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(54) **MORPHINANE DERIVATIVES CONTAINING A CARBOXAMIDE GROUP AS OPIOID RECEPTOR LIGANDS**

CARBOXAMID-BIOISOSTERE VON OPIATEN

BIOSIOSTÈRES DE CARBOXAMIDE D'OPIACÉS

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(56) References cited:

WO-A2-2007/014137

- **WENTLAND M P ET AL: "Redefining the structure-activity relationships of 2,6-methano-3-benzazocines. 4. Opioid receptor binding properties of 8-[N-(4'-phenyl)-phenethyl)carboxamido] analogues of cyclazocine and ethylketocycalzocine", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 18, 7 September 2006 (2006-09-07), pages 5635-5639, XP002550099, ISSN: 0022-2623, DOI: DOI:10.1021/JM060278N [retrieved on 2006-08-10]**
- **VANALSTINE ET AL: "Redefining the structure-activity relationships of 2,6-methano-3-benzazocines. 5. Opioid receptor binding properties of N-((4'-phenyl)-phenethyl) analogues of 8-CAC", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 23, 2 November 2007 (2007-11-02), pages 6516-6520, XP022325927, ISSN: 0960-894X, DOI: DOI:10.1016/J.BMCL.2007.09.082**

EP 2 550 253 B9

Description

Field of the Invention

[0001] The invention relates to opioid receptor binding compounds containing carboxamides that have large substituents on the nitrogen of the carboxamide. The compounds are useful as analgesics, anti-diarrheal agents, anticonvulsants, anti-obesity agents, antitussives, anti-cocaine, anti-inflammatory, and anti-addiction medications.

Background of the Invention

[0002] Opiates have been the subject of intense research since the isolation of morphine in 1805, and thousands of compounds having opiate or opiate-like activity have been identified. Many opioid receptor-interactive compounds including those used for producing analgesia (e.g., morphine) and those used for treating drug addiction (e.g., naltrexone and cyclazocine) in humans have limited utility due to poor oral bioavailability and a very rapid clearance rate from the body. This has been shown in many instances to be due to the presence of the 8-hydroxyl group (OH) of 2,6-methano-3-benzazocines, also known as benzomorphans [(e.g., cyclazocine and EKC (ethylketocyclazocine)] and the corresponding 3-OH group in morphinans (e.g., morphine). Furthermore, charts 1-3 depicts a set of opiate binding compounds that are used to treat diseases mediated by opiate receptors.

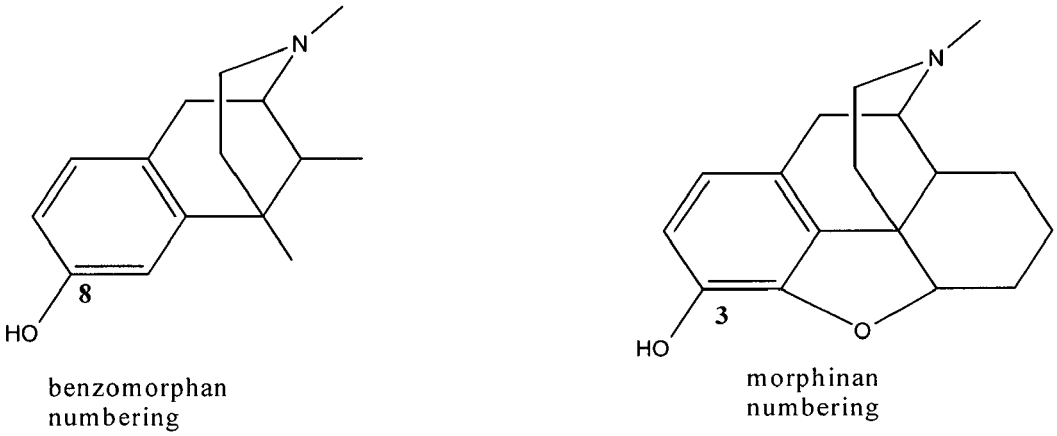
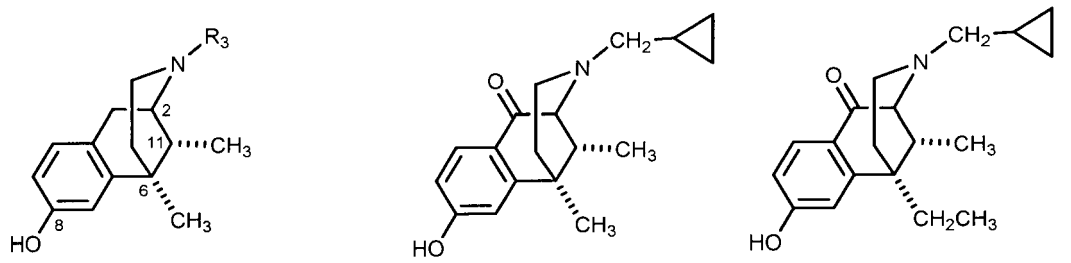


Chart 1. Opioid Receptor Ligands Benzomorphinans (a.k.a. 2,6-Methano-3-benzazocines)

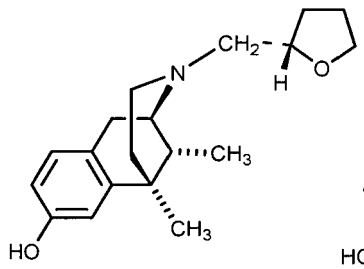
[0003]



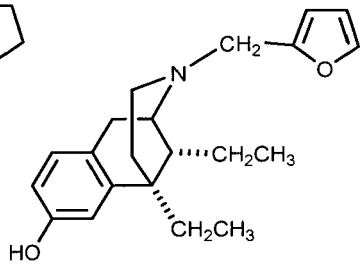
Cyclazocine, $R_3 = CH_2\text{-}c\text{-}C_3H_5$
Metazocine, $R_3 = CH_3$
Phenazocine, $R_3 = CH_2C_6H_5$
SKF 10,047, $R_3 = CH_2CH{=}CH_2$
Pentazocine, $R_3 = CH_2CH{=}C(CH_3)_2$
(all racemic)

Ketocyclazocine

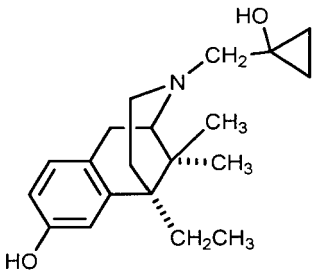
Ethylketocyclazocine (EKC)



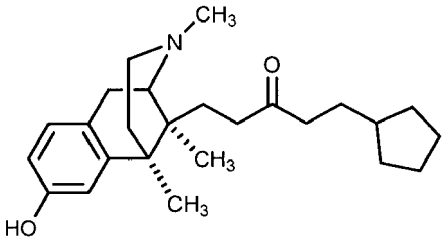
MR2034 - "Merz" core structure (opt. active)



MR2266



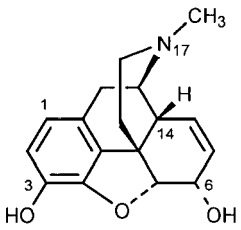
Bremazocine



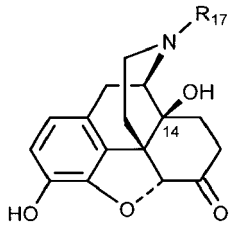
WIN 44,441

Chart 2. Opioid Receptor Ligands Morphine and Morphinans

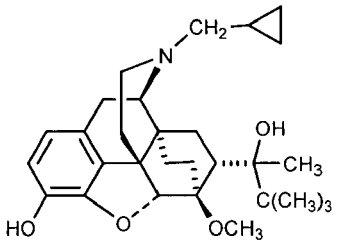
[0004]



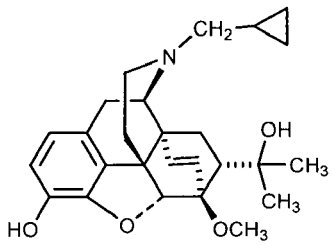
Morphine



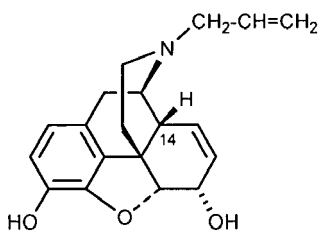
Naltrexone; R_{17} = CH_2-c-C_3H_5
Naloxone; R_{17} = $CH_2CH{=}CH_2$
Nalmexone; R_{17} = $CH_2CH{=}C(CH_3)_2$
Oxymorphone; R_{17} = CH_3



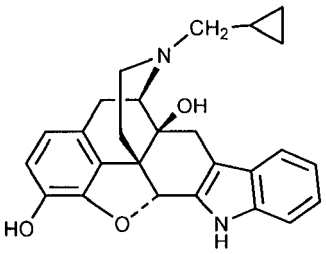
Buprenorphine



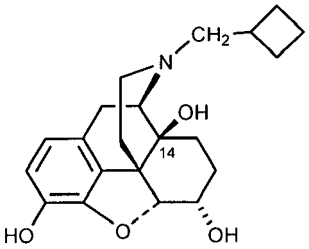
Diprenorphine
Etorphine (N-Me; n-Pr vs Me)



