] ⁺ 0.38 min	
I-252			0.10-0.15 (m, 2H), 0.34-0.38 (m, 2H), 0.73 (m, 1H), 1.26 (d, J = 9.6 Hz, 1H), 1.93-2.54 (m, 10H), 2.94 (d, J = 18.4 Hz, 1H), 3.10 (d, J = 6.0 Hz, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 4.58 (s, 1H), 4.84 (s, 1H), 6.42 (d, J = 8.0 Hz, 2H), 6.48 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 9.3 Hz, 2H), 6.69 (d, J = 9.2 Hz, 2H), 7.56 (dd, J = 2.8, 8.8 Hz, 1H), 7.66 (dd, J = 2.8, 8.8 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.76 (s, 1H), 8.97 (s, 1H), 10.78 (s, 1H).

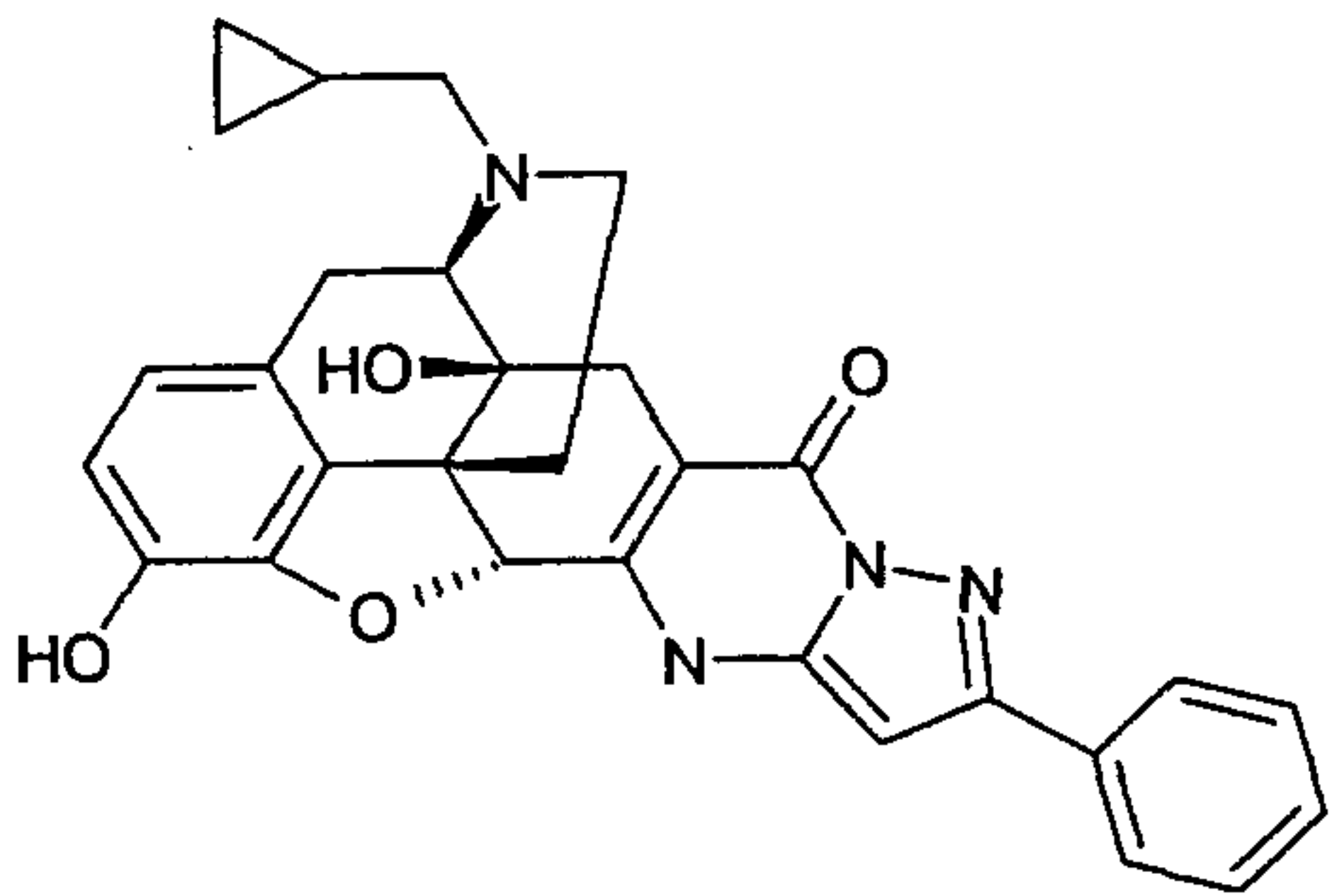
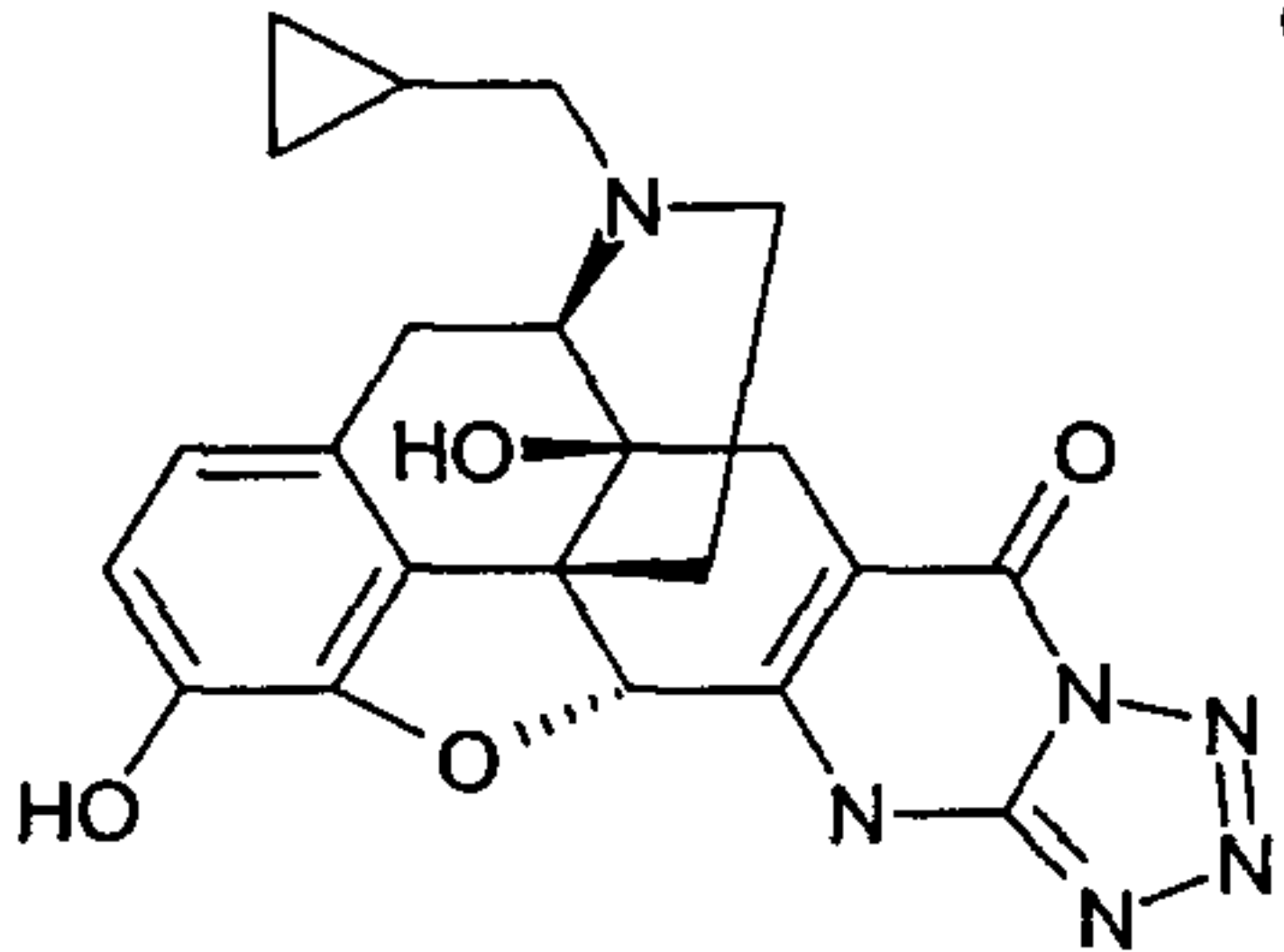
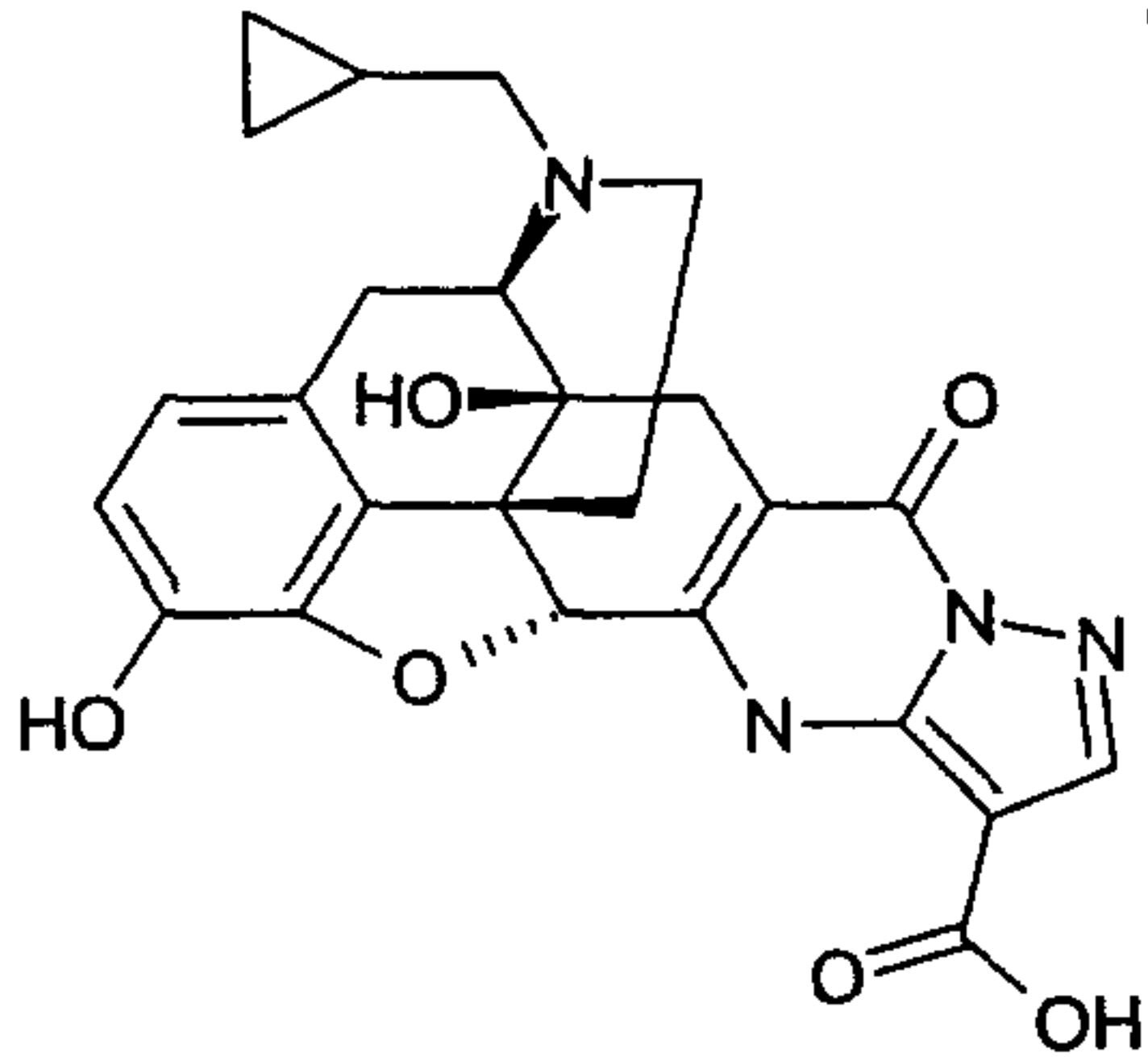
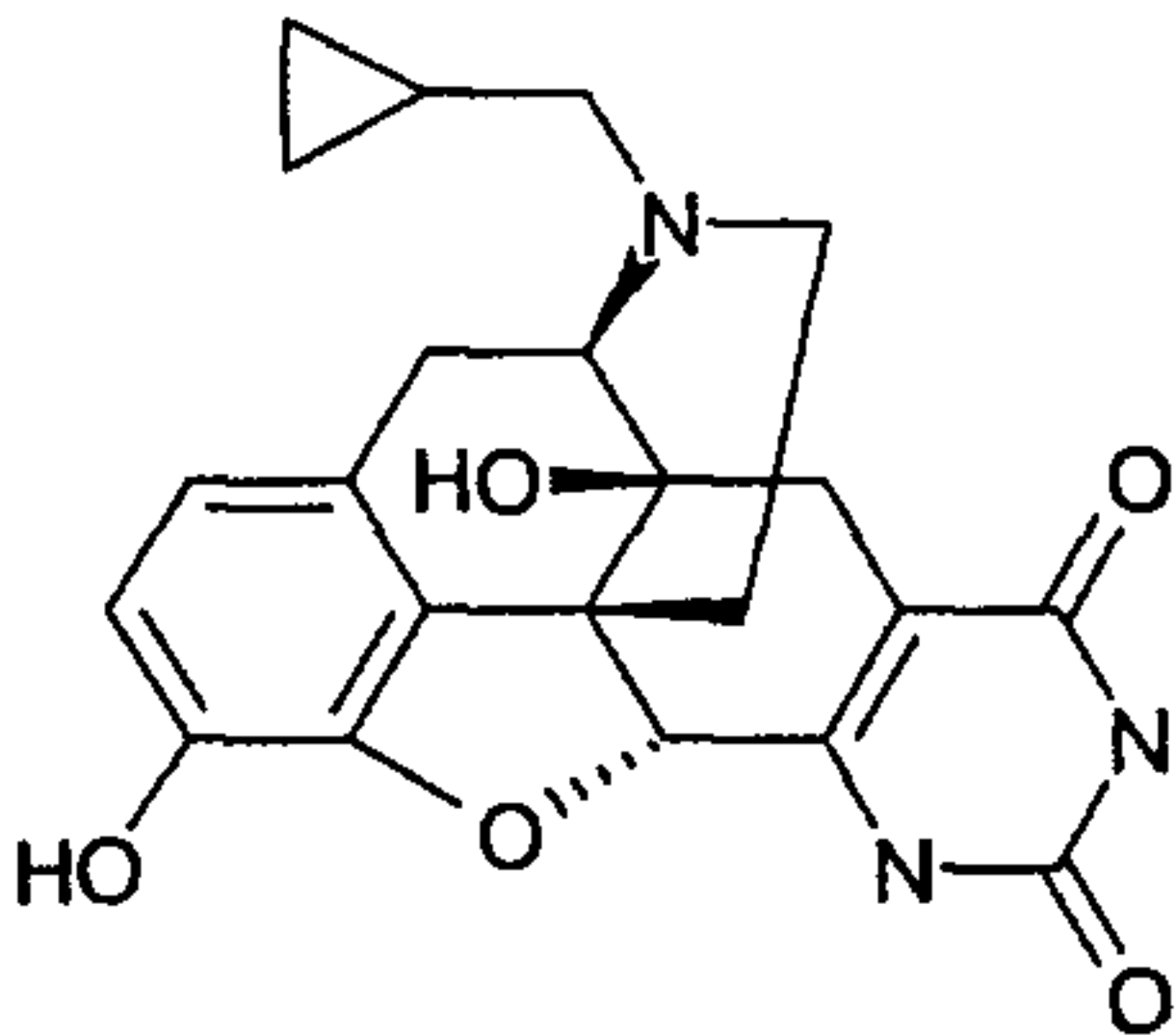
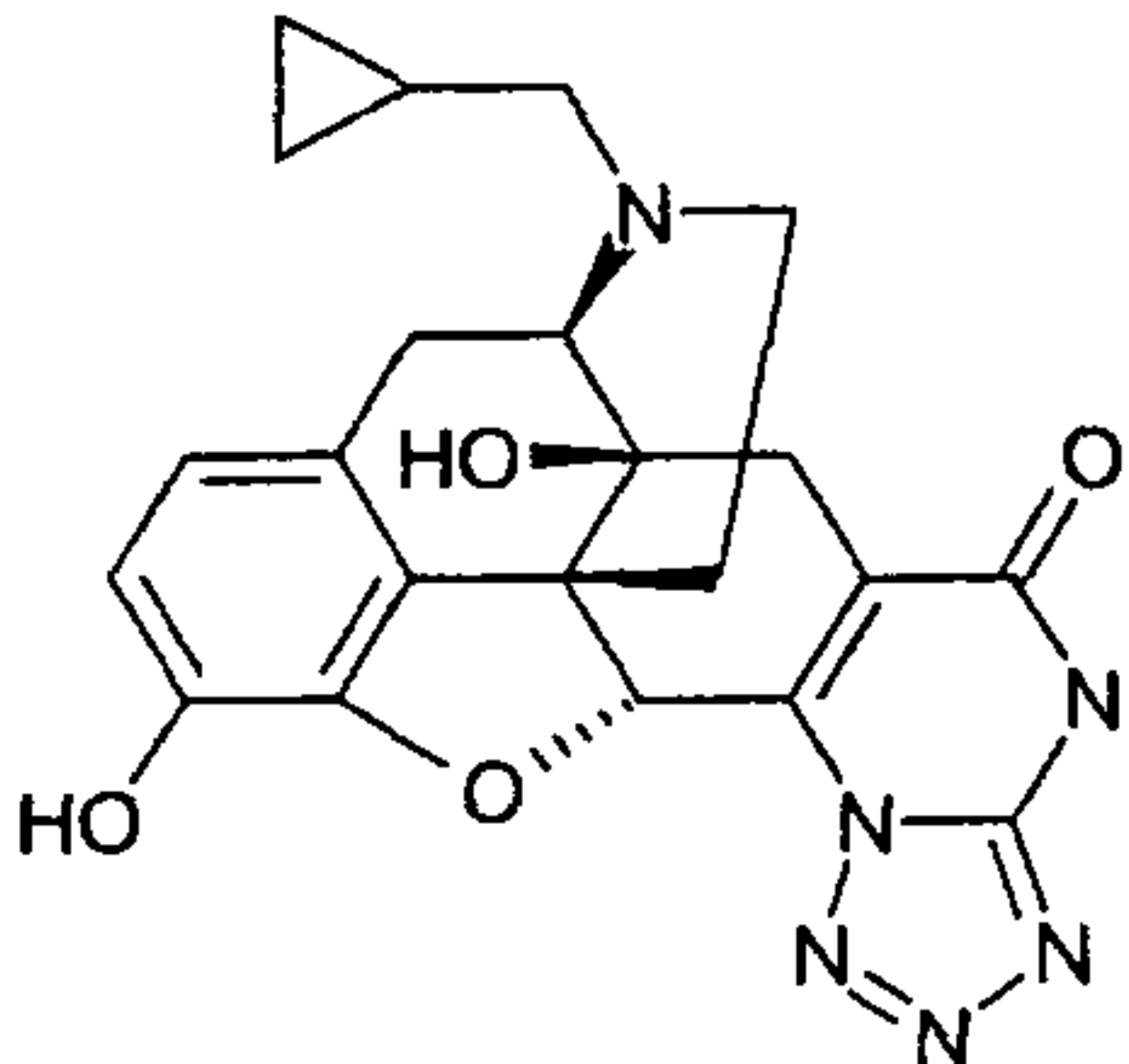
[0106]