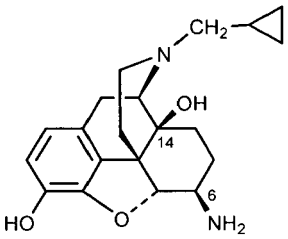
Nalorphine



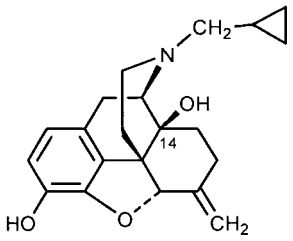
Naltrindole



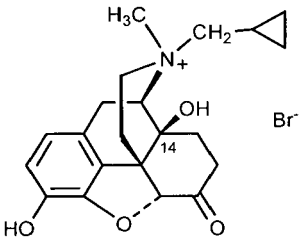
Nalbuphine



β-Naltrexamine



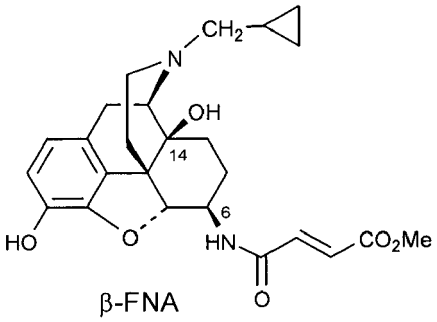
Nalmefene



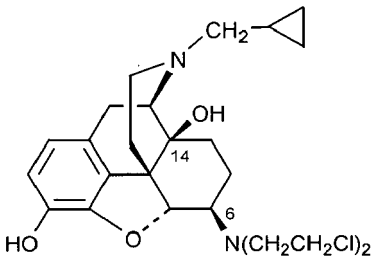
Methylnaltrexone

Chart 2 (continued). Opioid Receptor Ligands Morphine and Morphinans

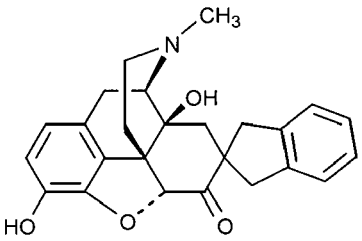
[0005]



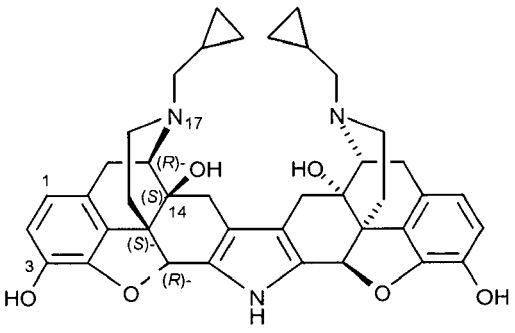
β-FNA



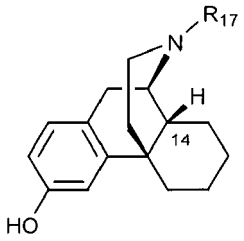
β-CNA



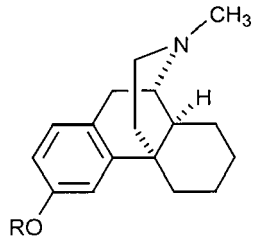
SIOM (δ agonist)



nor-BNI (Norbinaltorphimine)
Reg # = 105618-26-6



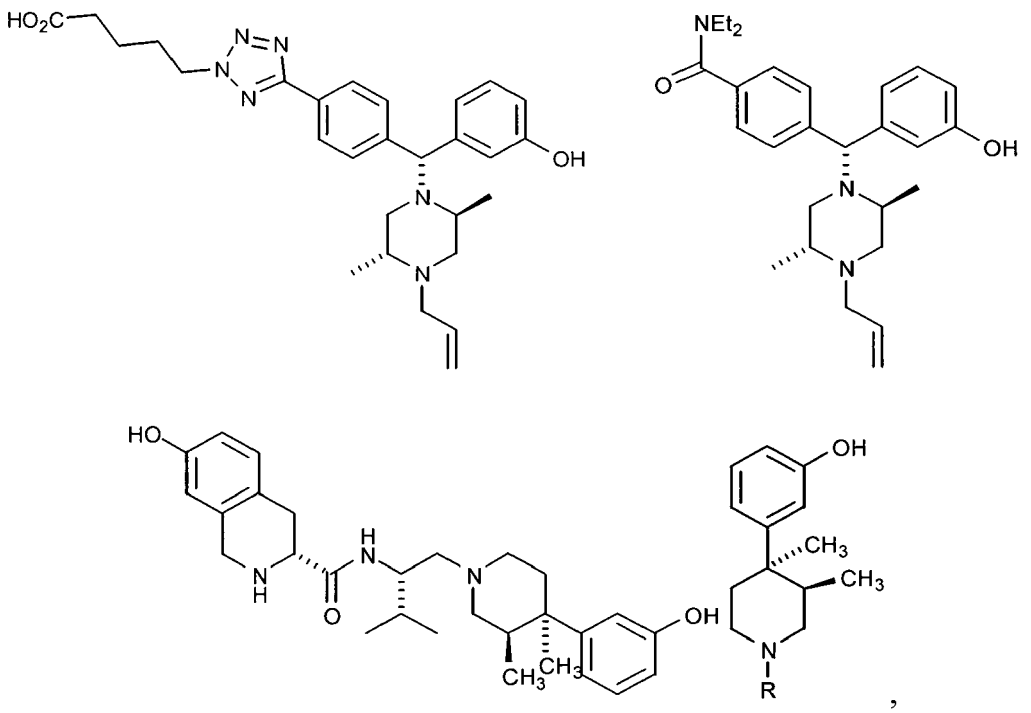
Levorphanol; $R_{17} = CH_3$
Cyclorphan; $R_{17} = CH_2\text{-}\underline{c}\text{-}C_3H_5$
MCL 101; $R_{17} = CH_2\text{-}\underline{c}\text{-}C_4H_7$
Butorphanol; $R_{17} = CH_2\text{-}\underline{c}\text{-}C_4H_7$ and 14-OH
Merz-morphinane hybrid core; R_{17} = CH_2-(S)-tetrahydrofurfuryl



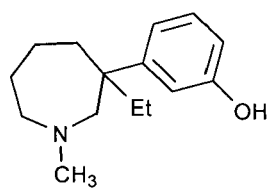
Dextromethorphan; R = CH_3
Dextrorphan; R = H
(note "opposite" sterochemistry)

Chart 3 - Miscellaneous Opioid Receptor Ligands

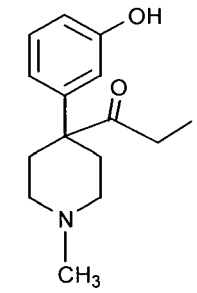
[0006]



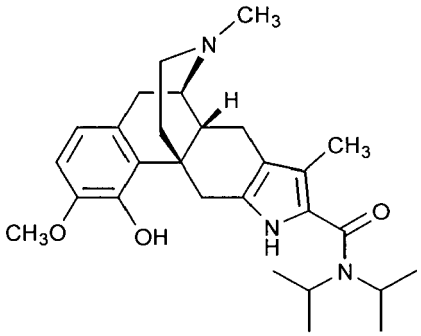
wherein, R is selected from CH_3, $CH_2CH_2CH(OH)C_6H_{11}$, $CH_2CH(CH_2Ph)CONHCH_2CO_2H$, $(CH_2)_3CH(CH_3)_2$, and $(CH_2)_3$-2-thienyl,

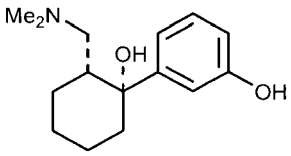


Meptazinol

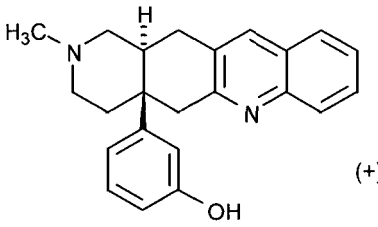


Ketobemidone

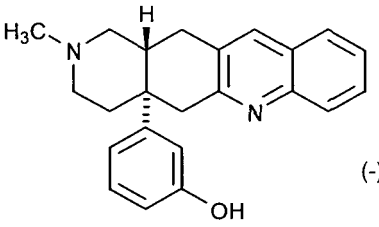




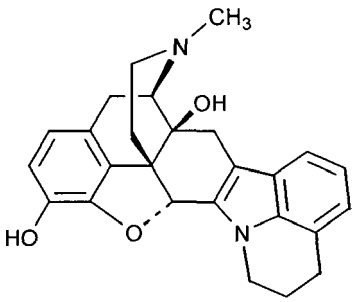
Tramadol active metabolite
Registry Number 80456-81-1

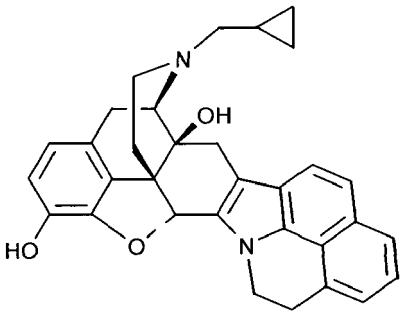


(+)-TAN 67



(-)-TAN 67





[0007] Other opioid receptor ligands are described in Aldrich, J.V. "Analgesics" in Burger's Medicinal Chemistry and Drug Discovery, M.E.Wolff ed., John Wiley & Sons 1996, pages 321-344 and WO2007/14137.

[0008] The high polarity of these hydroxyl groups retards oral absorption of the parent molecules. Furthermore, the 8-(or 3-)OH group is prone to sulfonation and glucuronidation (Phase II metabolism), both of which facilitate rapid excretion of the active compounds, leading to disadvantageously short half-lives for the active compounds. Until the publications of Wentland in 2001, the uniform experience in the art of the past seventy years had been that removal or replacement of the 8-(or 3-)OH group had led to pharmacologically inactive compounds.

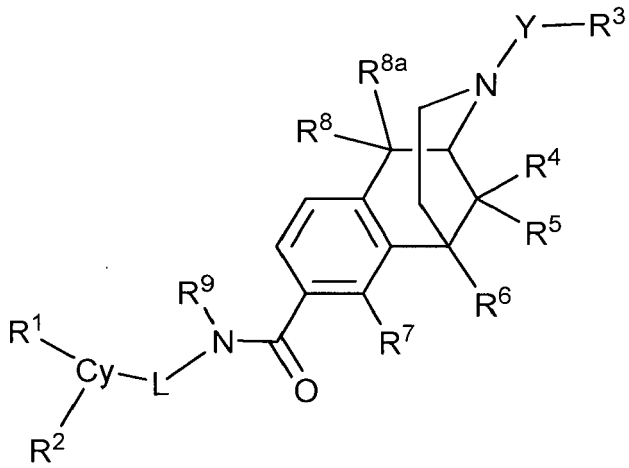
[0009] US patent 6,784,187 (to Wentland) disclosed that the phenolic OH of opioids could be replaced by $CONH_2$. In the cyclazocine series of opioids, it was shown that 8-carboxamidocyclazocine (8-CAC) had high affinity for μ and κ opioid receptors. In studies *in vivo,* 8-CAC showed high antinociception activity and a much longer duration of action than cyclazocine (15 h vs. 2 h) when both were dosed at 1 mg/kg ip in mice. Preliminary structure-activity relationship studies for 8-CAC revealed that mono-substitution of the carboxamide nitrogen with methyl or phenyl reduced binding

affinity for guinea pig μ receptors 75- and 2313-fold, respectively whereas dimethylation of the carboxamide group reduced binding affinity 9375-fold. The finding that substitution of the carboxamide nitrogen had such a detrimental effect suggested that the NH_2 of the amide was critical to opioid binding.

[0010] We recently reported that the nitrogen of the carboxamide can be substituted with fairly large and relatively non-polar groups, and that such compounds exhibit good opioid binding and, presumably, good metabolic stability. (WO 2010/011619) Compounds with improved activity can be used to reduce dosage, side effects and costs.

Summary of the Invention

[0011] In one aspect, the invention relates to a compound of formula I:



wherein

R^1 is selected from -OH, -CN, -CHO, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONH_2$, $-CSNH_2$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$ and $-C(=NR^{10})R^{11}$;
R^2 is selected from hydrogen, halogen, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$,$-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $-C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, heterocyclyl, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, and (C_1-C_6)alkylthio; or,
R^1 and R^2 together with the atoms to which they are attached, and a fragment selected from $-OCH_2O$-, or $-OCH_2CH_2O$-, form a ring,
R^3 is chosen from hydrogen, C_1-C_8 hydrocarbon, heterocyclyl, aryl and hydroxyalkyl;
R^4 is chosen from hydrogen, hydroxyl, amino, C_1-C_4 alkoxy, C_1-C_{20} alkyl and C_1-C_{20} alkyl substituted with hydroxyl or carbonyl;
R^5 is C_1-C_6 alkyl;
R^6 is C_1-C_6 alkyl;
R^7 is chosen from hydrogen, $NR^{10}R^{11}$ and $-OR^{10}$; or
together R^4, R^5, R^6 and R^7 may form from one, two, three, or four rings, said rings having optional additional substitution;
R^8 and R^{8a} are both hydrogen or taken together R^8 and R^{8a} are =O;
R^9 is chosen from hydrogen and C_1-C_6 alkyl;

R^{10} R^{11},R^{12} and R^{13} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, $-NR^{100}R^{101}$ or optionally substituted C_1-C_4 alkoxy, or R^{10} and R^{11}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;
t is 0, 1, 2, 3, 4, 5, or 6;
R^{100} and R^{101} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, or optionally substituted C_1-C_4 alkoxy, or R^{100} and R^{101}, together with the nitrogen atom to which they are attached, form an optionally substituted fused

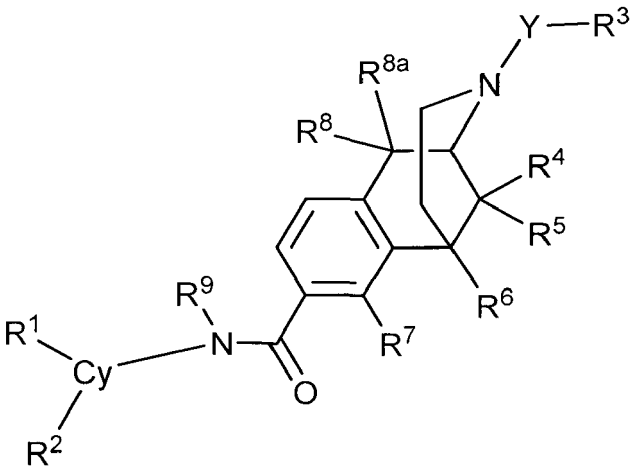
carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;

Y is a direct bond or -$(C(R^{10})(R^{11}))_q$-, wherein q is 0, 1, 2, 3, 4 or 5;
L is a direct bond or -$(C(R^{10})(R^{11}))_q$-; and
Cy is Ar^1-B-Ar^2, wherein

Ar^1 is absent, or an aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, -OR^{10}, -$NR^{10}R^{11}$, -CN, -COR^{10} or -$COOR^{10}$;
B is a direct bond, -O-, -NR^{10}, -SO_2, or -$(C(R^{10})(R^{11})_s$-, wherein s is 0, 1, 2, 3, 4 or 5; and

Ar^2 is aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, -OR^{10}, -$NR^{10}R^{11}$, -CN, -COR^{10} or -$COOR^{10}$.

[0012] In another aspect, the invention relates to compounds of formula Ia:



Ia,

wherein L is a direct bond, and all other substituents are defined as above.

[0013] In one aspect of the invention, the compounds described in charts 1-3 are substituted at the phenolic hydroxyl position. For instance, compounds of charts 1-3 are substituted at the phenolic hydroxyl position with -$C(O)N(R^9)LCy(R^1)(R^2)$, wherein the carboxamido moiety replaces the hydroxyl group to give a compound of formula I or formula Ia.

[0014] In another aspect, the invention relates to a pharmaceutical formulation comprising a compound of formula I or formula Ia and a pharmaceutically acceptable carrier.

[0015] In another aspect, the invention relates to compounds and compositions as defined by the claims for use in preventing or treating a condition or disease associated with binding opioid receptors in a patient in need thereof, comprising the step of administering to said patient a composition comprising an effective amount of a compound of formula I or formula Ia.

[0016] The compounds of the invention are therefore useful as analgesics, anti-inflammatory agents, anti-pruritics, anti-diarrheal agents, anticonvulsants, antitussives, anorexics and as treatments for hyperalgesia, anti-addiction, respiratory depression, dyskinesia, pain (including evidence in the literature that the compounds may also be useful as immunosuppressants and antiinflammatories and for reducing ischemic damage (and cardioprotection), for improving learning and memory, and for treating urinary incontinence. In particular, the compounds of the invention are useful for the treatment of osteoarthritis.

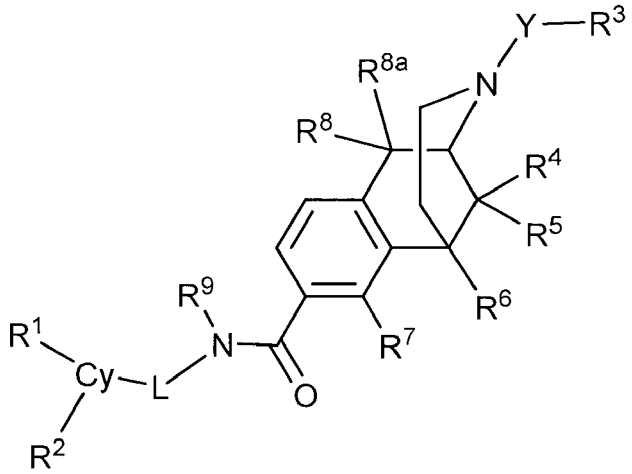
[0017] In another aspect, the invention relates to compounds and compositions as defined by the claims for use in preventing or treating a condition or disease associated with binding opioid receptors in a patient in need thereof, comprising the step of administering to said patient a composition comprising an effective amount of a compound of formula I or formula Ia. In further embodiments, drug addiction encompasses heroin, cocaine, amphetamine, nicotine or alcohol addiction. In other embodiments, the condition is pain and the composition further comprises an effective

amount of an opioid. In yet a further embodiment, the condition is osteoarthritis and the composition further comprises an effective amount of an opioid.