[Table 61]

Compound No.	Chemical structure
I-253	Chiral 
I-254	Chiral 
I-255	Chiral 
I-256	Chiral 
I-257	Chiral 

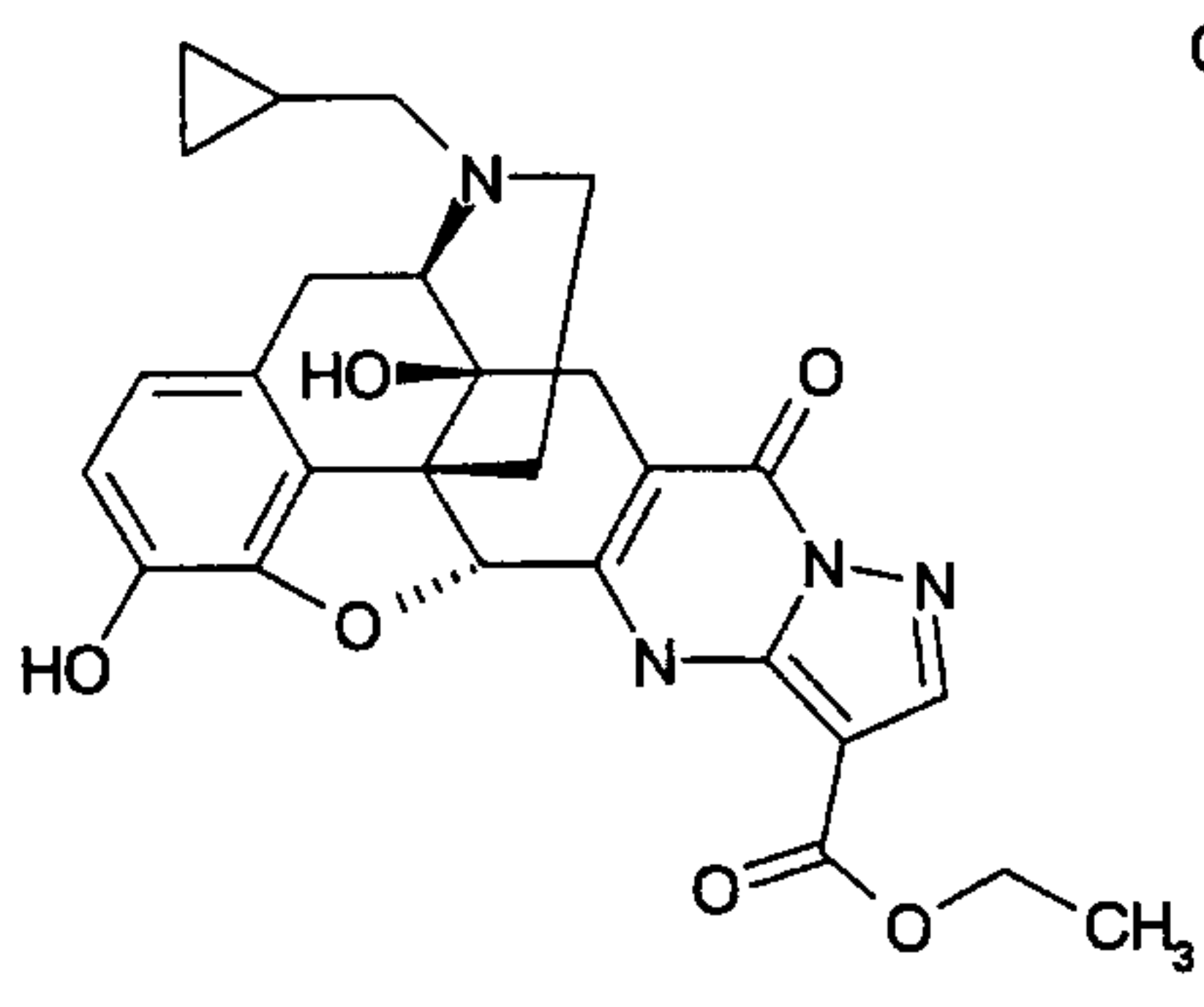
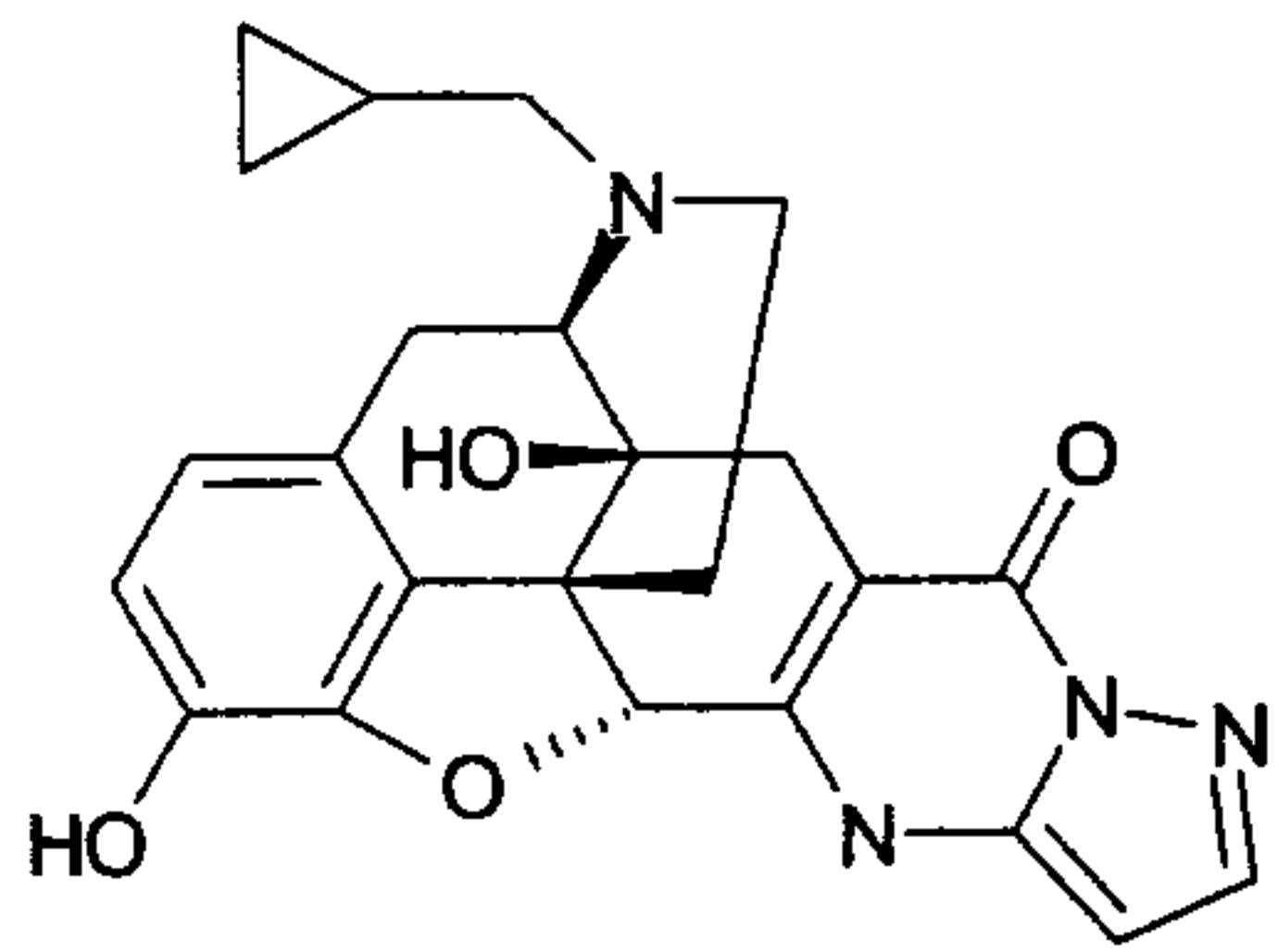
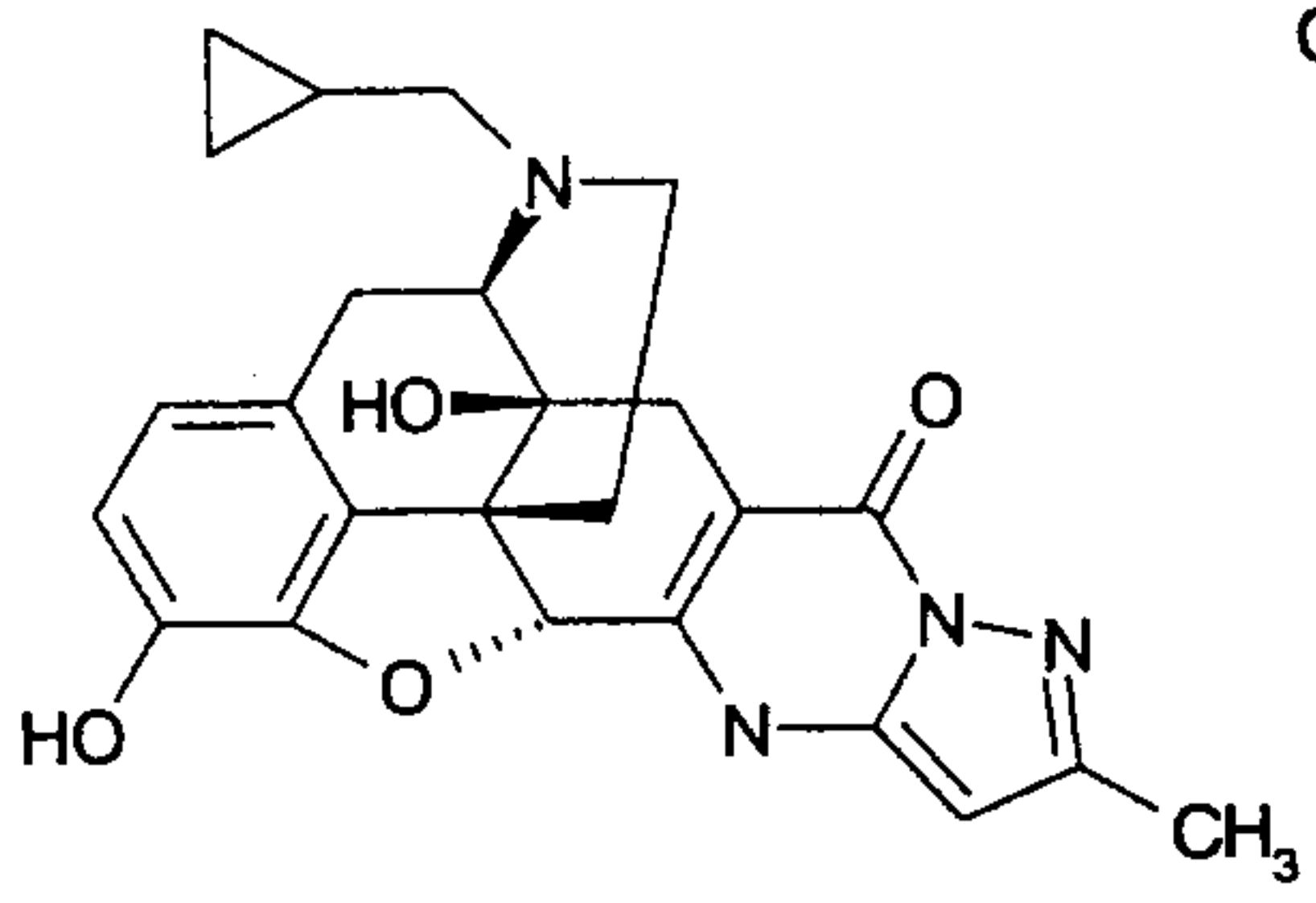
[0107]

[Table 62]

Compound No.	Chemical structure
I-258	Chiral 
I-259	Chiral 
I-260	Chiral 
I-261	Chiral 
I-262	Chiral 