Detailed Description of the Invention

[0018] From many years of SAR studies, it is known that the hydroxyl of morphinans and benzomorphans interacts with a specific site in the opiate receptor. Our recent studies have found that the hydroxyl can be replaced with a carboxamide residue. A fairly wide range of secondary carboxamides exhibits binding in the desired range below 25 nanomolar. We recently reported a set of compounds with cyclic groups attached at the carboxamide position (US 20070021457, WO 2010/011619, and 12/506,354). It has been surprisingly found that a selected groups of substituents on the cyclic group provides significantly improved binding properties.

[0019] In one aspect the invention relates to compounds of formula I:



wherein

R^1 is selected from -OH, -CN, -CHO, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONH_2$, $-CSNH_2$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$ and $-C(=NR^{10})R^{11}$;

R^2 is selected from hydrogen, halogen, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$, $-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $-C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, heterocyclyl, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, and (C_1-C_6)alkylthio; or,

R^1 and R^2 together with the atoms to which they are attached, and a fragment selected from $-OCH_2O-$, or $-OCH_2CH_2O-$, form a ring,

R^3 is chosen from hydrogen, C_1-C_8 hydrocarbon, heterocyclyl, aryl and hydroxyalkyl;

R^4 is chosen from hydrogen, hydroxyl, amino, C_1-C_4 alkoxy, C_1-C_{20} alkyl and C_1-C_{20} alkyl substituted with hydroxyl or carbonyl;

R^5 is C_1-C_6 alkyl;

R^6 is C_1-C_6 alkyl;

R^7 is chosen from hydrogen, $NR^{10}R^{11}$ and $-OR^{10}$; or

together R^4, R^5, R^6 and R^7 may form from one, two, three, or four rings, said rings having optional additional substitution;

R^8 and R^{8a} are both hydrogen or taken together R^8 and R^{8a} are =O;

R^9 is chosen from hydrogen and C_1-C_6 alkyl;

R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, $-NR^{100}R^{101}$ or optionally substituted C_1-C_4 alkoxy, or R^{10} and R^{11}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;

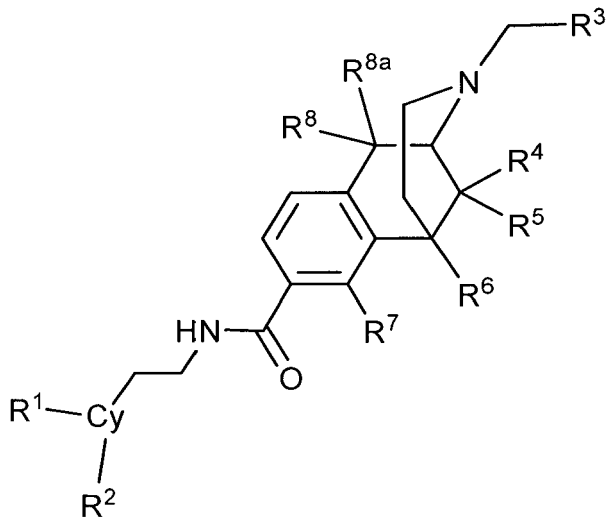
t is 0, 1, 2, 3, 4, 5, or 6;

R^{100} and R^{101} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, or optionally substituted C_1-C_4 alkoxy, or R^{100} and R^{101}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;

Y is a direct bond or -(C(R^{10})(R^{11}))q-, wherein q is 0, 1, 2, 3, 4 or 5;
L is a direct bond or -(C(R^{10})(R^{11}))q-; and
Cy is Ar^1-B-Ar^2, wherein

Ar^1 is absent, or an aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, -OR^{10}, -$NR^{10}R^{11}$, -CN, -COR^{10} or -$COOR^{10}$;
B is a direct bond, -O-, -NR^{10}, -SO_2, or -(C(R^{10})(R^{11})s-, wherein s is 0, 1, 2, 3, 4 or 5; and
Ar^2 is aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, -OR^{10}, -$NR^{10}R^{11}$, -CN, -COR^{10} or -$COOR^{10}$.

[0020] In part, the invention provides a compound of formula II:

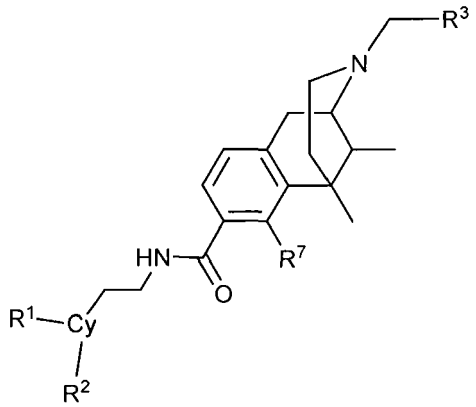


Formula II

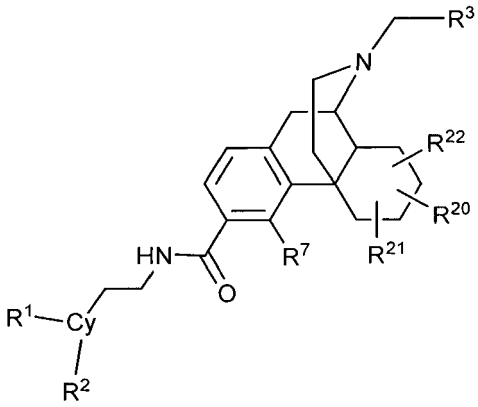
wherein, Cy, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^{8a} are as defined above. In some embodiments, R^1 is selected from -OH, -CHO, -$CONH_2$ -CON(H)CH_2CONH_2, -CON(H)$CH_2CH_2CONH_2$, -CON(H)CH_2COOH, -CON(H)CH_2CH_2COOH, -COOH and -$COOCH_3$; or R^1 and R^2 together with the atoms to which they are attached forms a -OCH_2O-fused ring.

[0021] In other embodiments, R^2 is H, and R^1 is selected from -OH, -CHO, -$CONH_2$, -CON(H)CH_2CONH_2, -CON(H)$CH_2CH_2CONH_2$, -CON(H)CH_2COOH, -CON(H)CH_2CH_2COOH, -COOH and -$COOCH_3$.

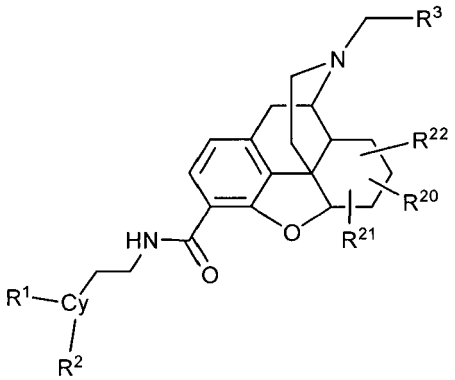
[0022] In part, the invention provides a compound of formula III, IV, V or VI below:



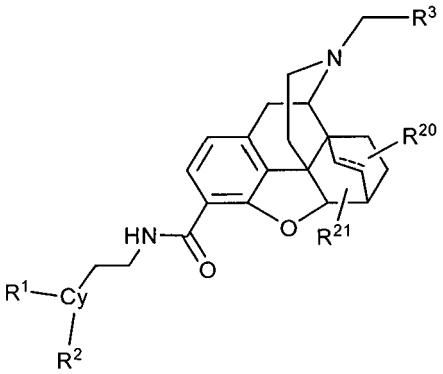
Formula III



Formula IV



Formula V



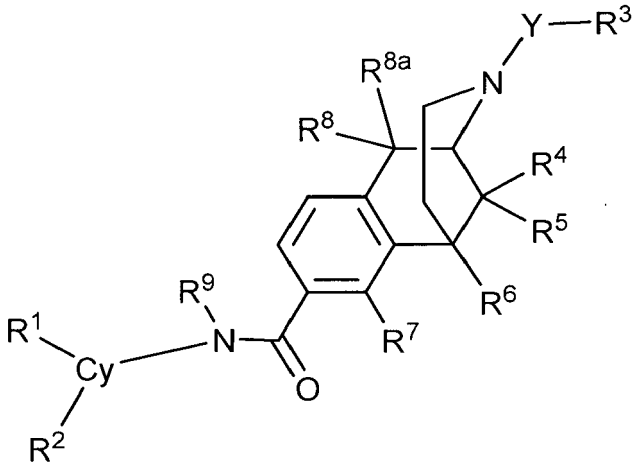
Formula VI

wherein, R^1, R^2, R^3, R^7 and Cy are as defined above;

each R^{20}, R^{21} and R^{22} is chosen from hydrogen, hydroxyl, amino, C_1-C_4 alkoxy, C_1-C_{20} alkyl and C_1-C_{20} alkyl substituted with hydroxyl or carbonyl; or together, R^{20} and R^{21} together with the carbon to which they are attached, form -CO, or -CS; or together, R^{20} and R^{21}, together with the carbon(s) to which they are attached, form a ring. In some embodiments, such a ring is a spiral ring.