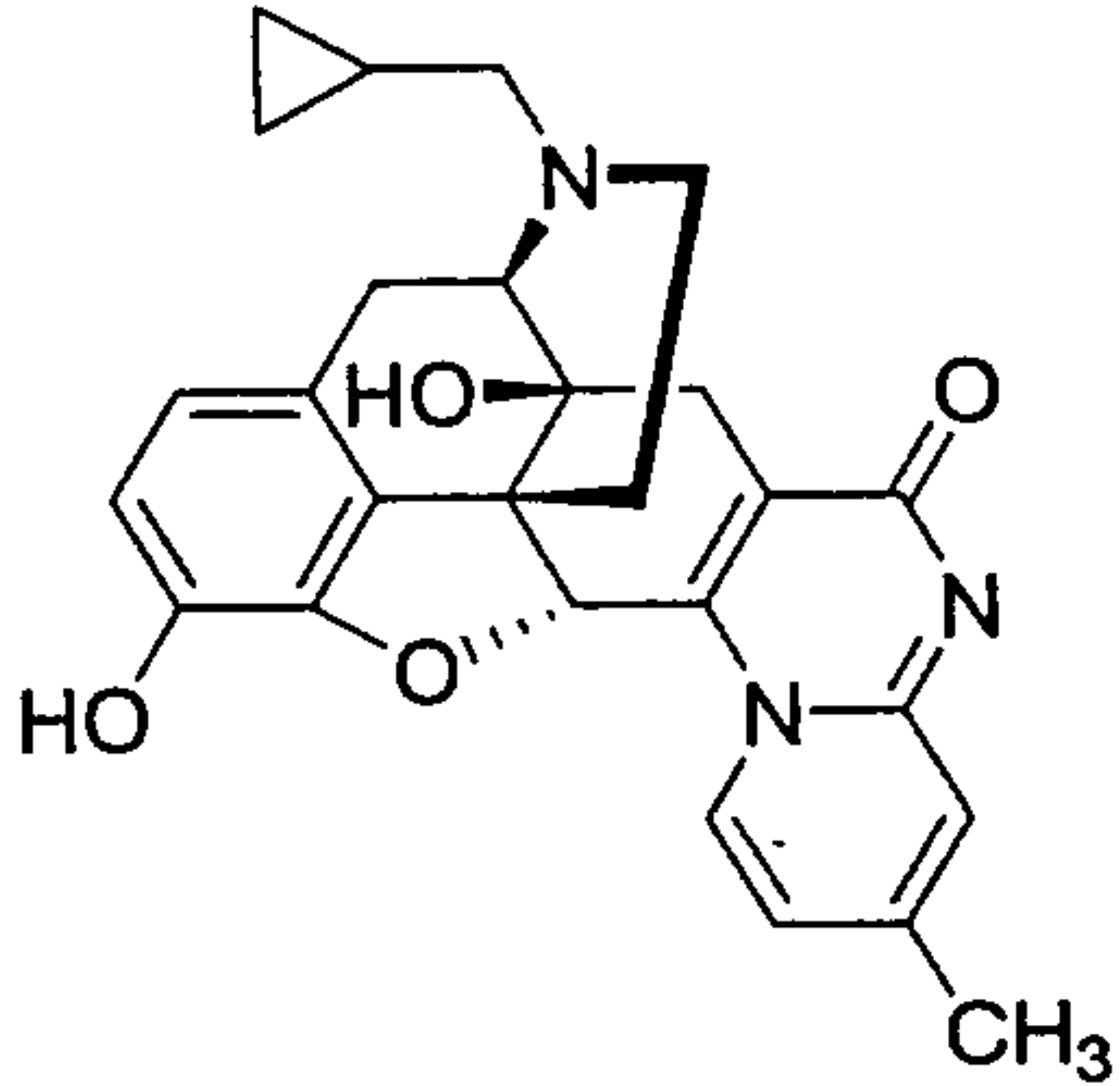
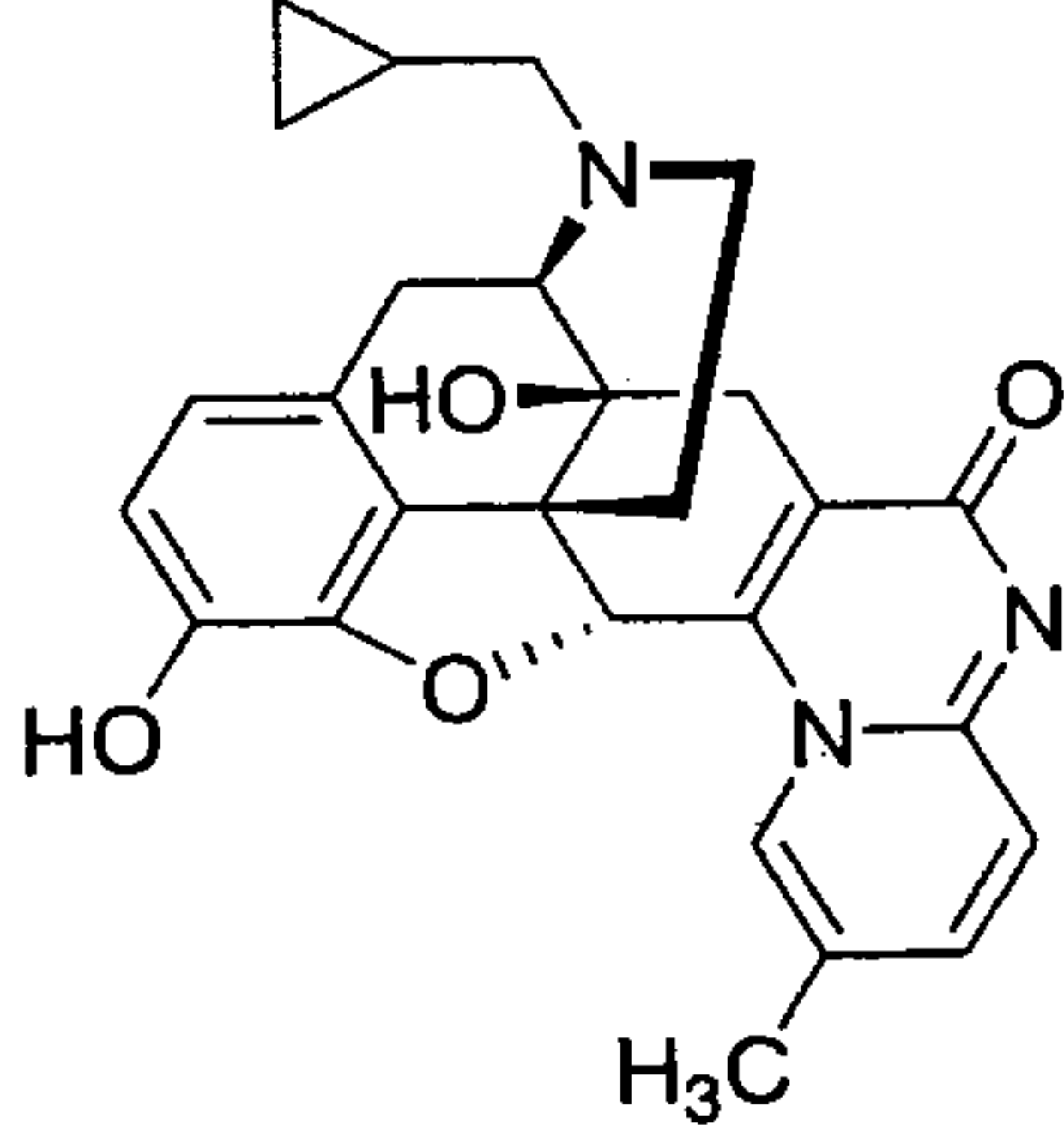
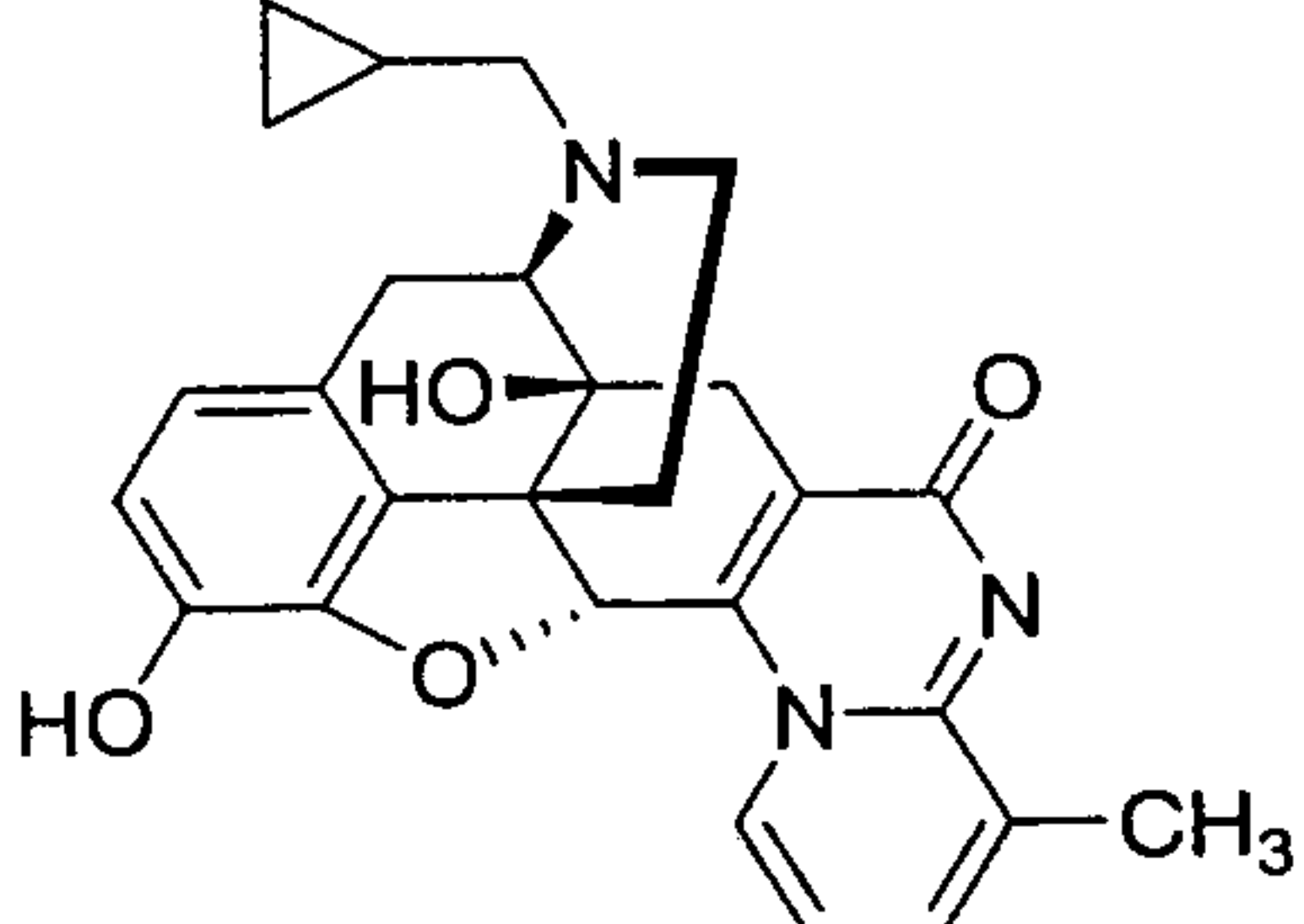
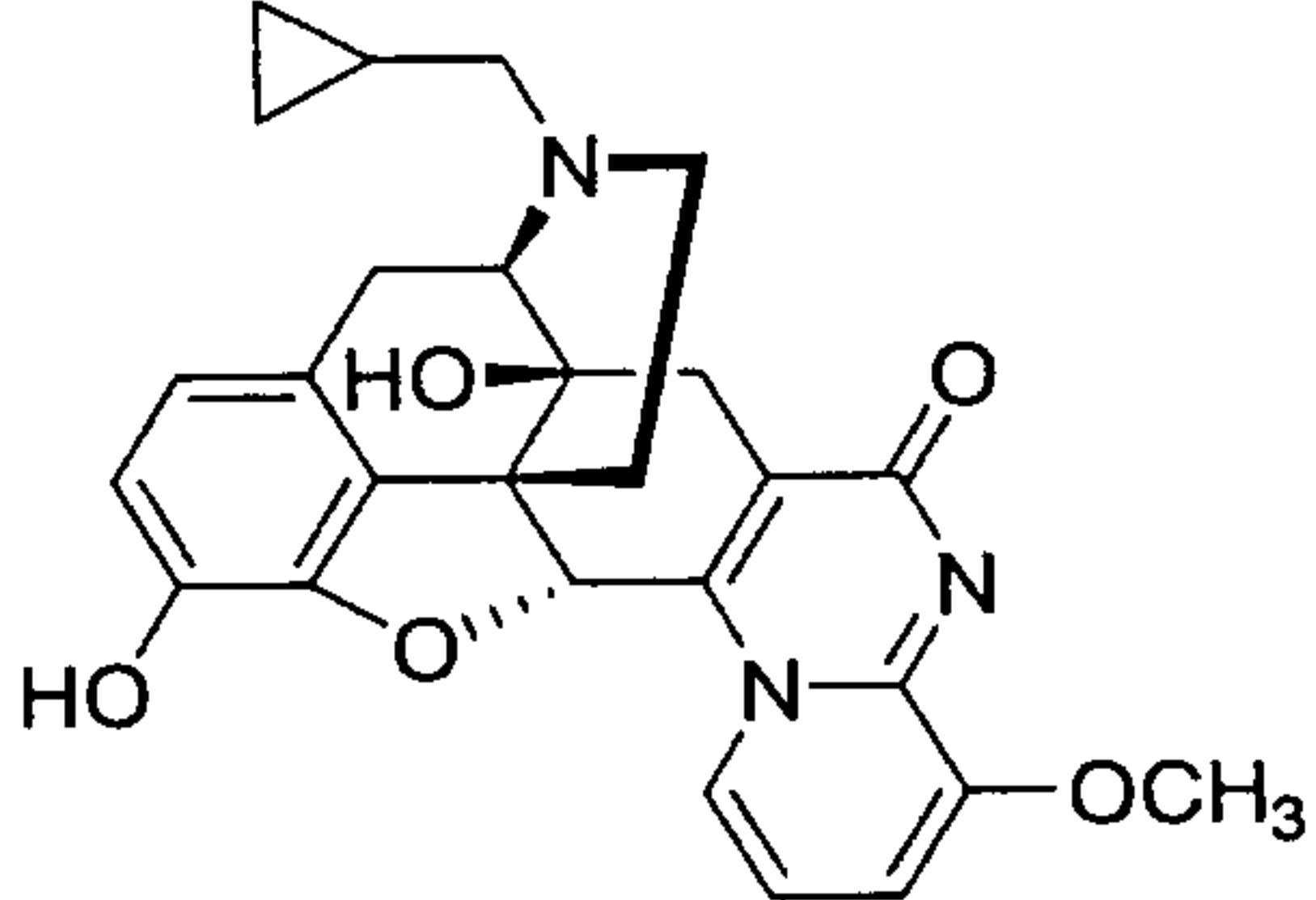
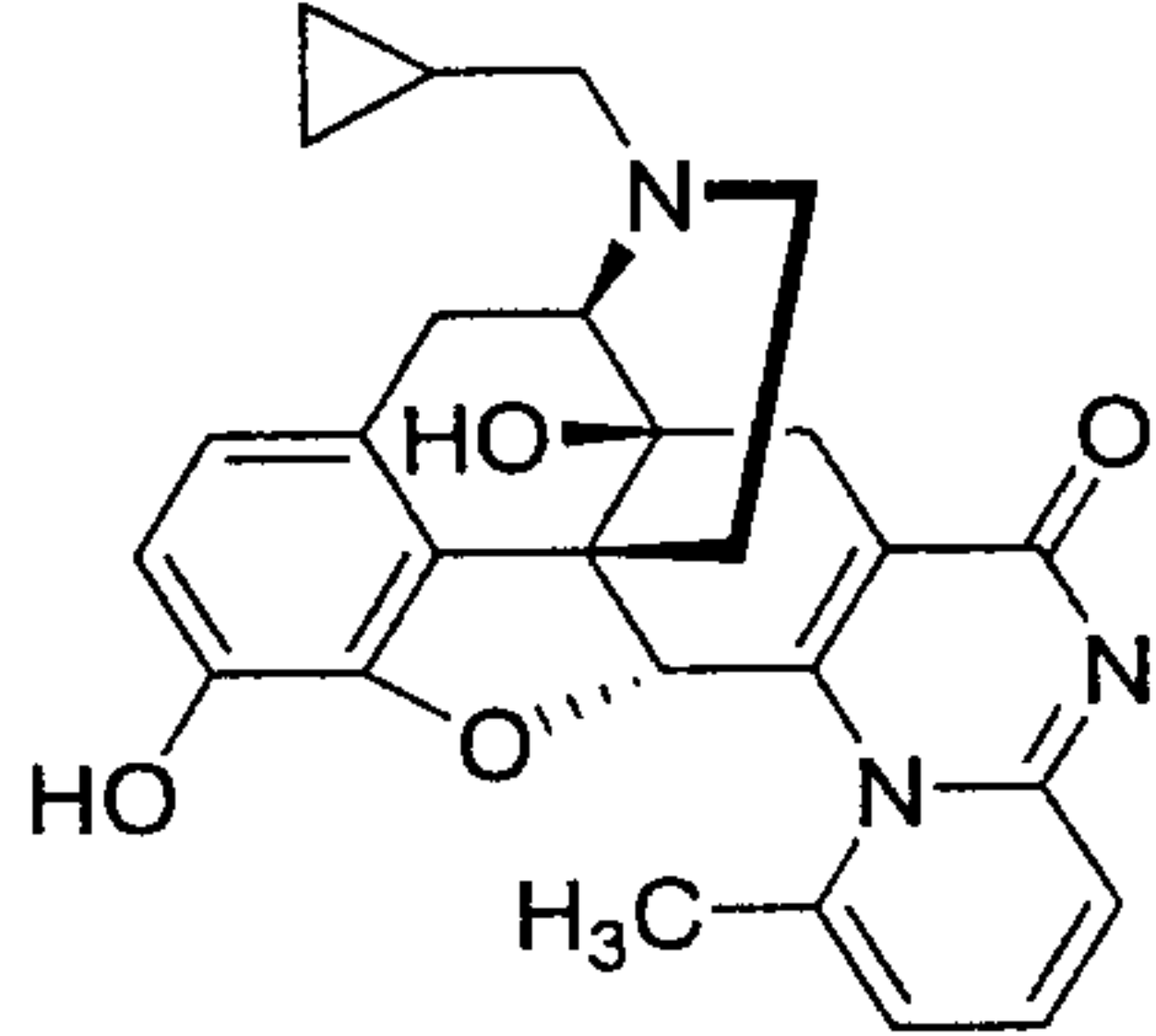
[0108]

[Table 63]