[0023] In one embodiment, a compound of formula III, IV, V or VI is disclosed wherein R^1 is selected from -OH, -CHO, $-CONH_2$ $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, $-CON(H)CH_2CH_2COOH$; or R^1 and R^2 together with the atoms to which they are attached forms a $-OCH_2O$-fused ring. In another embodiment, R^2 is H, and R^1 is selected from -OH, -CHO, $-CONH_2$ $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, $-CON(H)CH_2CH_2COOH$.

[0024] In part, the invention provides a compound of formula Ia:

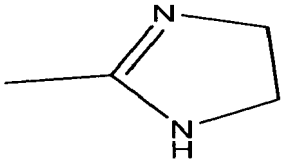


Formula Ia

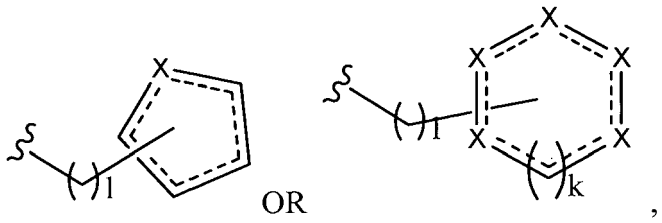
wherein L is a direct bond, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{8a}, R^9 and Cy are as defined above.

[0025] R^1 and R^2 can be, independently, small, polar, neutral residues and, in particular, can be selected from the group consisting of substituted or unsubstituted amide groups, including but not limited to carboxamide, thiocarboxamide, acylamine and formamide groups; substituted or unsubstituted amines; substituted or unsubstituted amidines, such as hydroxyamidines; and alkyls substituted by polar neutral residues.

[0026] According to the present disclosure, R^1 and R^2 can be, independently, Z, wherein Z is a polar neutral residue, such as CH_2OR_a, $CH_2NR_bR_c$, -CN, - NR_bSO_2-R_c, -C(=W)R_a, -NR_aCOR_b, -NR_aCSR_b, -$SO_2NR_bR_c$, -NR_b-Q_a-Rc, -C(=W)NR_bR_c, -C(O)OR_a, heterocycle, substituted heterocycle, heteroaryl, and substituted heteroaryl, such as



OR



wherein 1 is 0,1,2, 3, 4 or 5; k is 0, 1 or 2;
X is C, N, S or O and ------ represents a single or double bond;
R_a, R_b, R_c are each independently selected from: hydrogen; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocyclic or substituted heterocyclic; and substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, or cycloalkenyl each containing 0, 1, 2, or 3 or more heteroatoms selected from O, S, or N;
alternatively, R_a, R_b and R_c taken together with the attached atom form a heterocyclic or substituted heterocyclic;
Q_a is absent or selected from (C=O), (SO_2), (C=NH), (C=S), or ($CONR_a$); and W is O, S, NOR_a or NR_a.

[0027] In other examples, R^1 can be selected from -OH, -CN, -CHO, COR^{10}, -$COOR^{10}$, -SO_2R^{10}, -$CONH_2$, -$CSNH_2$, -$CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, -$CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, -C(=S)$R^{10}$ and -C(=NR^{10})R^{11}.

[0028] In other examples, R^2 can be selected from hydrogen, halogen, -OH, -CN, -CHO, -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -NO_2, -COR^{10}, -$COOR^{10}$, -SO_2R^{10}, -$CONR^{10}R^{11}$, -$CSNR^{10}R^{11}$, -$CONR^{10}NR^{11}R^{12}$, -$CONR^{10}OR^{11}$,

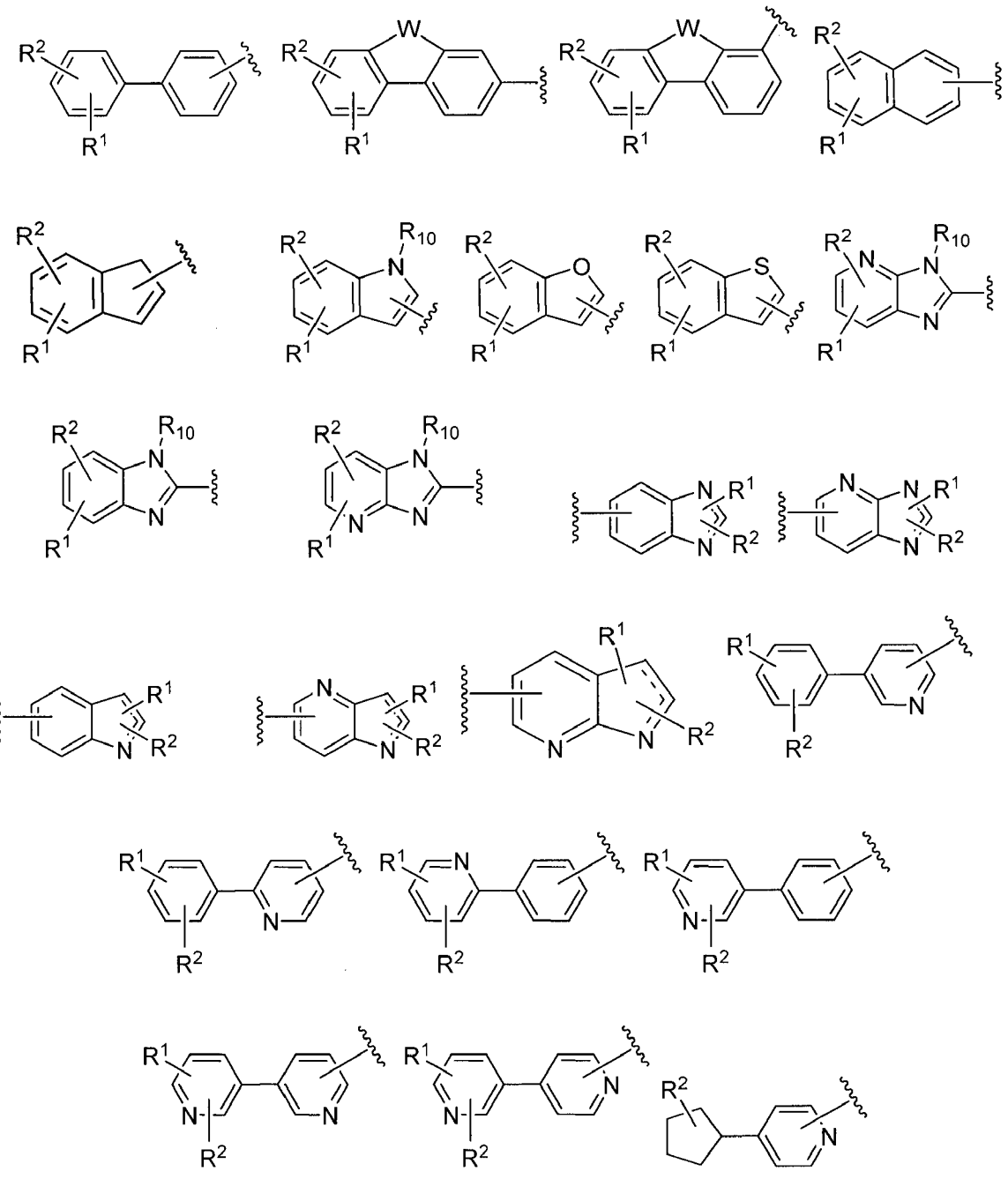
$-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, heterocyclyl, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, and (C_1-C_6)alkylthio.

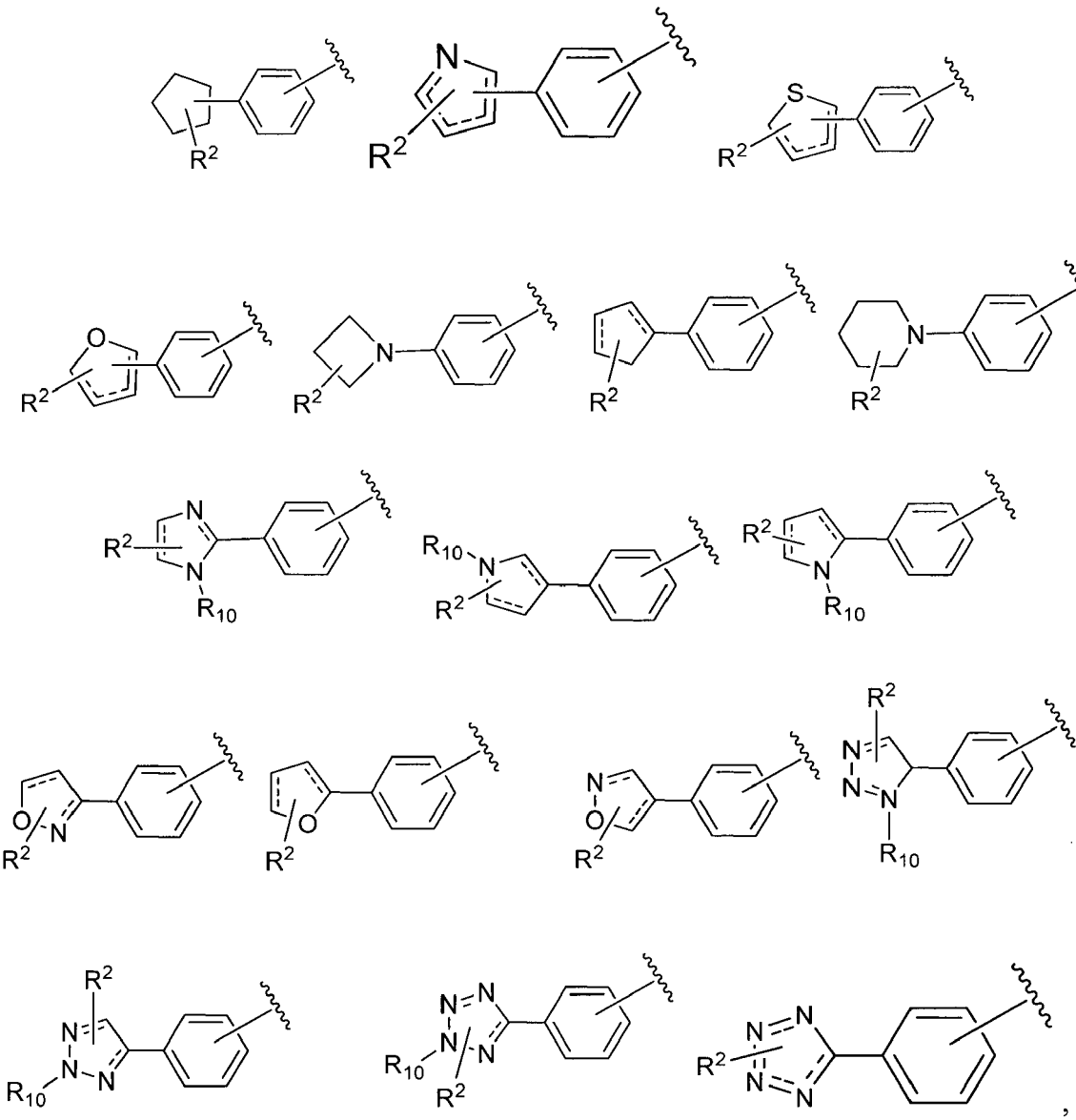
[0029] In other examples, R^1 and R^2 can be each independently selected from hydrogen, halogen, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$, $-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, heterocyclyl, optionally substituted lower alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, and (C_1-C_6)alkylthio.

[0030] In other examples, R^1 and R^2, together with the atoms to which they are attached, and a fragment selected from $-OCH_2O-$, or $-OCH_2CH_2O-$, form a ring.

[0031] In some embodiments, one of R^1 or R^2 is hydrogen or methyl and the other is $-CONH_2$, -COH, $-CO_2H$, $-CO_2CH_3$, -OH, (C_1-C_6)alkoxy or CN.

[0032] In some embodiments, Cy is selected from:





wherein W is selected from $[C(R^9)_2]_n$, CR^8R^{8a}, O, NR^9, S and $CR^9=CR^9$; and n is 1, 2, 3, 4 or 5.

[0033] In some embodiments, R^3 is hydrogen. In other embodiments, R^3 is heterocyclyl. In still other embodiments, R^3 is hydroxyalkyl. In yet other embodiments, R^3 is C_1-C_8 hydrocarbon. In further embodiments, R^3 is cyclopropyl or cyclobutyl.

[0034] In some embodiments, R^4 is hydrogen. In other embodiments, R^4 is hydroxyl or amino. In still other embodiments, R^4 is C_1-C_4 alkoxy. In yet other embodiments, R^4 is C_1-C_{20} alkyl or C_1-C_{20} alkyl substituted with hydroxyl or carbonyl. In further embodiments, R^4 is methyl or ethyl.

[0035] In some embodiments, R^5 is C_1-C_6 alkyl. In some embodiments, R^5 is methyl.

[0036] In some embodiments, R^6 is C_1-C_6alkyl. In some embodiments, R^6 is methyl.

[0037] In some embodiments, R^7 is hydrogen. In other embodiments, R^7 is $-OR^{10}$. In further embodiments, R^7 is hydroxyl. In still other embodiments, R^7 is $NR^{10}R^{11}$. In further embodiments, R^7 is NH_2, $NHCH_3$ or $NH(CH_3)_2$.

[0038] In some embodiments, R^4, R^5, R^6 and R^7 may form from one, two, three or four rings, said rings having optional additional substitution.

[0039] In an embodiment of the invention, R^8 and R^{8a} are both hydrogen. In another embodiment, R^8 and R^{8a} are taken together to form =O.

[0040] In some embodiments, R^9 is hydrogen. In other embodiments, R^9 is C_1-C_6 alkyl.

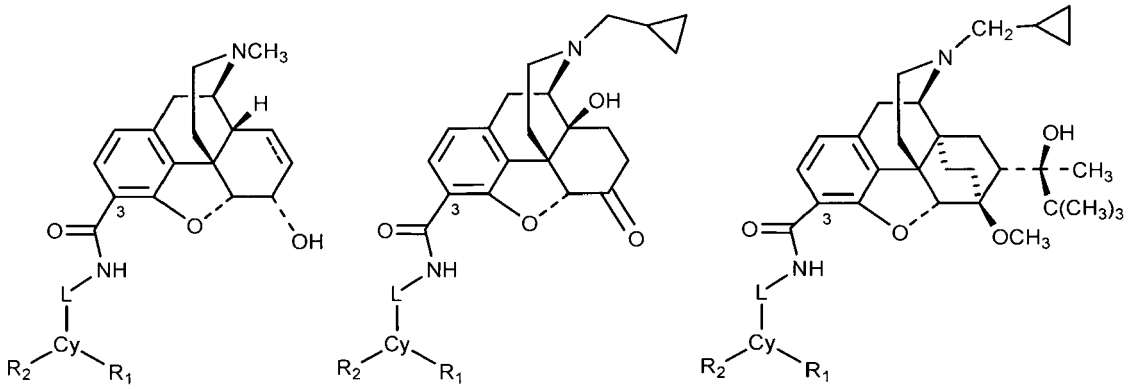
[0041] In some embodiments, R^{10} and R^{11} are each independently hydrogen. In other embodiments, R^{10} is optionally substituted C_1-C_4 alkoxy and R^{11} is hydrogen or methyl. In still other embodiments, R^{10} is optionally substituted C_1-C_6

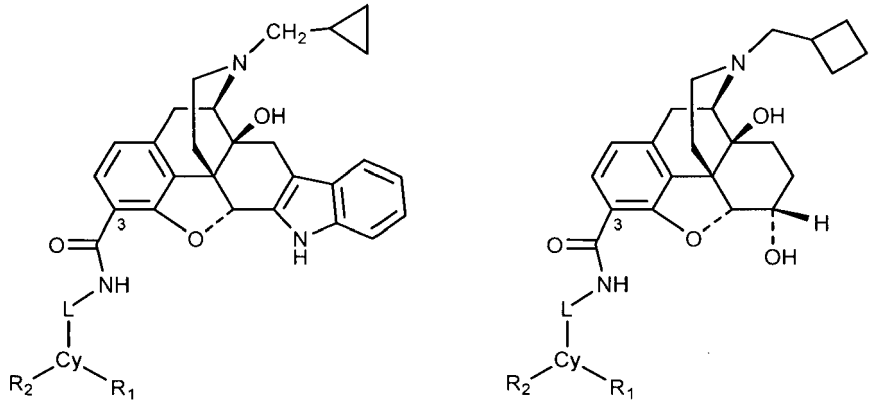
alkyl and R^{11} is hydrogen or methyl. In yet other embodiments, R^{10} is optionally substituted aryl and R^{11} is hydrogen or methyl. In yet other embodiments, R^{10} is hydroxyl or amino and R^{11} is hydrogen or methyl. In some embodiments, R^{10} and R^{11}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S. In some embodiments, R^{10} and/or R^{11} is $-NR^{100}R^{101}$.

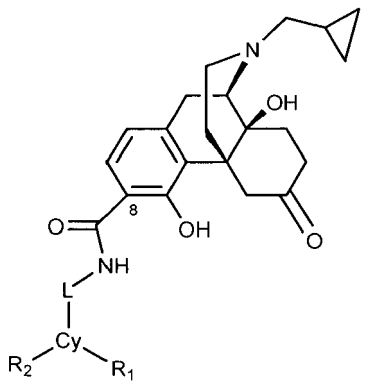
[0042] In these embodiments, R^{100} and R^{101} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, and optionally substituted C_1-C_4 alkoxy. In some embodiments, R^{100} and R^{101}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S.