Compound No.	Chemical structure
I-253	 Chiral
I-254	 Chiral
I-255	 Chiral

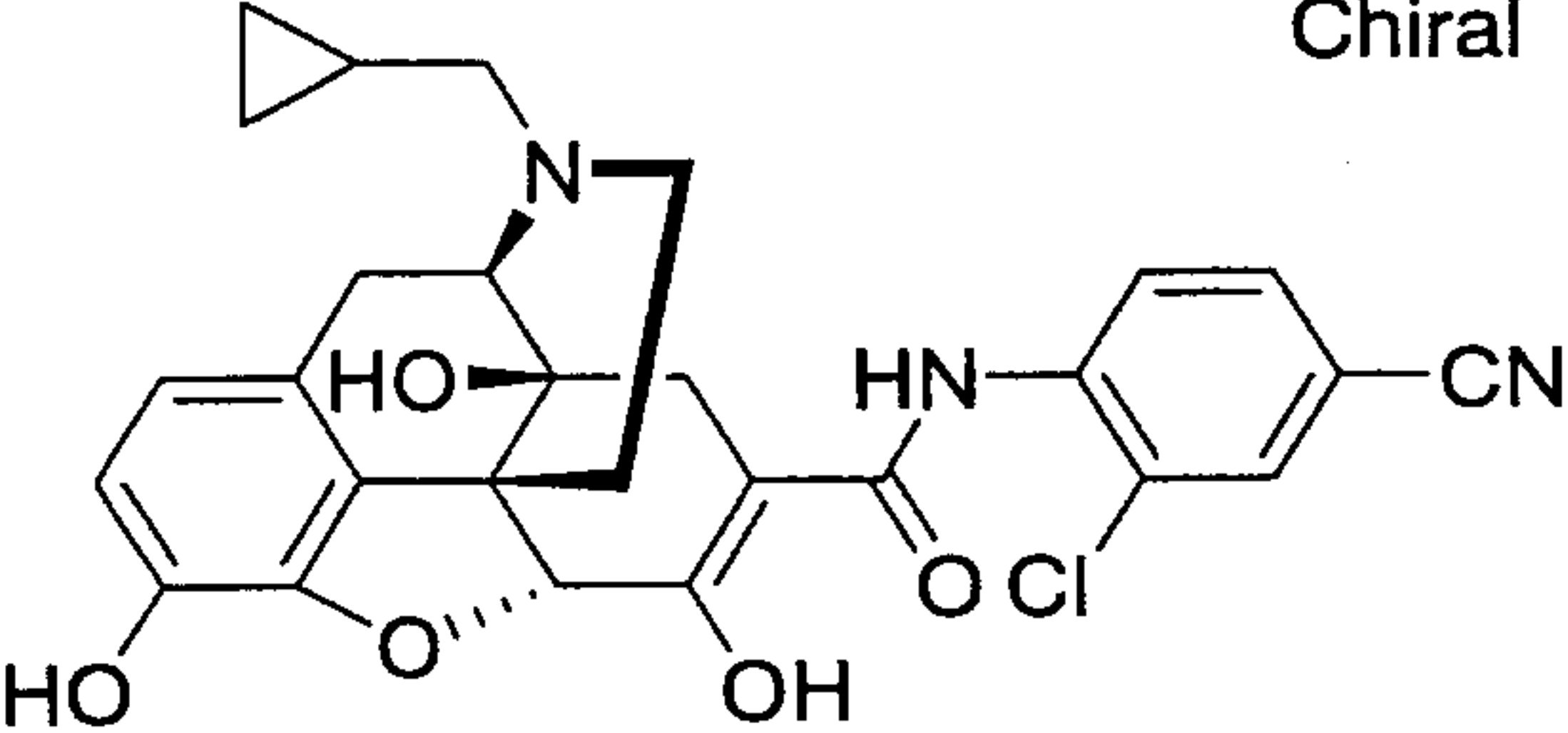
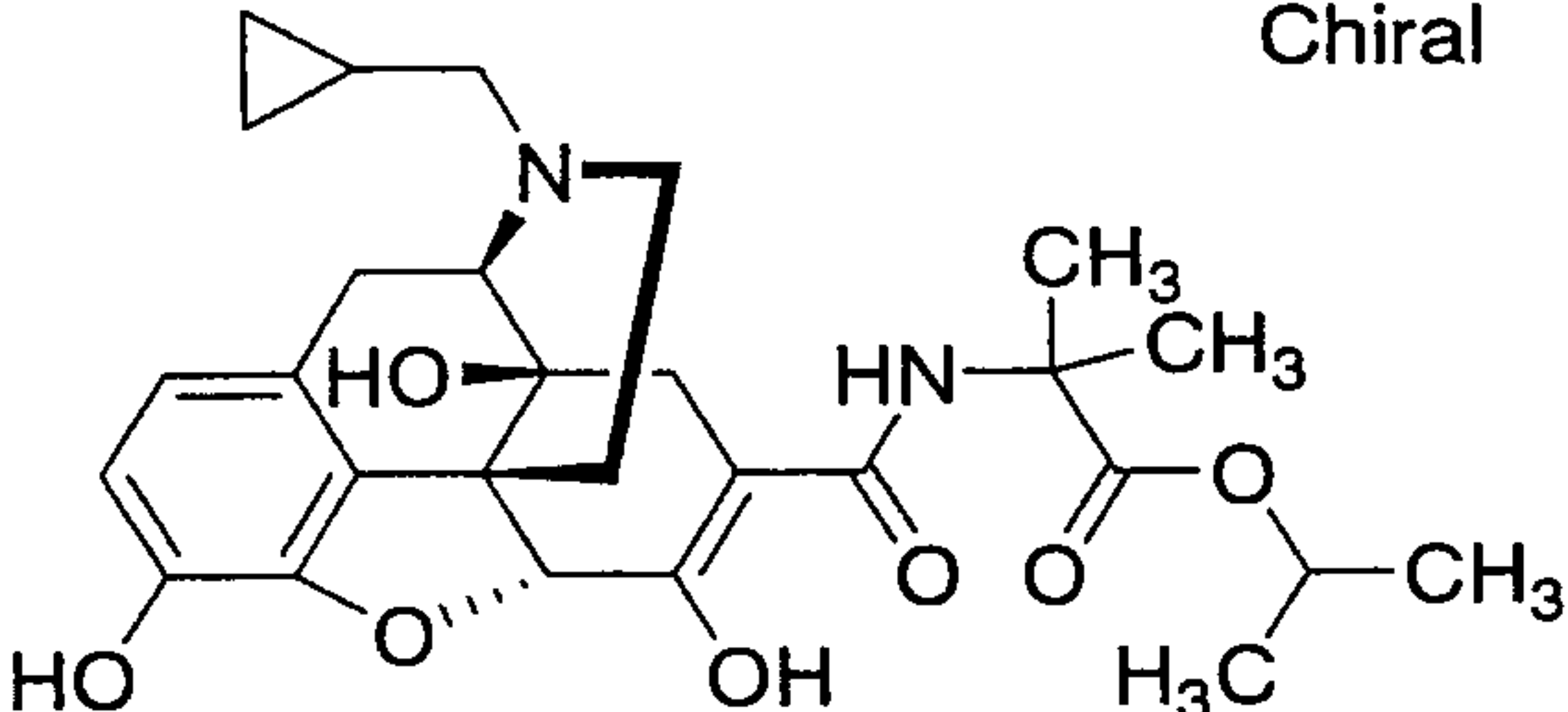
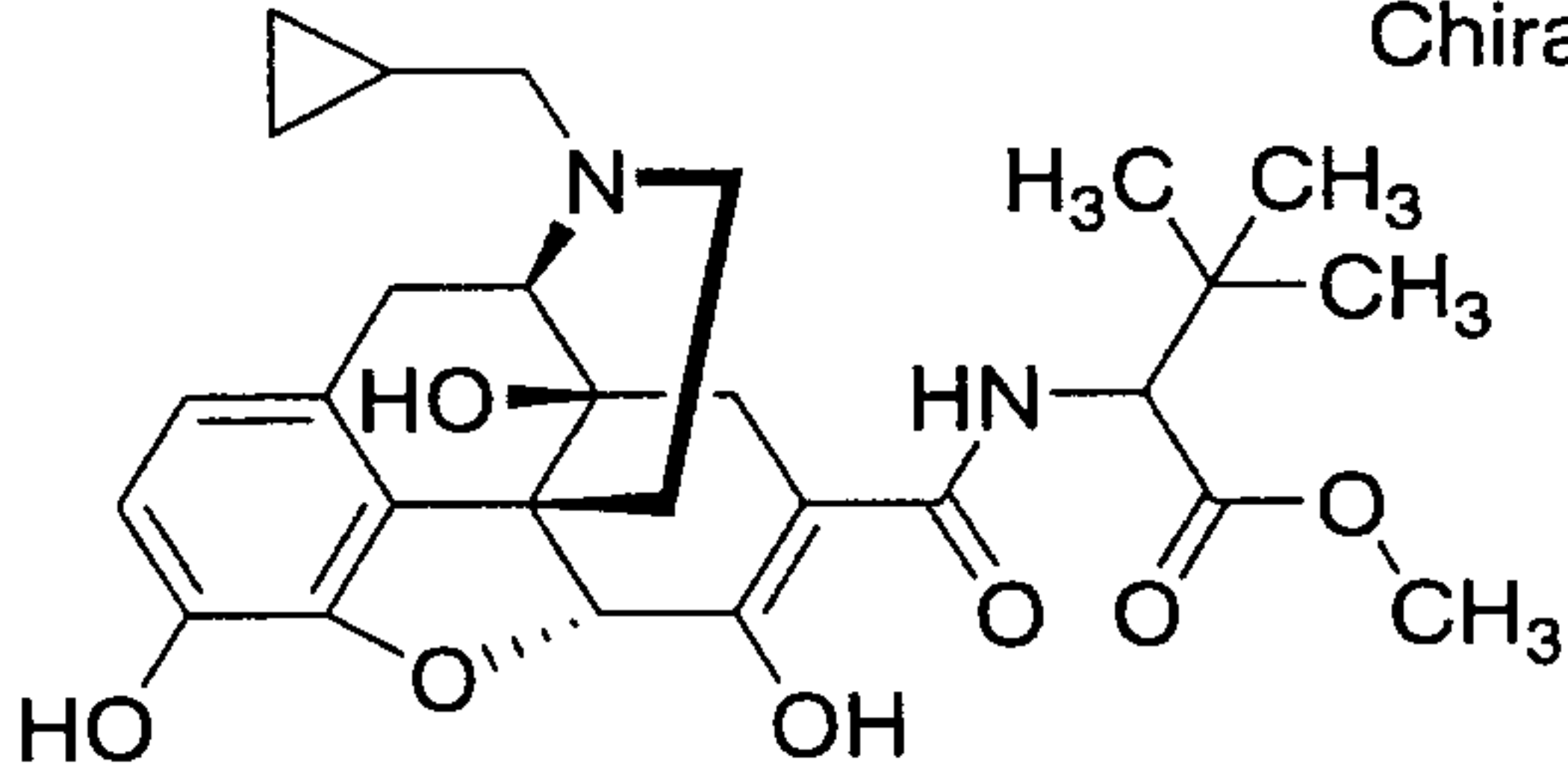
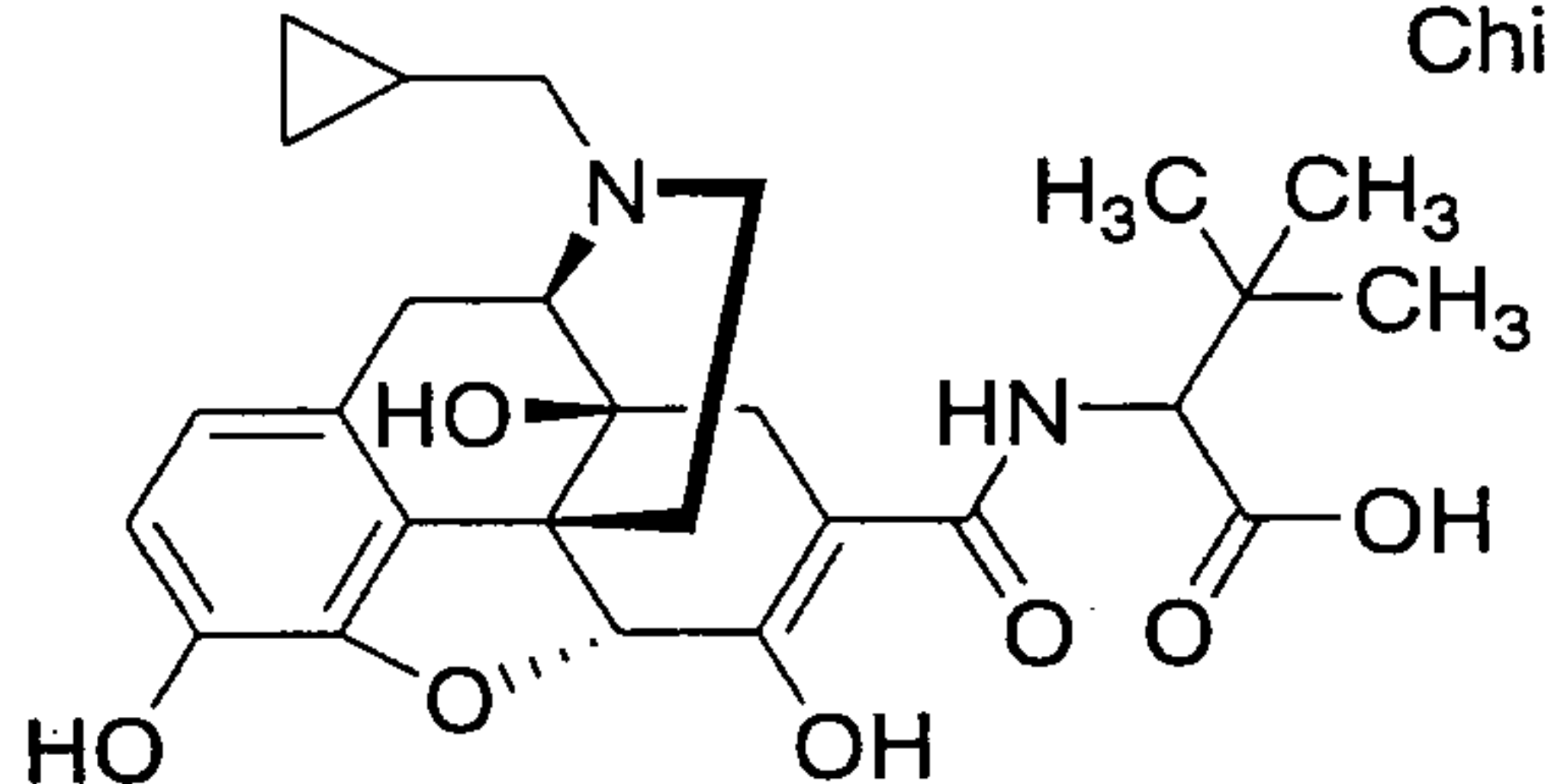
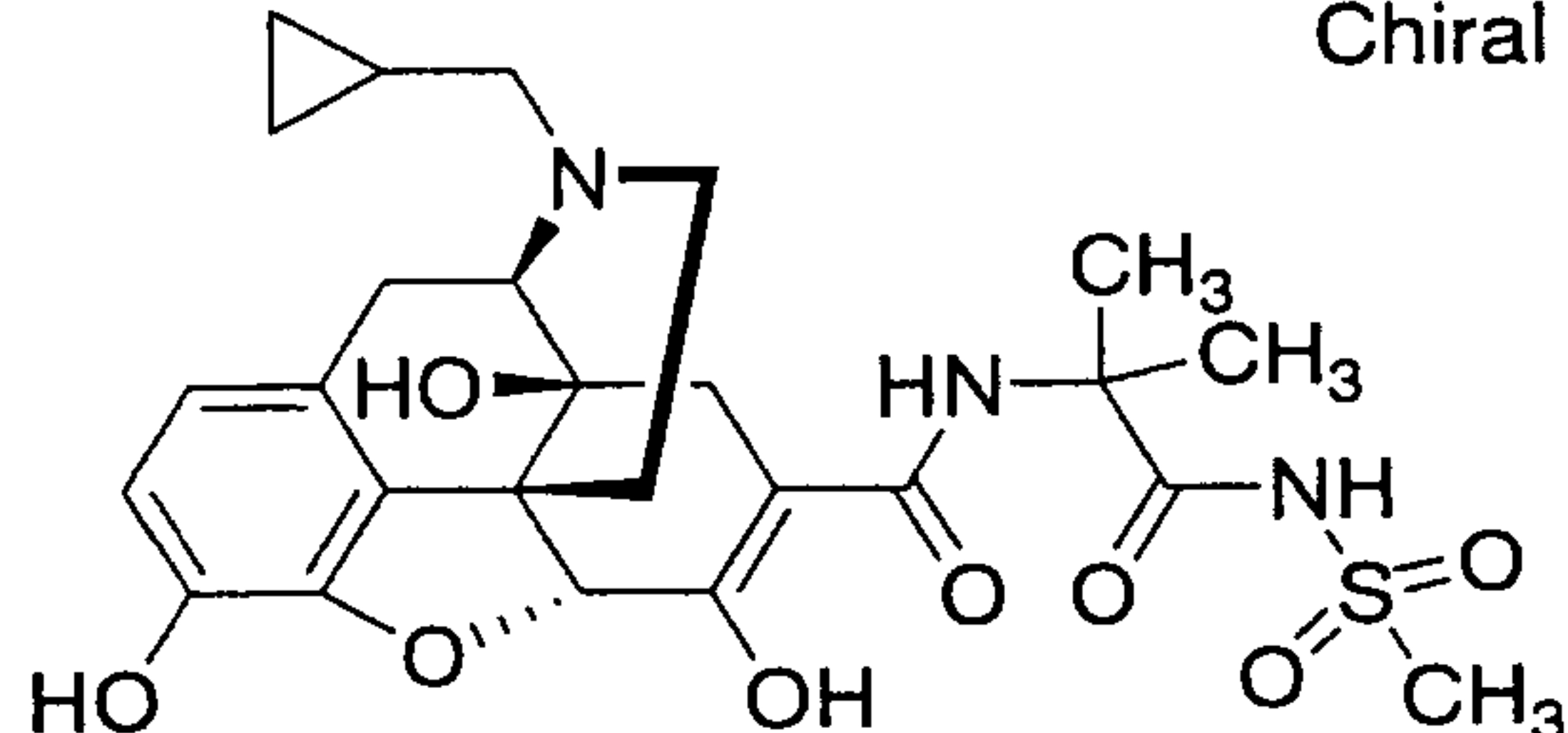
[0109]

[Table 64]

Compound No.	Chemical structure	
I-266		m/z 457.91 [M+H] ⁺ +0.97min
I-267		m/z 457.91 [M+H] ⁺ +0.62min
I-268		m/z 457.91 [M+H] ⁺ +0.87min
I-269		m/z 473.91 [M+H] ⁺ +0.69
I-270		m/z 457.91 [M+H] ⁺ +0.97min