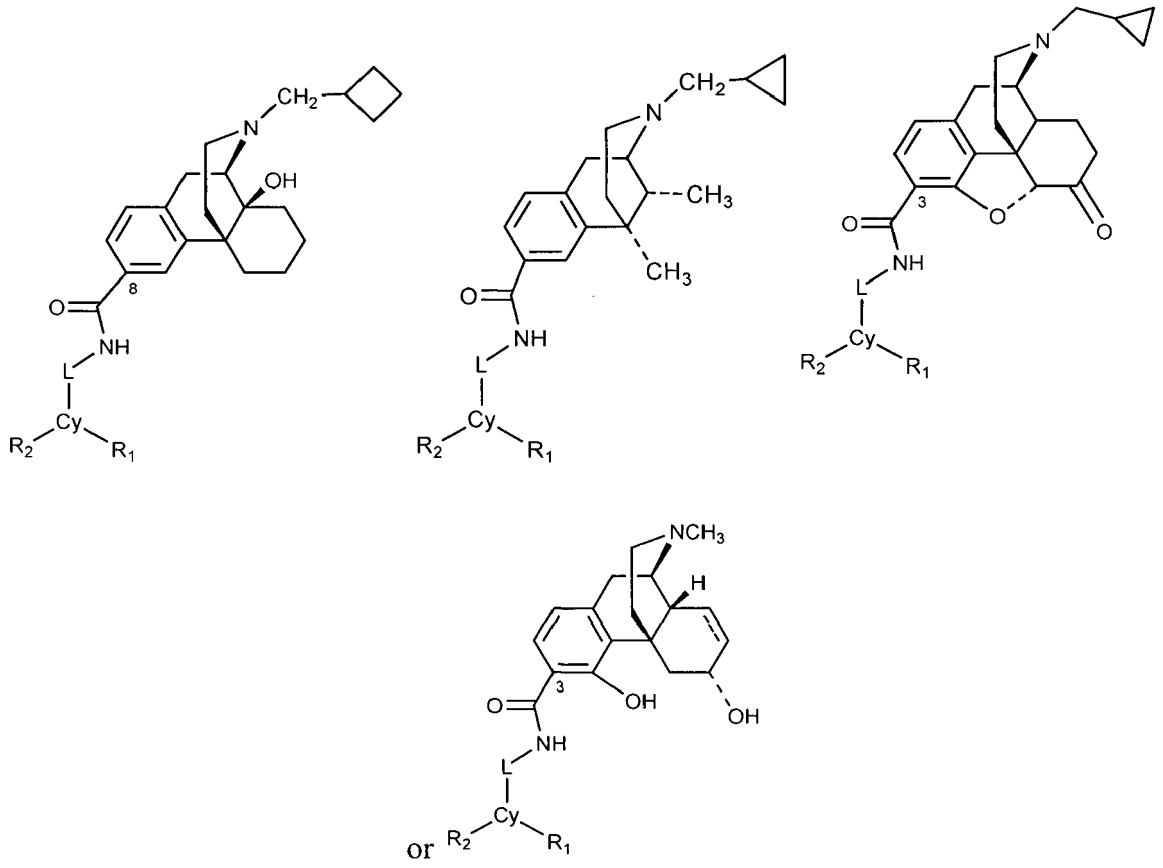
[0043] In one aspect of the invention, the compounds described in charts 1-3 are substituted at the phenolic hydroxyl position. For instance, compounds of charts 1-3 are substituted at the phenolic hydroxyl position with $-C(O)N(R_9)LCy(R_1)(R_2)$, wherein the carboxamido moiety replaces the hydroxyl group to give a compound of formula I or formula Ia.

[0044] In some embodiments, the compound of formula I or formula Ia is selected from:



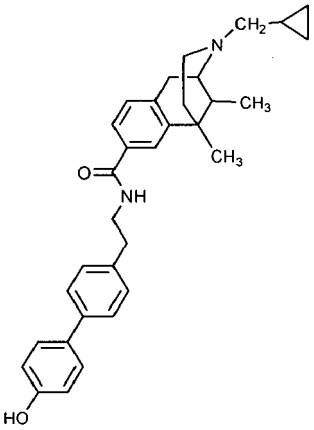
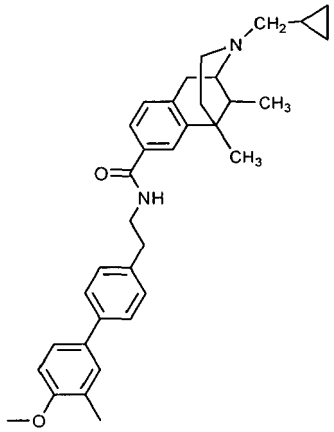




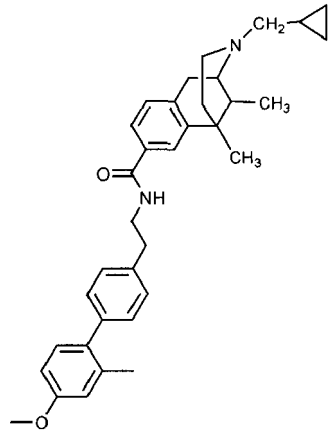
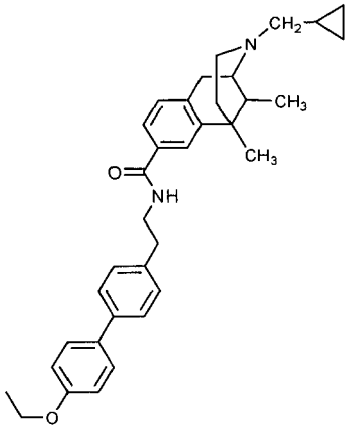
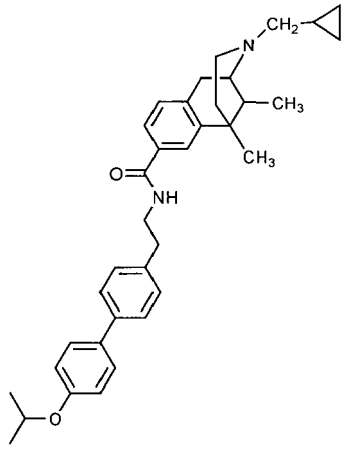
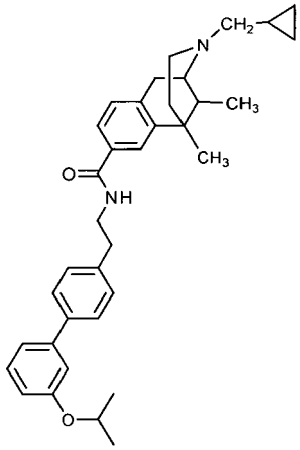
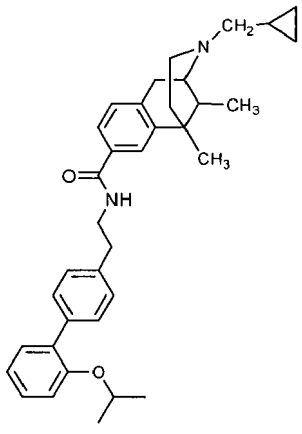
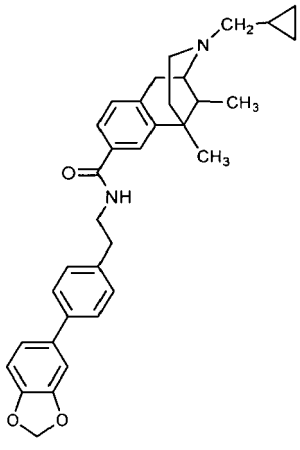


[0045] In some embodiments, the invention provides a compound selected from table 1:

Table 1

No	Structure	No	Structure
1		2	 (not claimed)

(continued)

No	Structure	No	Structure
3	 (not claimed)	4	 (not claimed)
5	 (not claimed)	6	 (not claimed)
7	 (not claimed)	8	