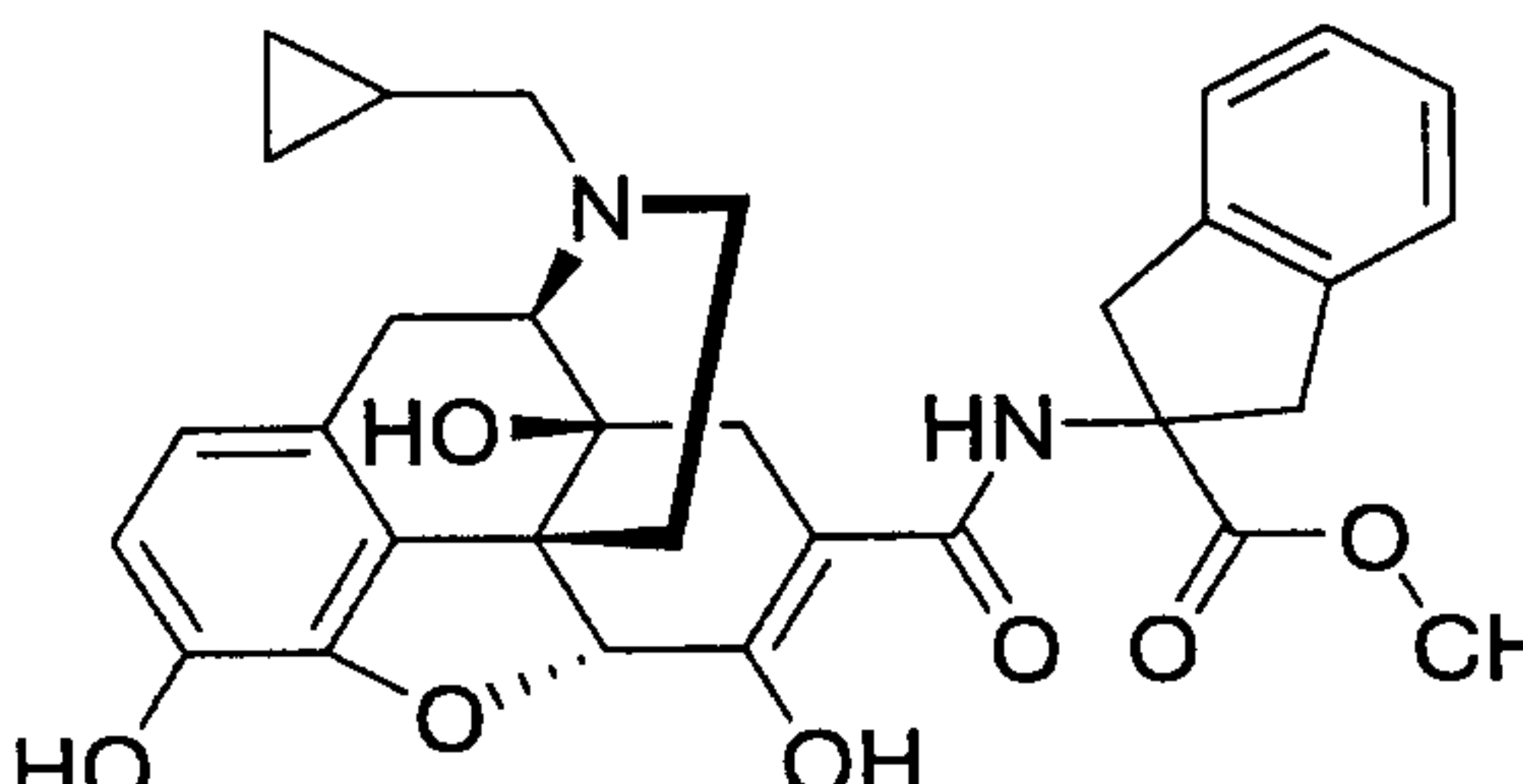
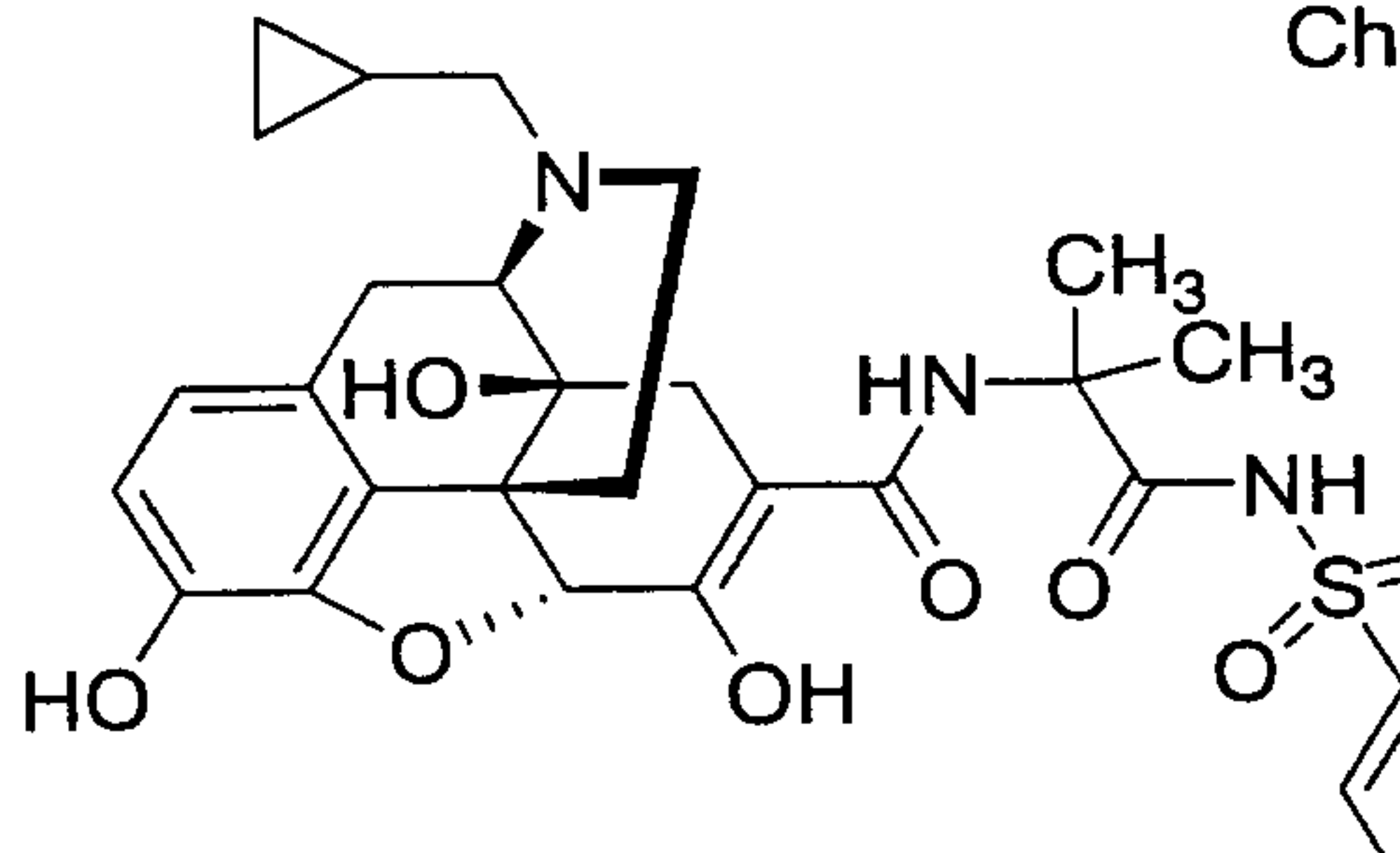
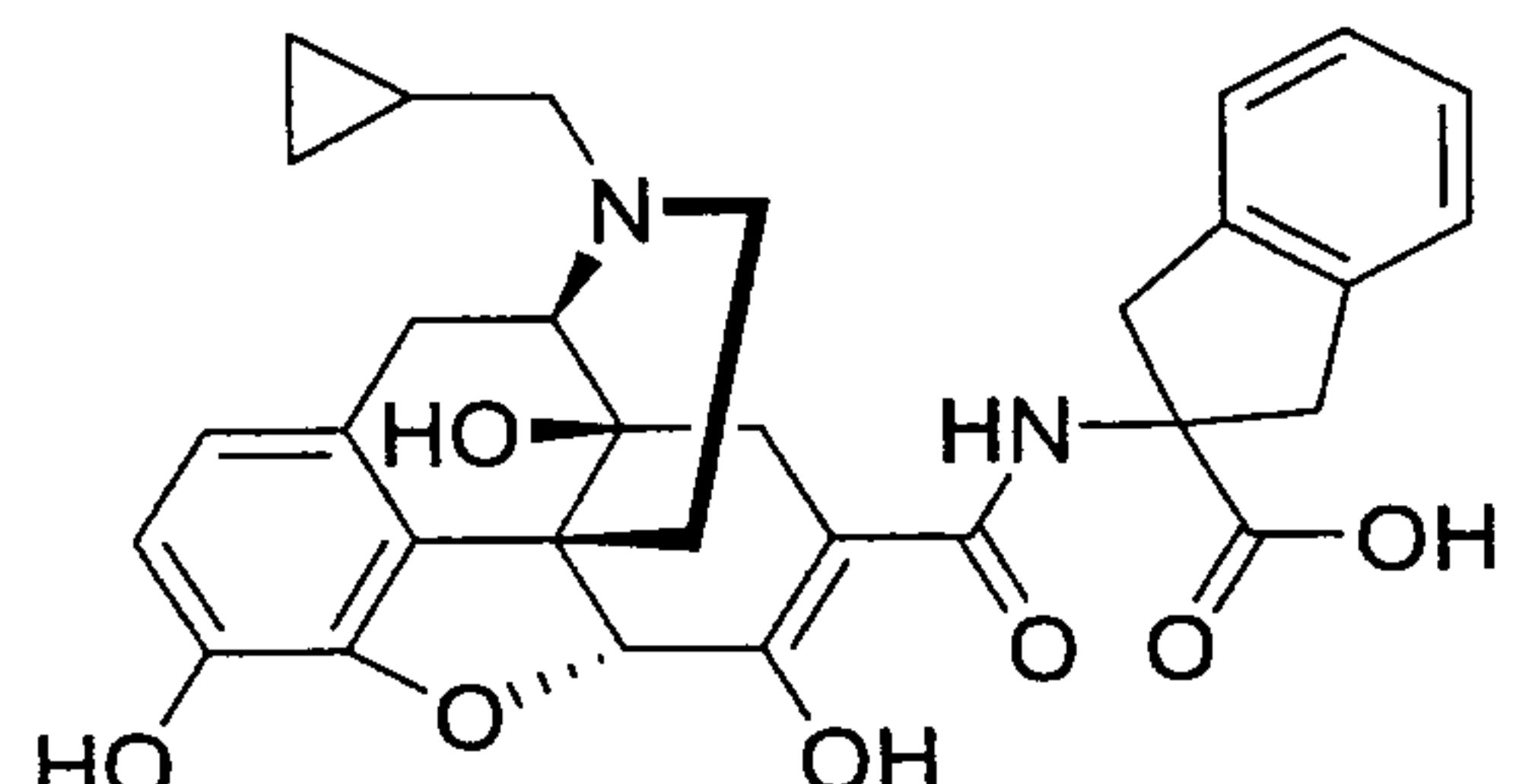
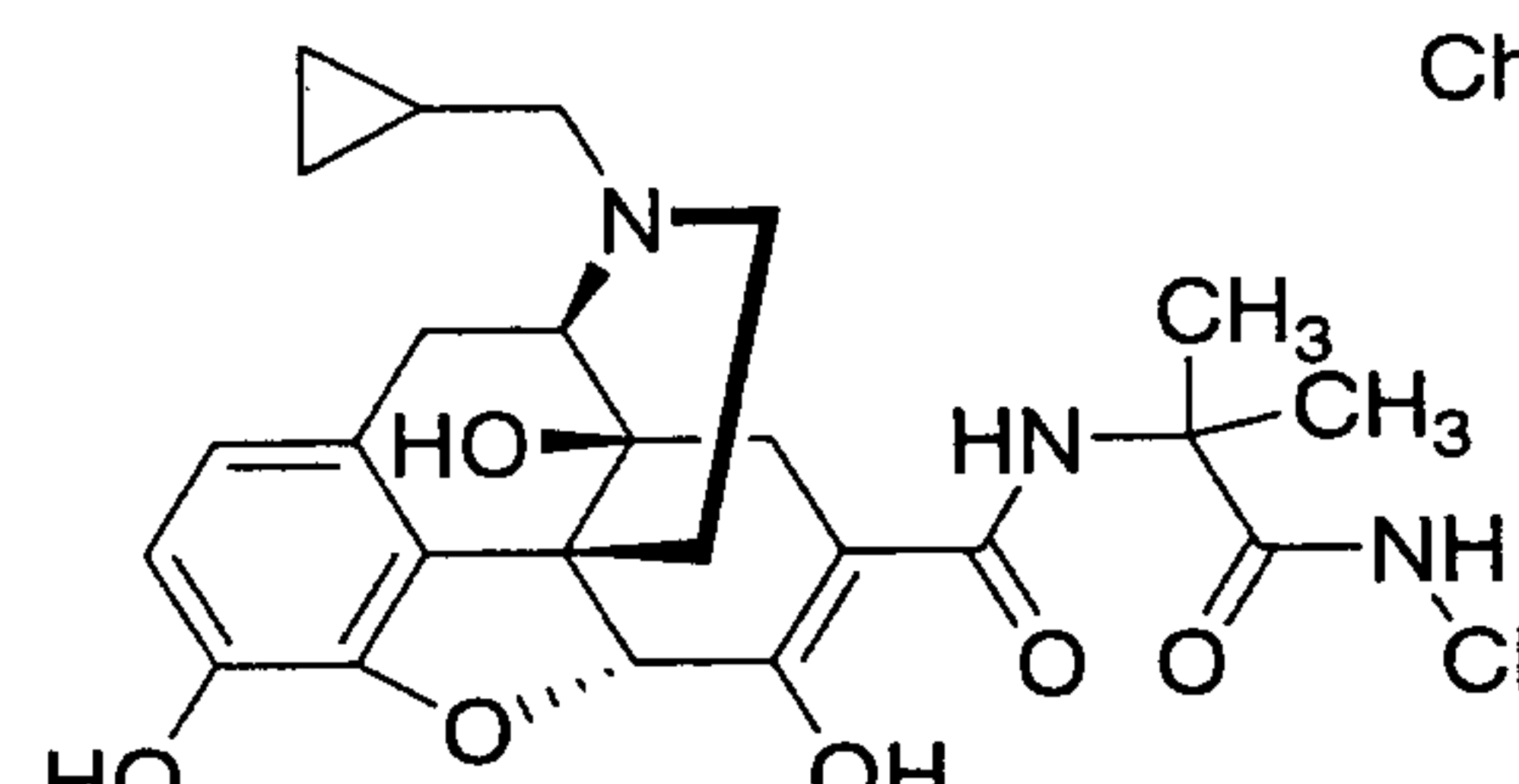
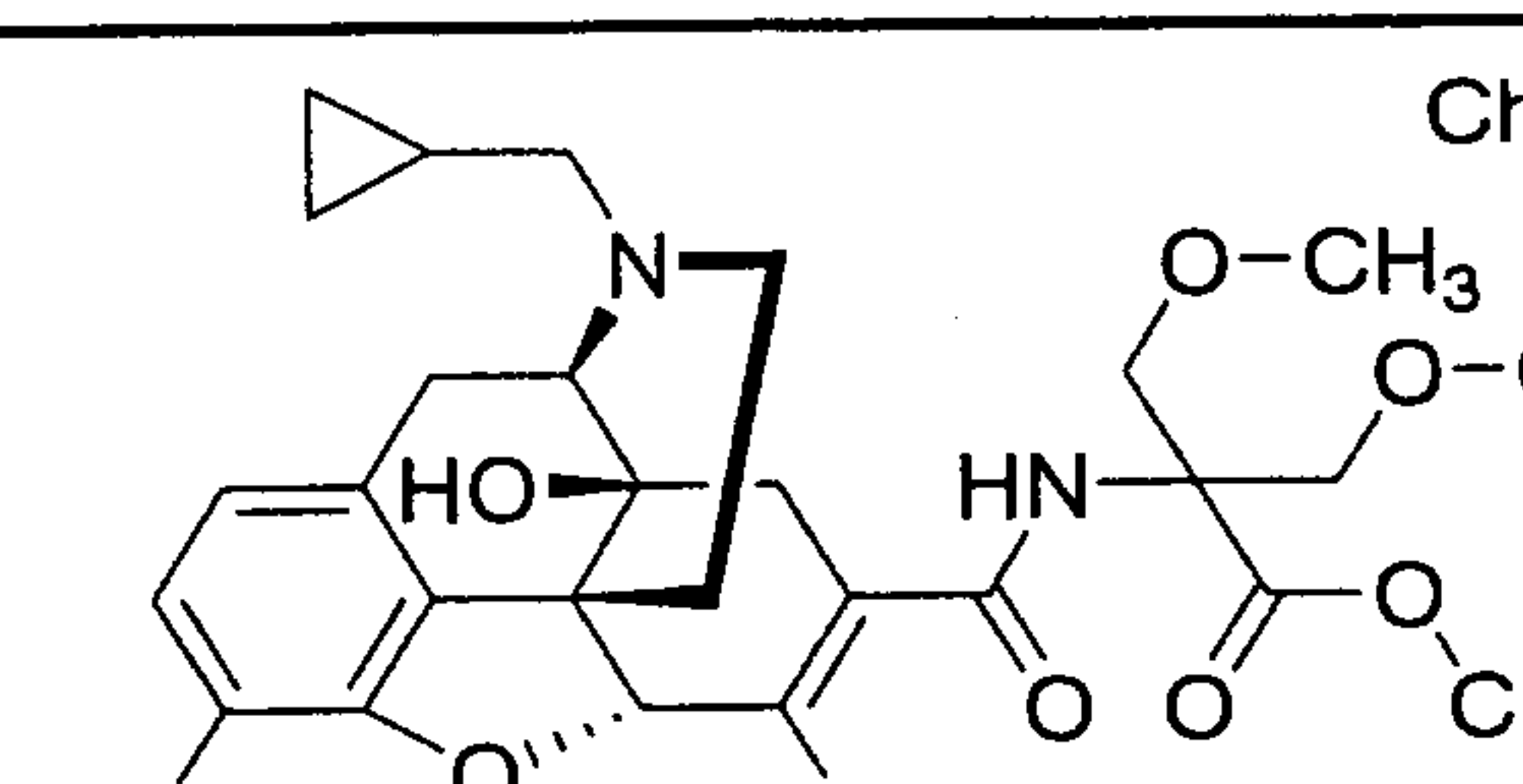
[0110]

[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

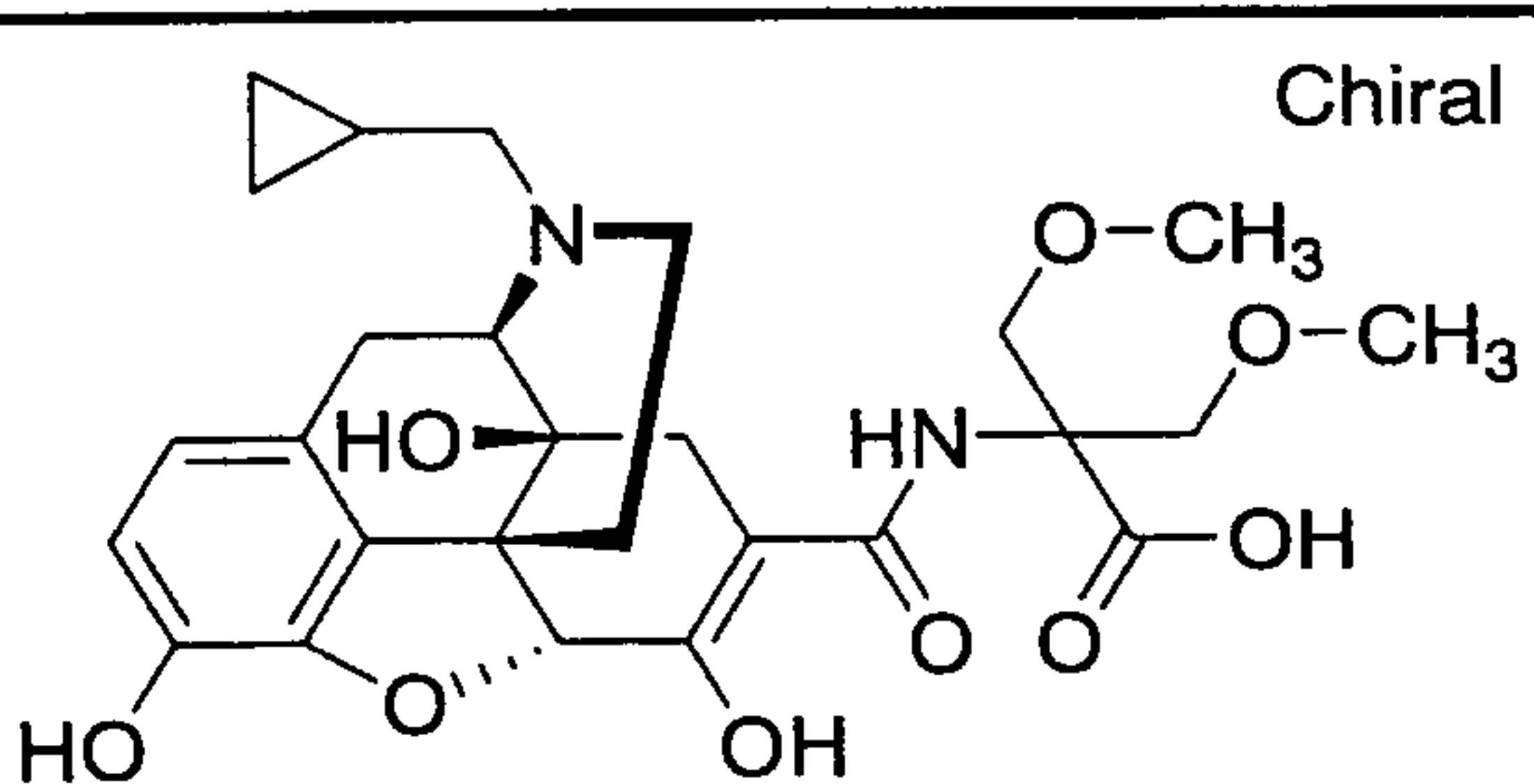
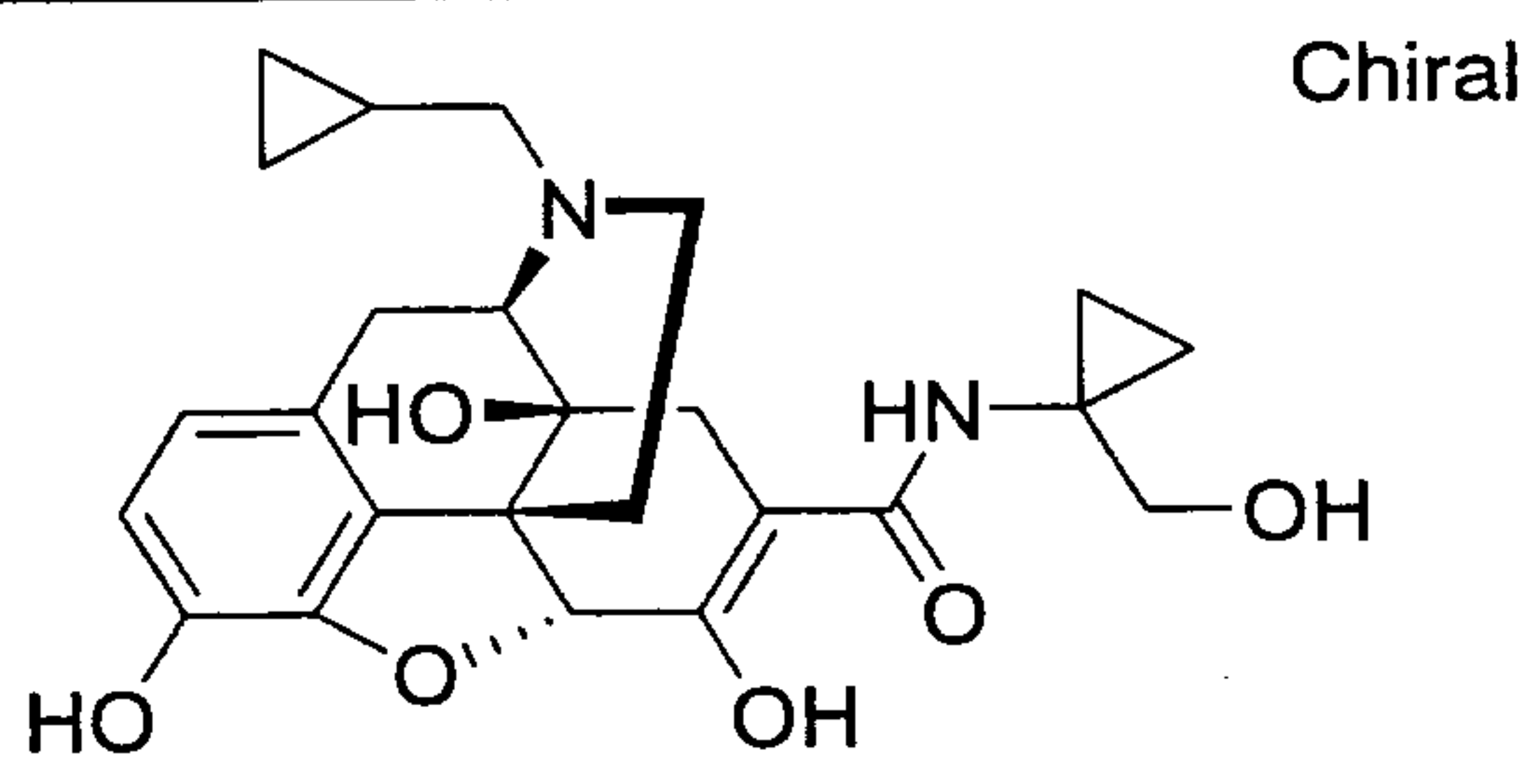
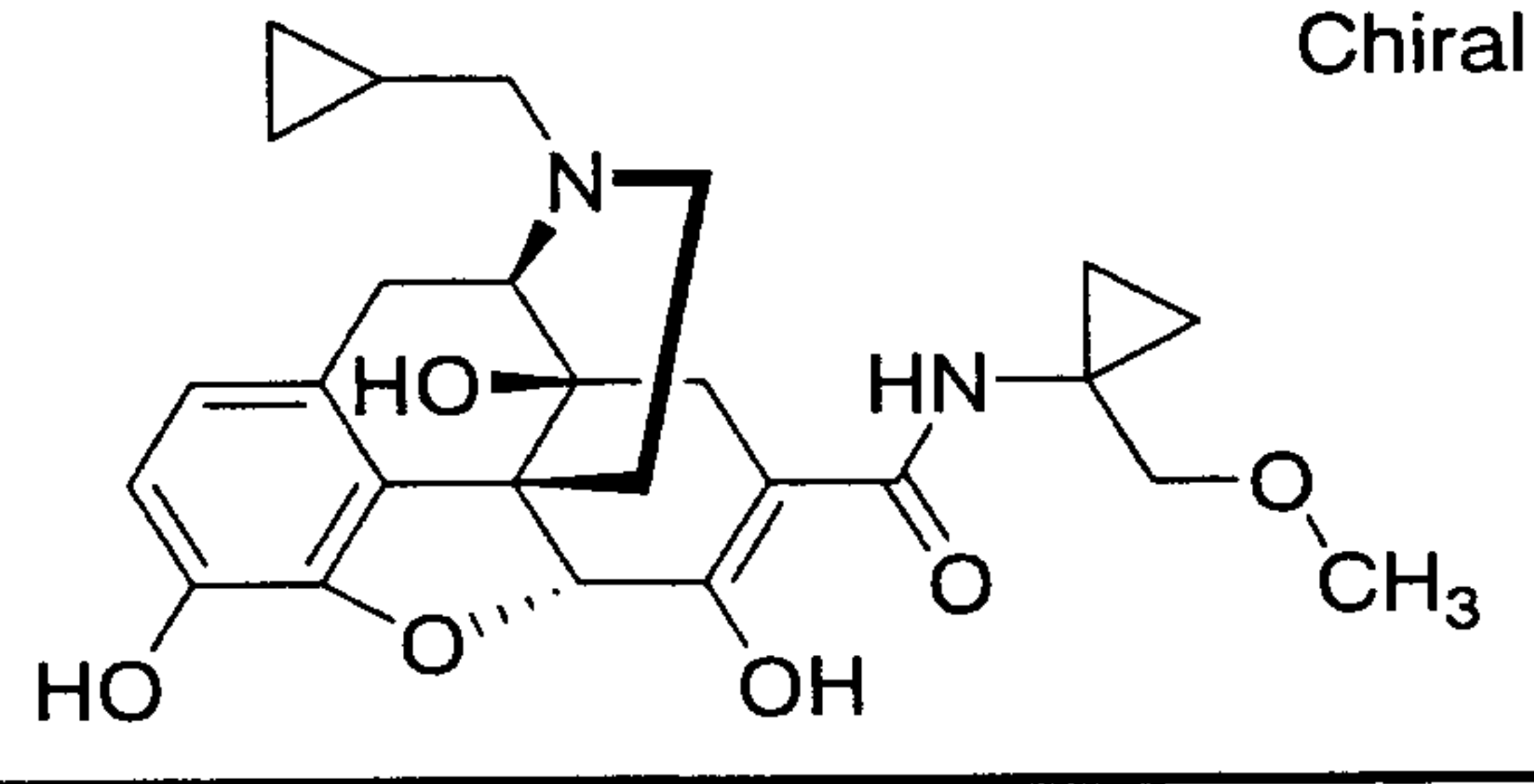
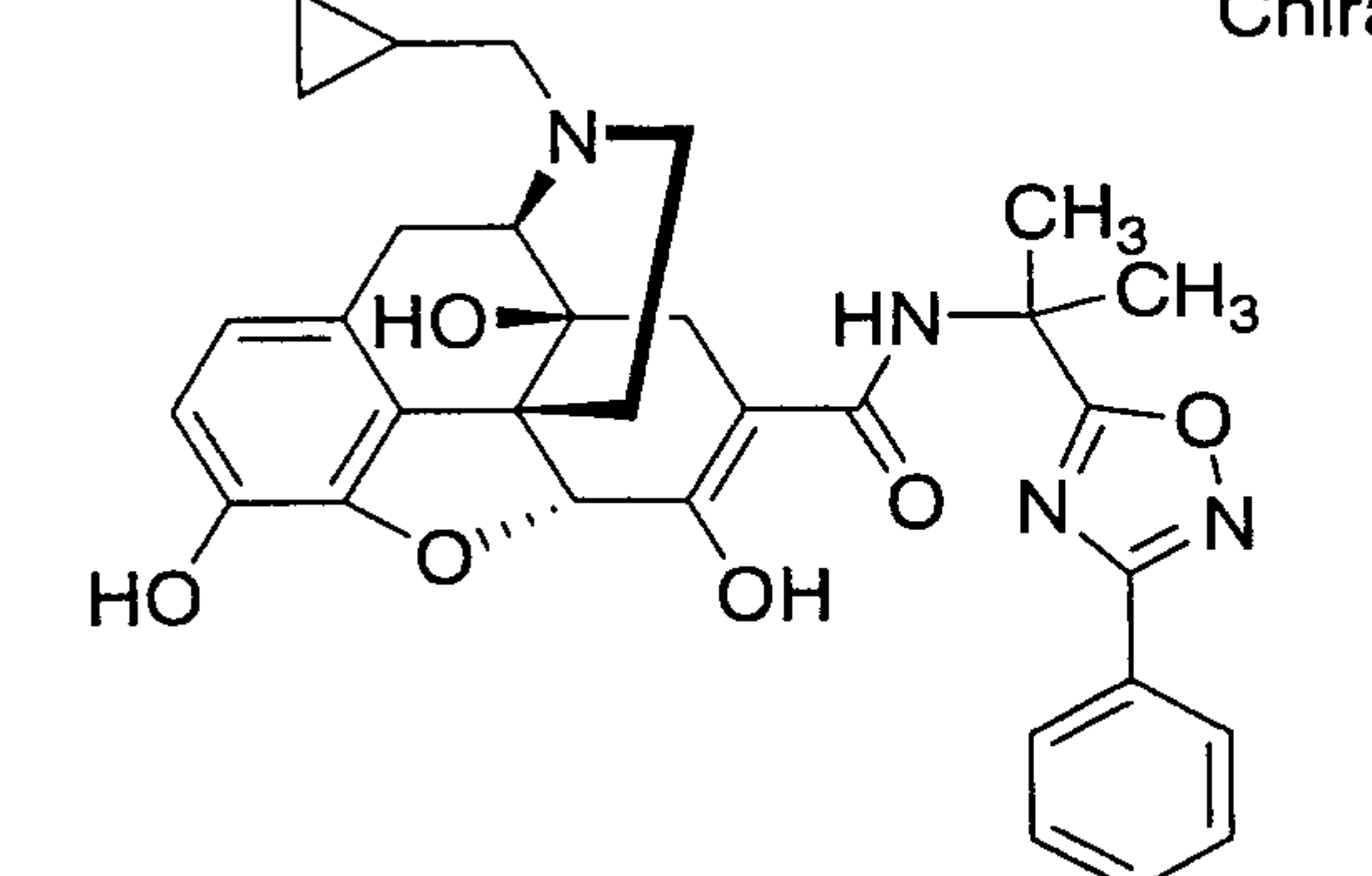
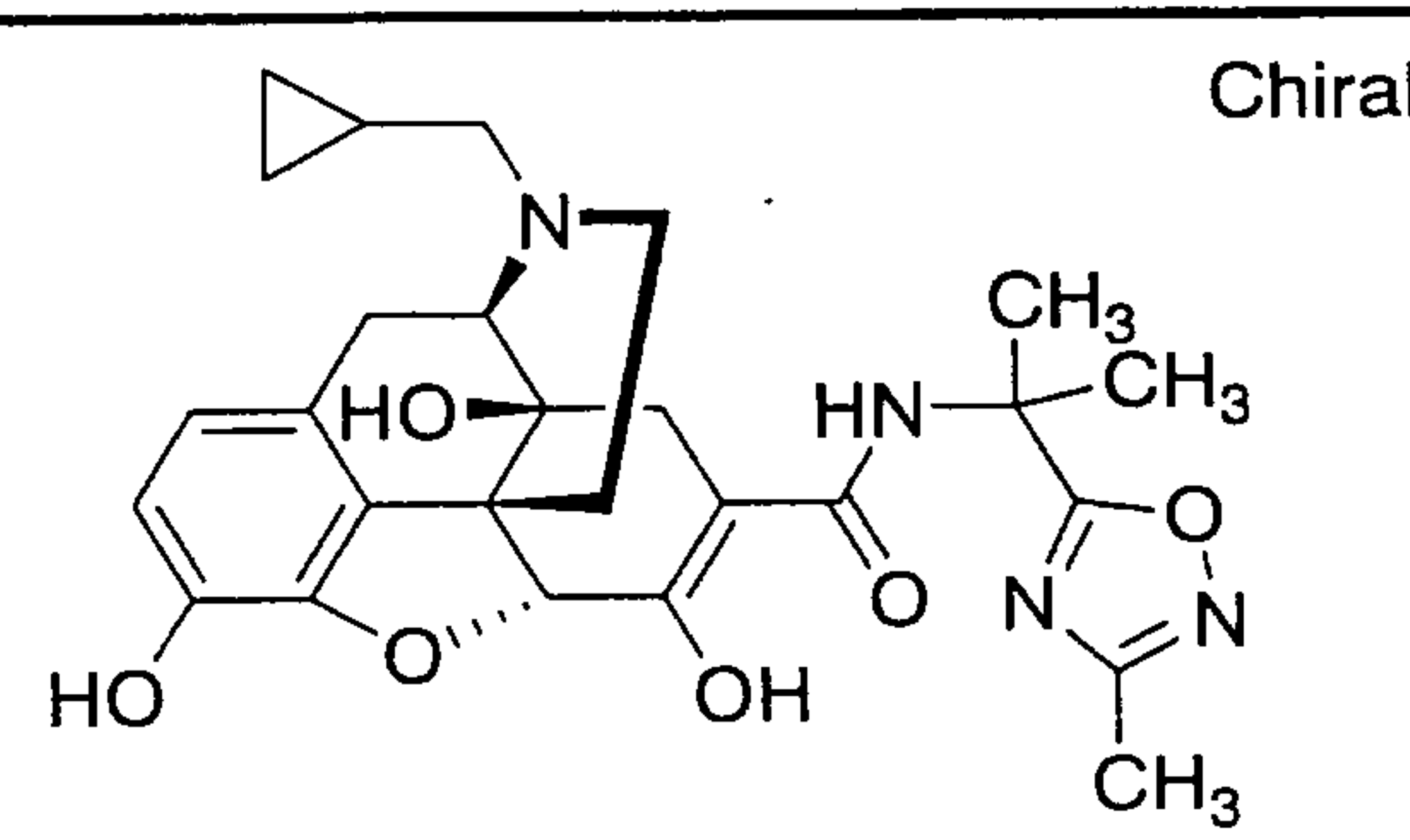
[0111]

[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] ⁺ 0.97min

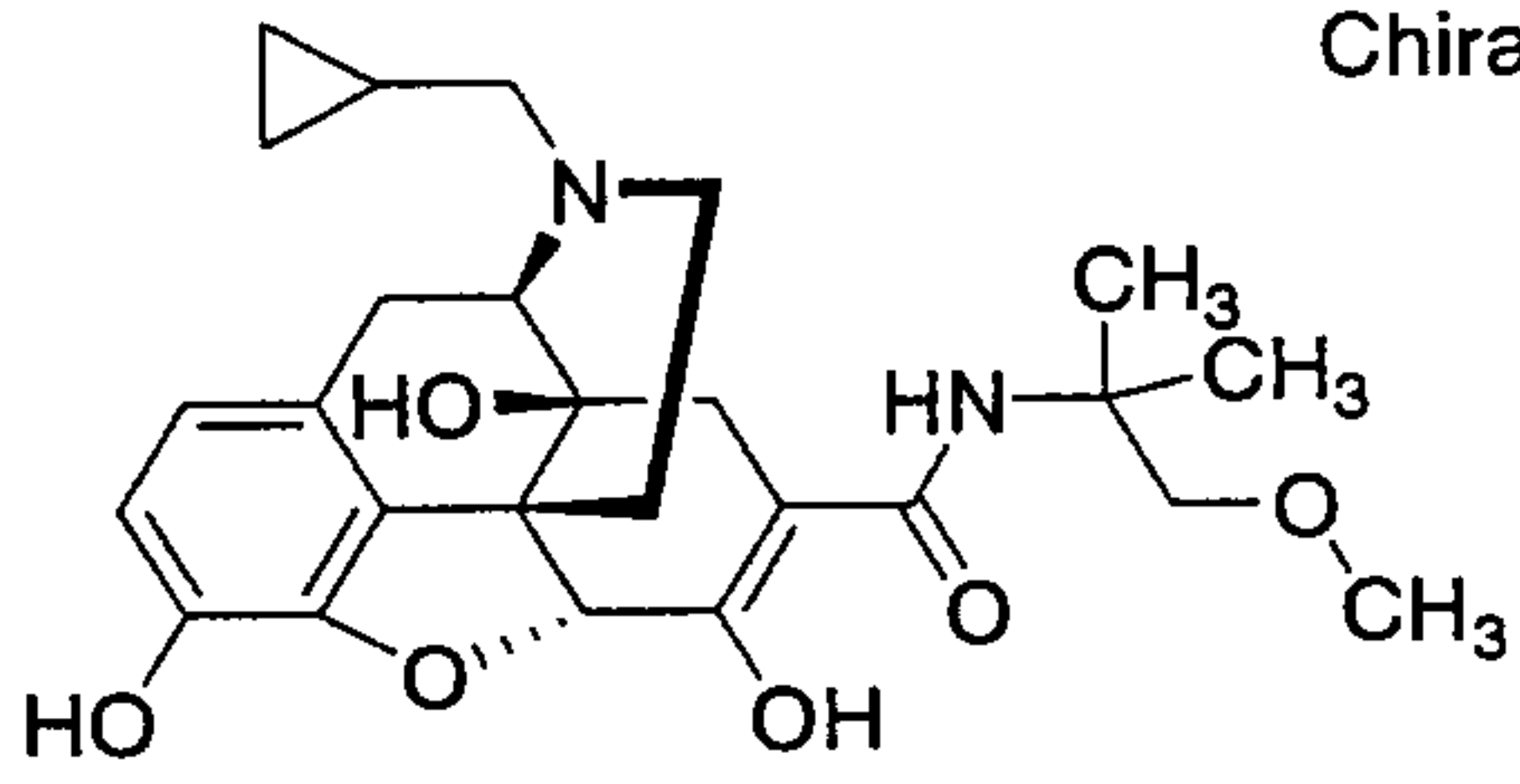
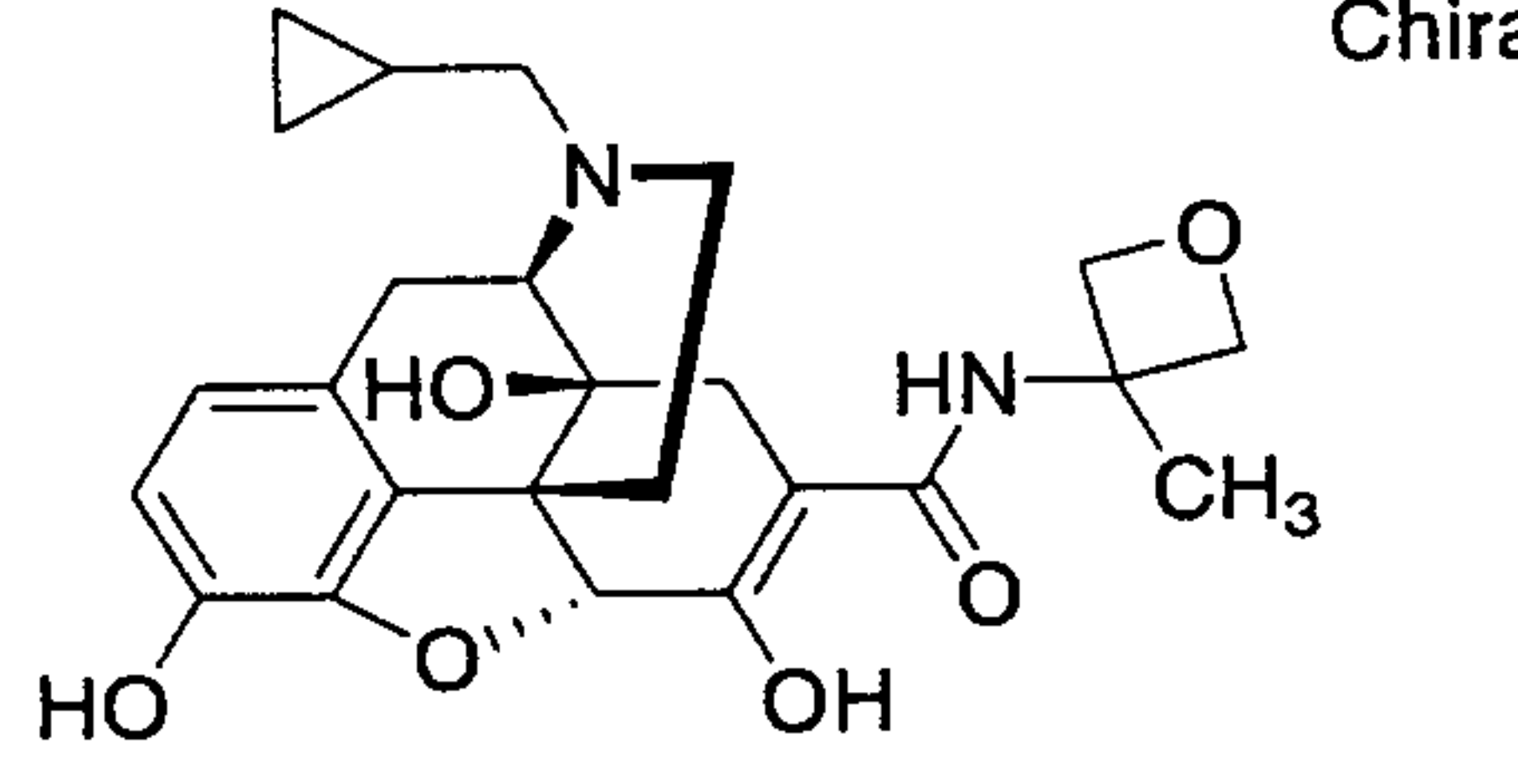
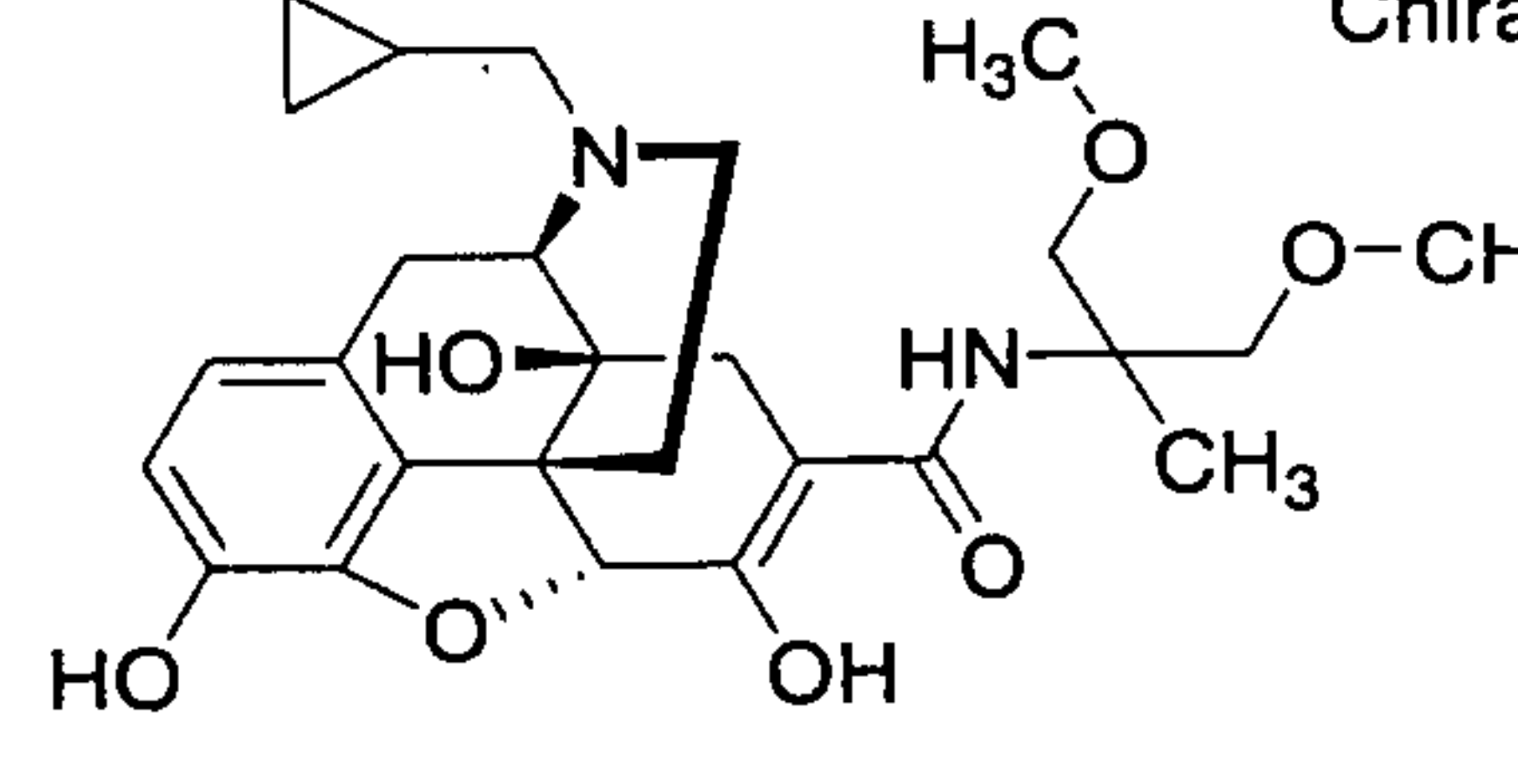
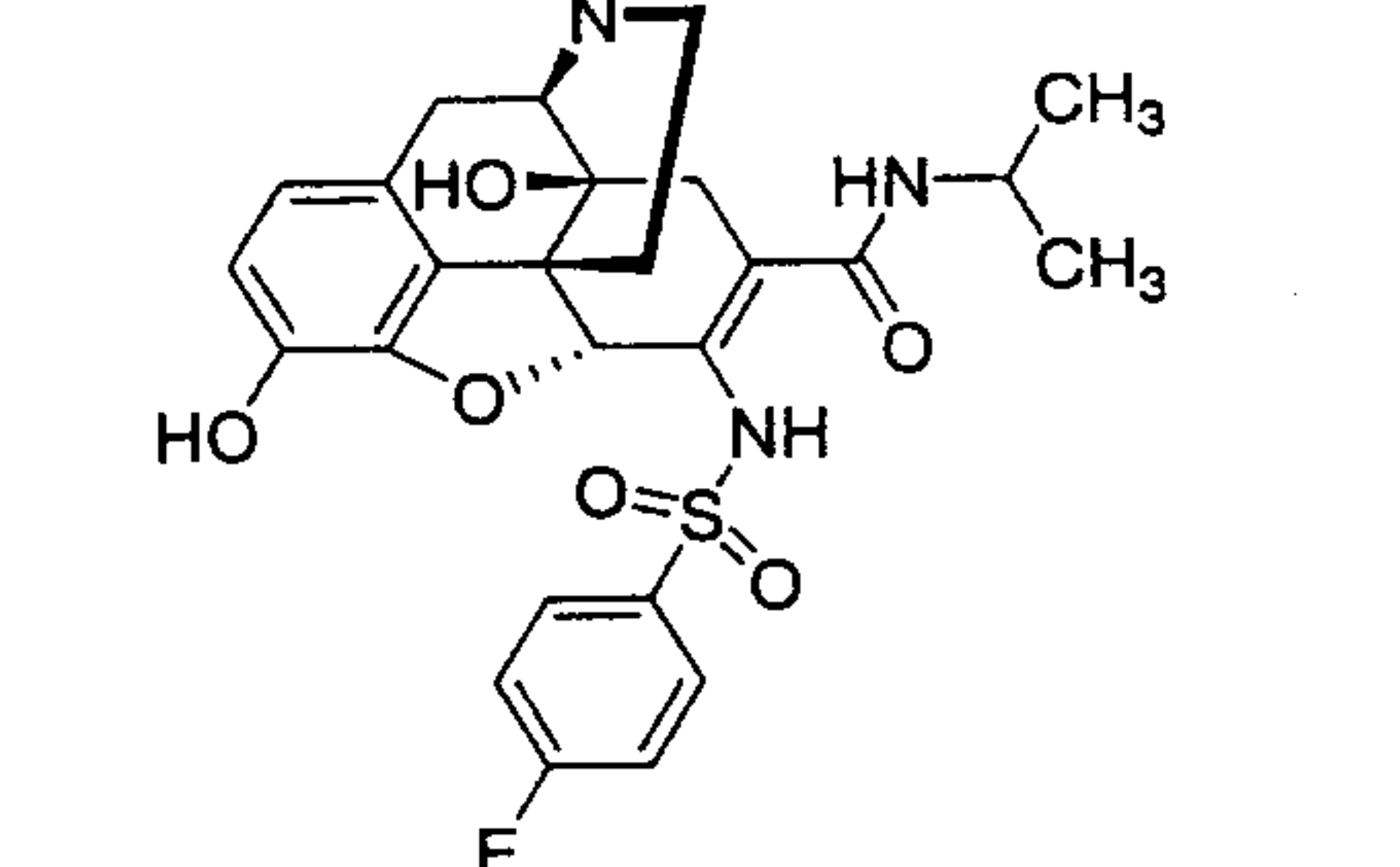
[0112]

[Table 67]

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

[0113]

[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] ⁺ 0.90min
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 measurement)*1:
Column: Chromolith Flash ROD RP-18e,
25X4.6mmI.D.

Flow Rate: 2ml/min

UV Detector: 280nm

Solvent System: [A]=H₂O_0.05%HCOOH
[B]=MeOH_0.05%HCOOH

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

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

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

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

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

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

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

[0114]

Test Example 1 Binding assay of opioid δ 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 $36600 \times g$ for 20 minutes. To the resulting pellet was added 15ml of the same buffer, and the mixture was treated with Histocolon similarly, and centrifuged. This washing work was performed two times. After centrifugation, to the resulting pellet was added 15 mL of a 50 mM Tris-HCl buffer (pH 7.4), and this was treated with Histocolon, and finally resuspended in a 10-fold amount of the same buffer, which was used as a crude membrane fraction (Life Sci. 48, 111-116, 1991). The prepared membrane specimen was frozen and stored at -80°C , and at an assay, the specimen was rapidly thawed, and diluted to about $900 \mu\text{g/mL}$ 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 $10 \mu\text{l}$ of the test compound diluted at 10-fold stage was added $10 \mu\text{l}$ of final 3nM [^3H]-DADLE (51.5 Ci/mmol: PerkinElmer) as a ligand. Into a tube was placed $480 \mu\text{l}$ of a rat cerebrum membrane fraction to which 100 mM choline chloride, 3 mM MnCl_2 and 100 nM DAMGO had been added, and this was incubated at 25°C for 2 hours. After incubation, this was

suction-filtered with a Whatman™ GF/C filter which had been pre-treated with 0.5% polyethyleneimine, and washed with 2.5 mL of an ice-cooled 10mM Tris-HCl buffer (pH7.4) four times. After washing, the filter was transferred to a mini vial for liquid scintillation counter, 5 mL of a scintillator (Cleasol I) was added, this was allowed to stand overnight, and the radioactivity was measured for 3 minutes with a liquid scintillation counter Tri-Carb 2200CA (PACKARD). DMSO was used for total binding (Total bound: TB) for data analysis, and 20 µM levallorphan was used for non-specific binding (Non-specific bound: NB), and a K_i value of the test compound was calculated using a K_D value (2.93 nM) obtained in advance by Scatchard plot analysis.

Results are shown in Table 69.

[0115]

[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 (I) has an affinity for an opioid δ receptor.

[0116]

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 $36600 \times g$ for 20 minutes. To the resulting pellet was added 15ml 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 2nM [³H]-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 2.5mL of an ice-cooled 10mM Tris-HCl buffer (pH 7.4) four times. After washing, the filter was transferred to a mini vial for liquid scintillation counter, 5mL of a scintillator (Cleasol 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 K_i value of the test compound was calculated using a K_D value (1.72nM) obtained in advance by

Scatchard plot analysis (Anal.Biochem. 107(1), 220-239, 1980).

Results are shown in Table 70.

[0117]

[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

[0118]

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)) $\times$ 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)} $\times$ 100

[0119]

[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

[0120]

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
	<u>HPC-L</u>	<u>16 mg</u>
		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.

[0121]

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
	<u>HPC-L</u>	<u>3 mg</u>
		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.

[0122]

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
	<u>Magnesium stearate</u>	<u>5 mg</u>
		150 mg

The compound represented by the formula (I), lactose, microcrystalline cellulose, 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 tableting. The present mixed powder is compressed to obtain 150 mg of a tablet.

[0123]

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

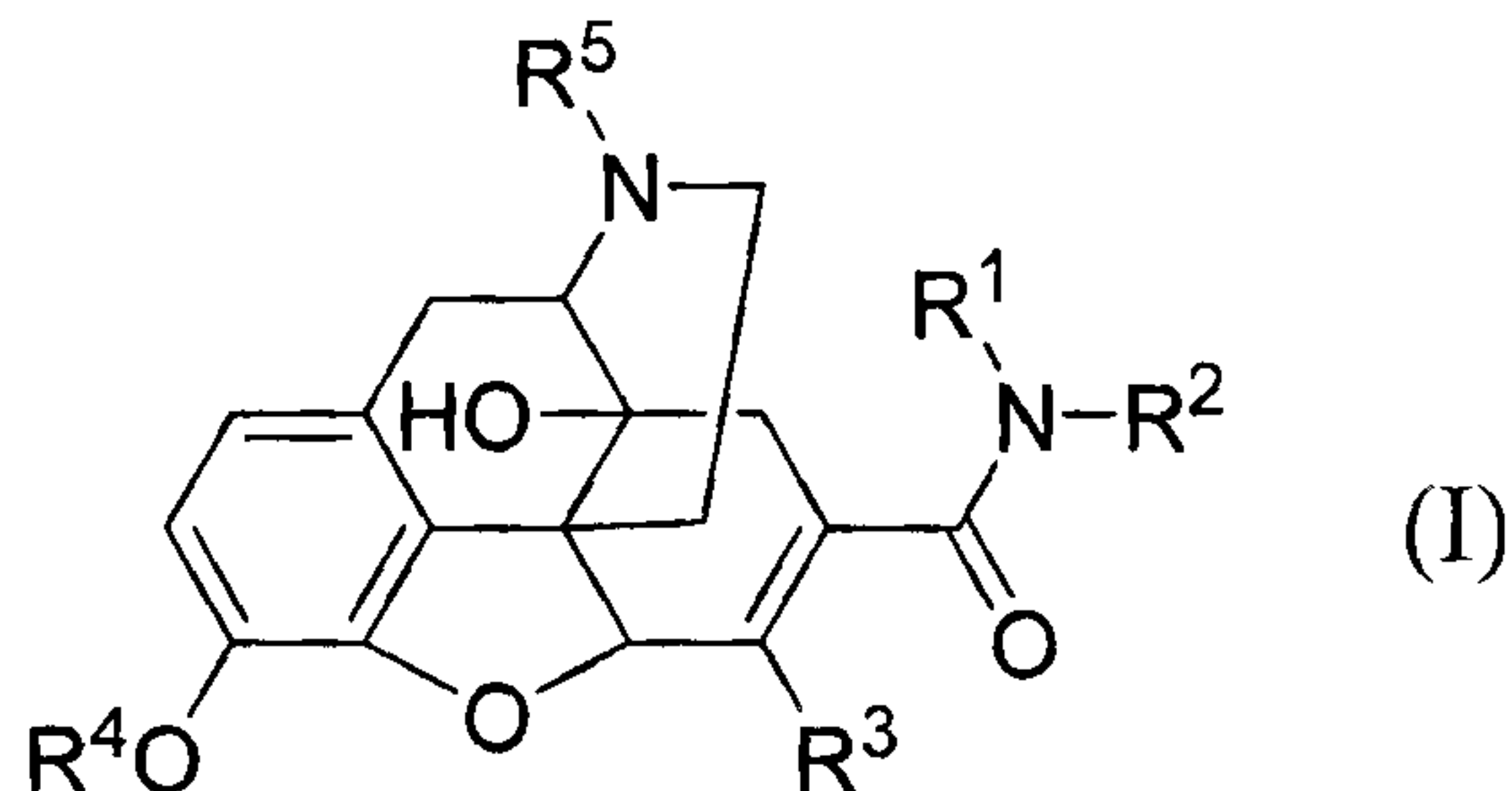
[Industrial applicability]

[0124]

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

CLAIMS

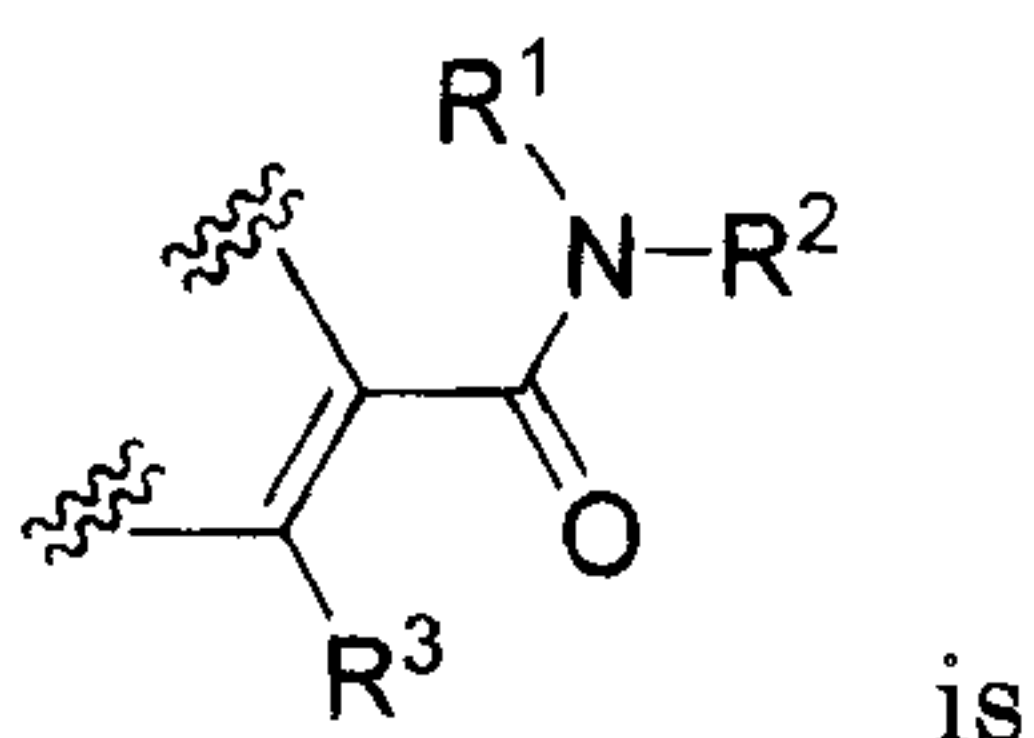
1. A compound represented by the formula (I):

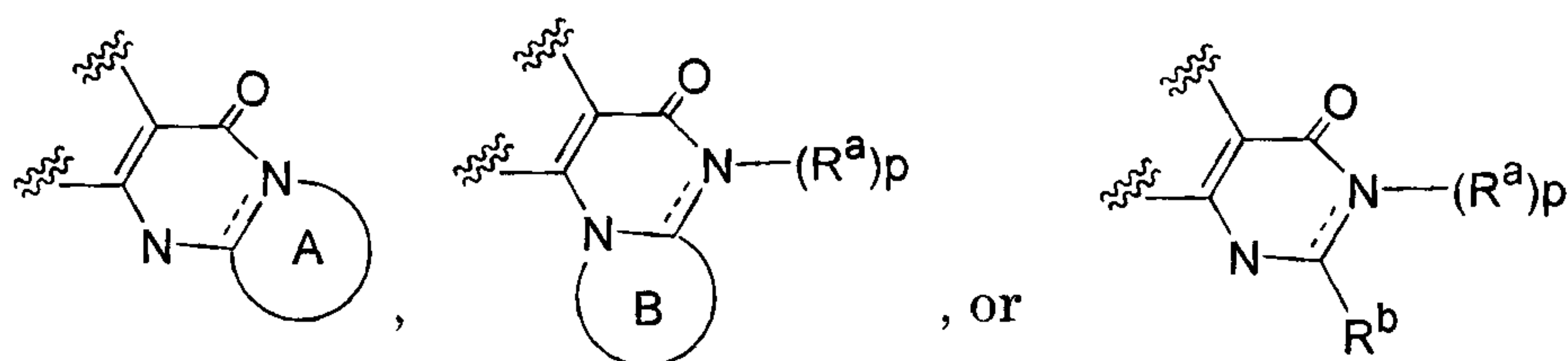


wherein R^1 and R^2 are each independently hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted lower alkylsulfonyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl,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

a group represented by the formula:





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;

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

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

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

4. The compound as defined in any one of claims 1 to 3 or a pharmaceutically

acceptable salt, 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.

5. The compound according to any one of claims 1, 2, and 4 or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen,

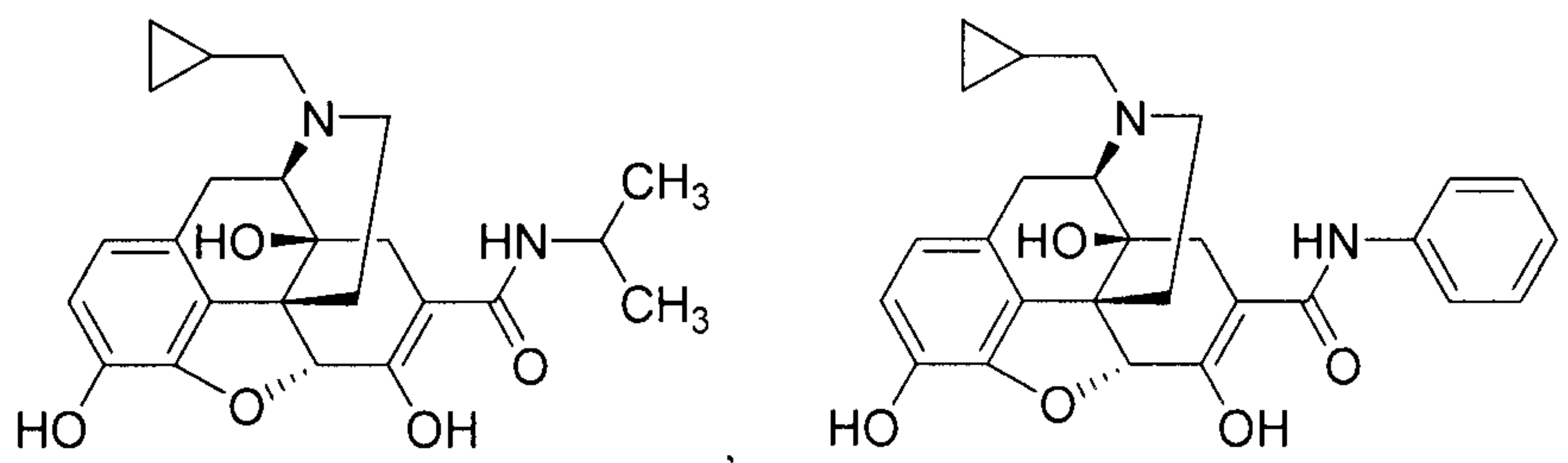
R^2 is lower alkyl optionally substituted with a heterocyclic group optionally substituted with aryl or lower alkoxy; phenyl optionally substituted with lower alkyl or lower alkoxy; cycloalkyl substituted with lower alkylcarbonyl, or a heterocyclic group substituted with lower alkoxy or aryl,

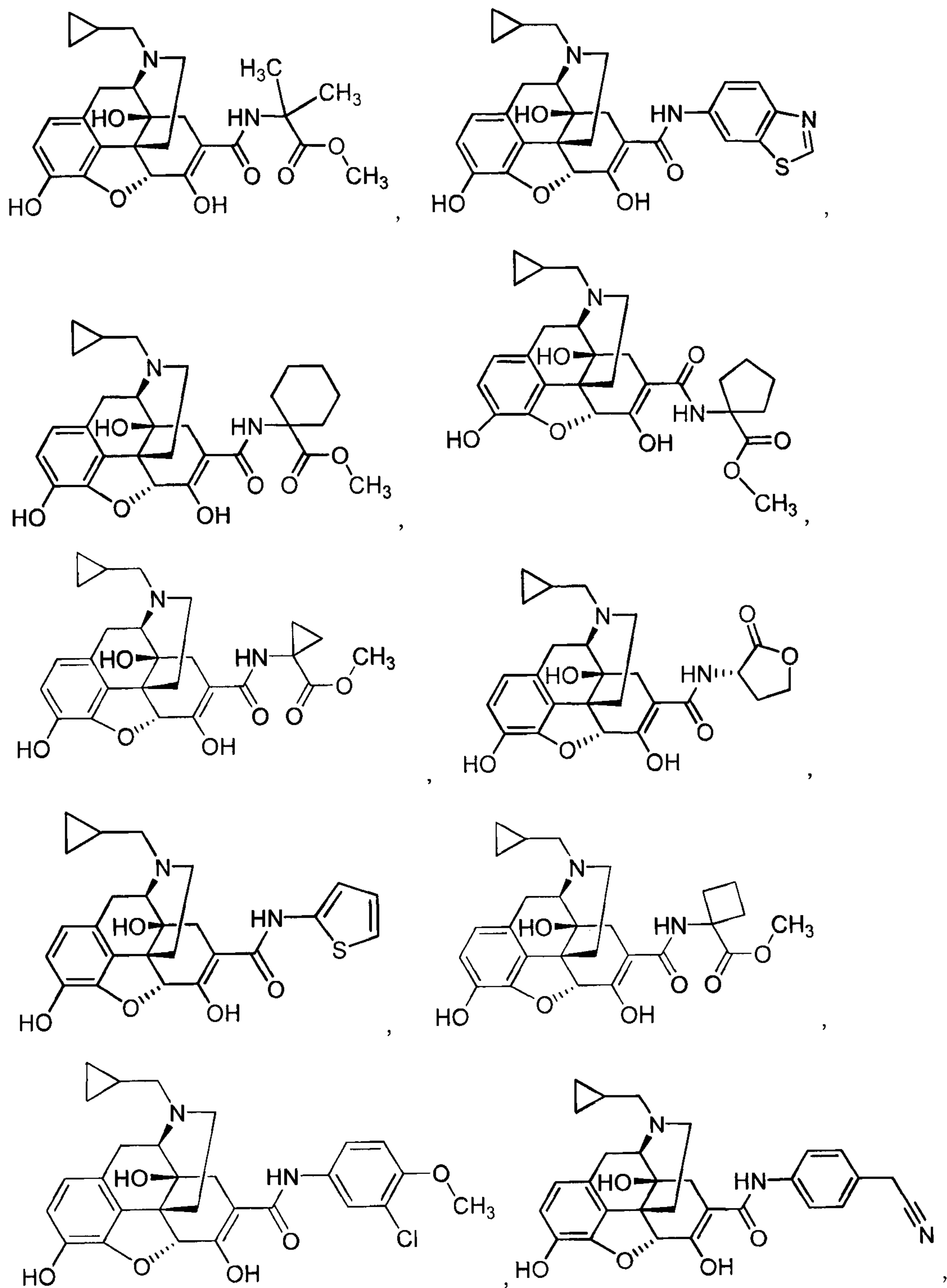
R^3 is hydroxyl,

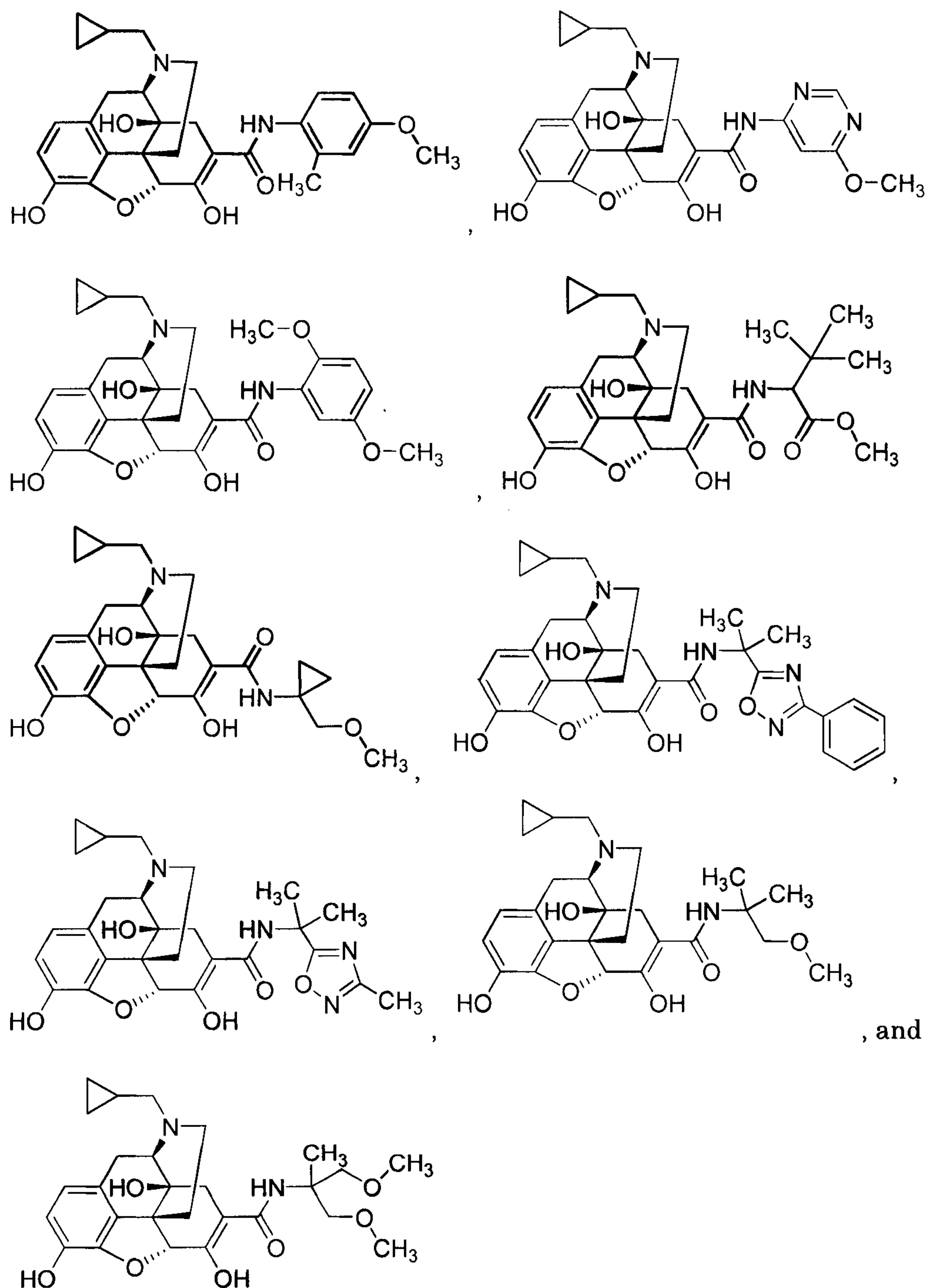
R^4 is hydrogen, and

R^5 is cyclopropylmethyl.

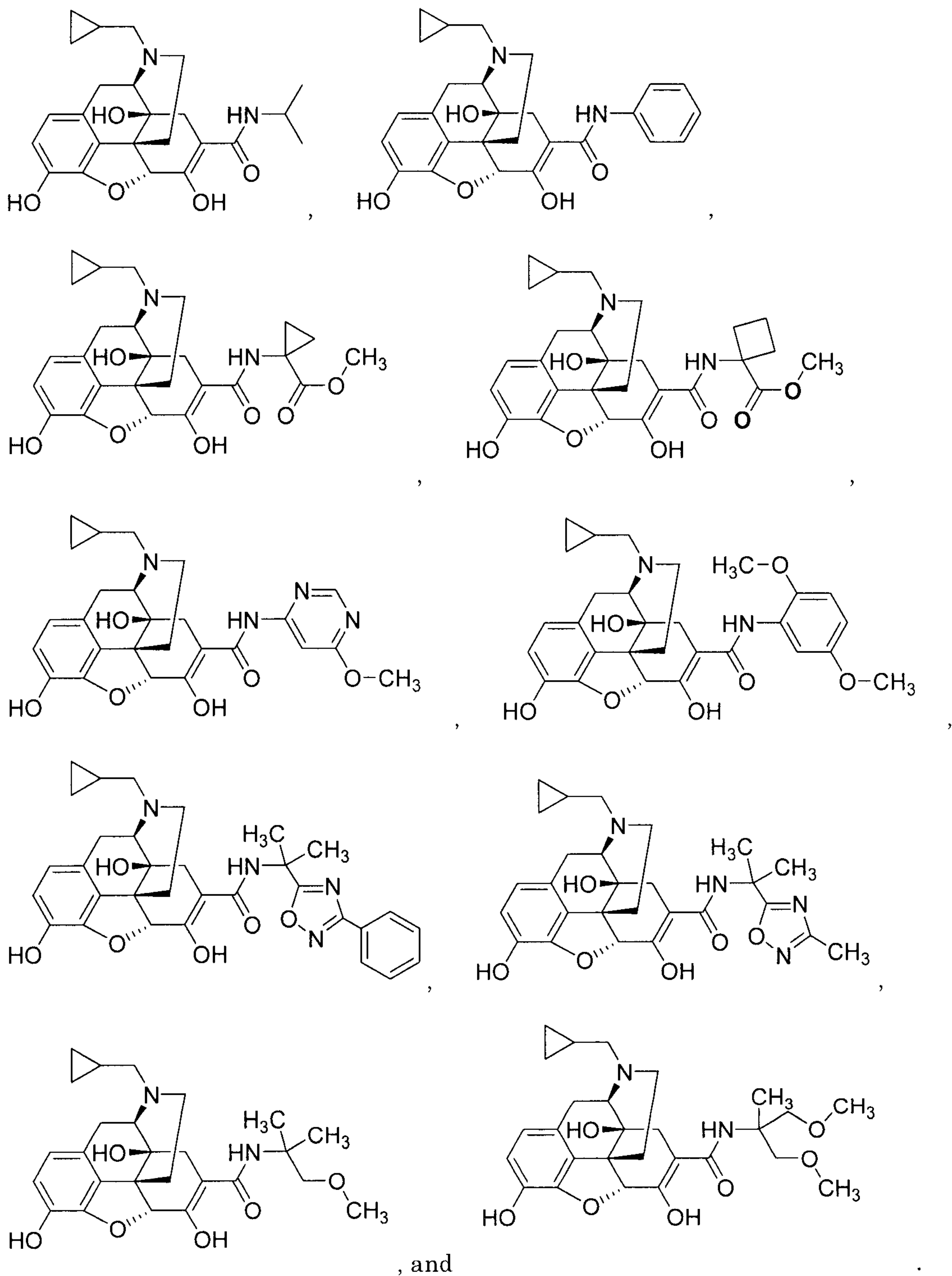
6. The compound according to any one of claims 1, 2 and 4 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:







7. The compound as defined in any one of claims 1, 2 and 4 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



8. A pharmaceutical composition containing a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, and a pharmaceutically

acceptable carrier.

9. An opioid receptor antagonistic composition containing a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

10. A composition for treating and/or preventing emesis, vomiting and/or constipation containing a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

11. A composition for alleviating and/or preventing a side effect induced by a compound having opioid receptor agonistic activity containing a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

12. A composition according to claim 11, wherein the side effect is emesis, vomiting and/or constipation.

13. A composition according to claim 11 or 12, wherein the compound having the opioid receptor agonistic activity is morphine, oxycodone, or a pharmaceutically acceptable salt.

14. Use of the compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, for preparation of a pharmaceutical composition

for treating and/or preventing emesis, vomiting and/or constipation.

15. An analgesic composition comprising:

a compound having an opioid receptor agonistic activity;

an effective amount of compound according to any one of claims 1 to 7, or a

pharmaceutically acceptable salt thereof, for alleviating and/or preventing a side

effect induced by administering the compound having an opioid receptor agonistic

activity; and

a pharmaceutically acceptable carrier.