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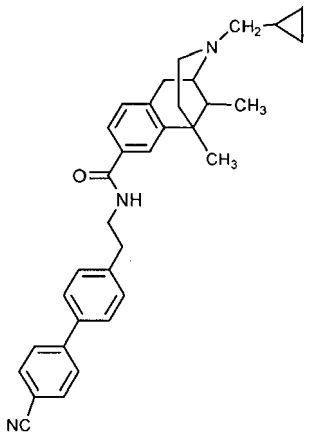
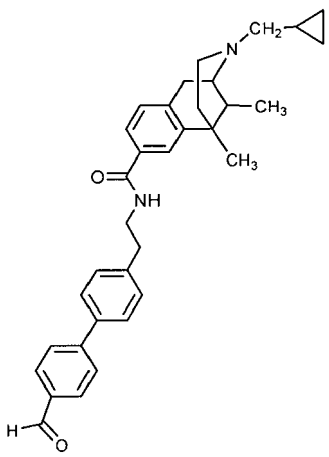
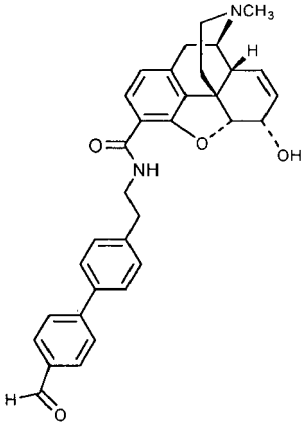
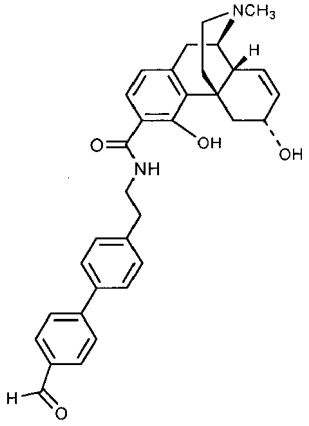
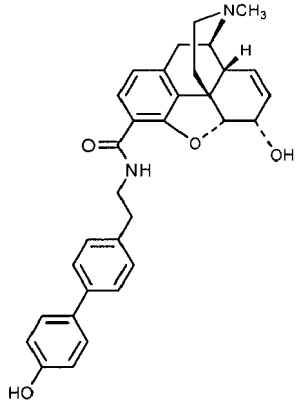
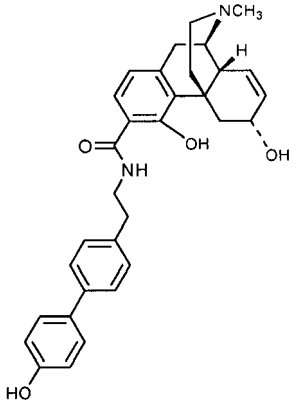
No	Structure	No	Structure
9		10	
11		12	
13		14	

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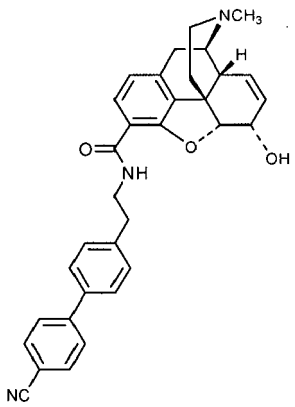
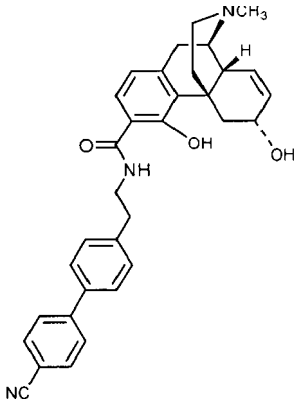
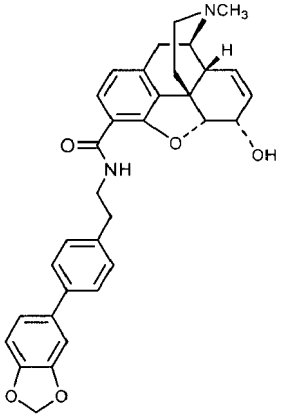
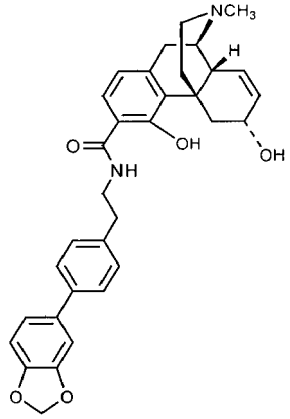
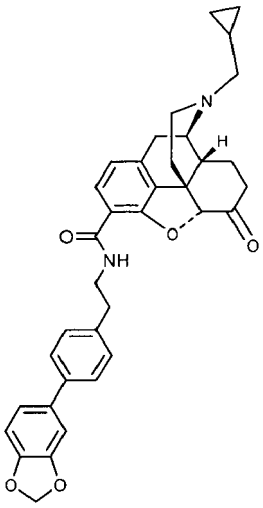
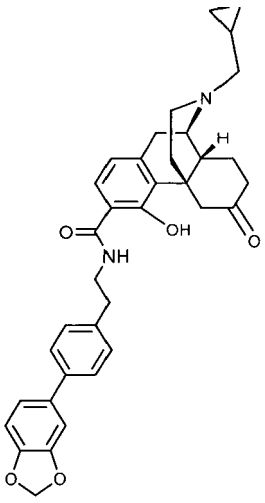
15		16	
17		18	
19		20	

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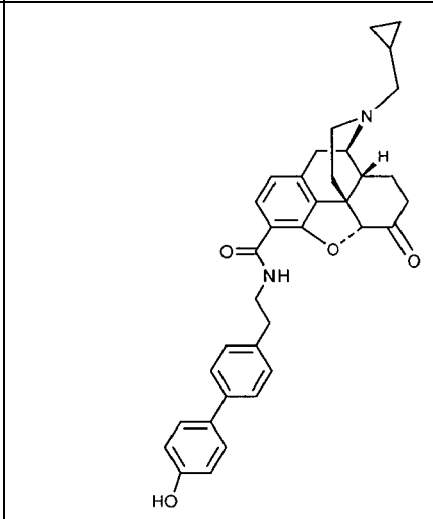
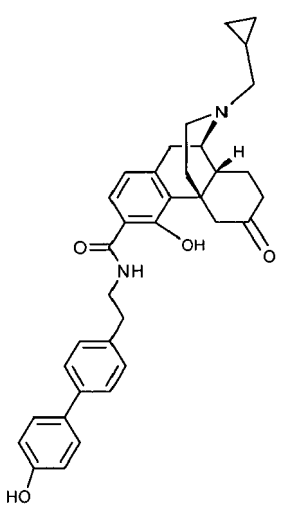
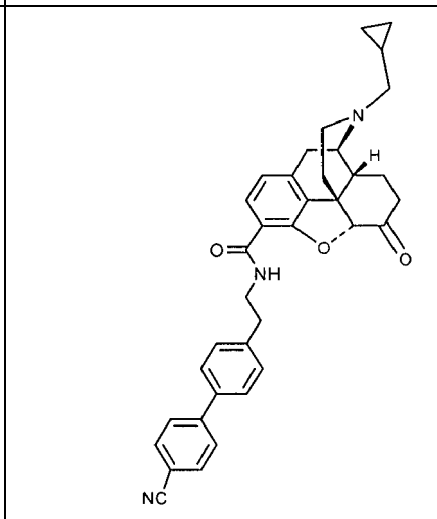
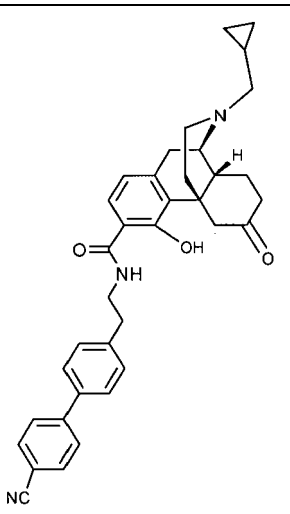
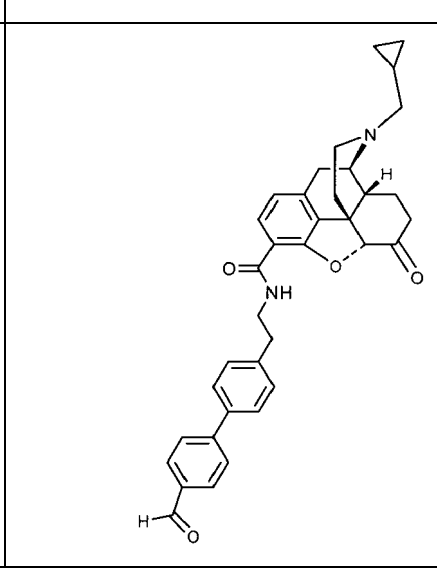
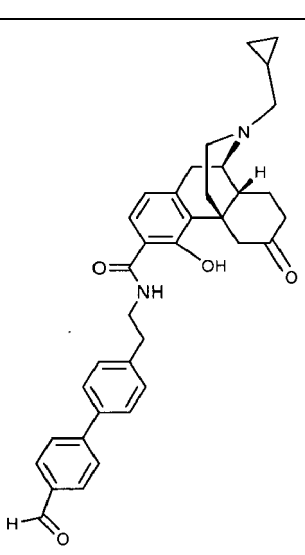
21		22	
23		24	
25		26	

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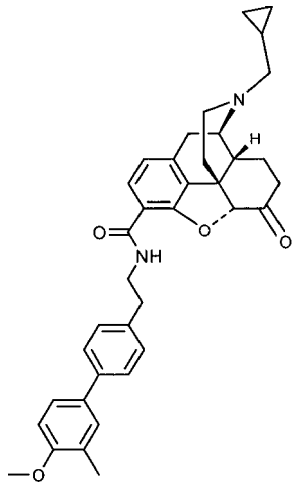
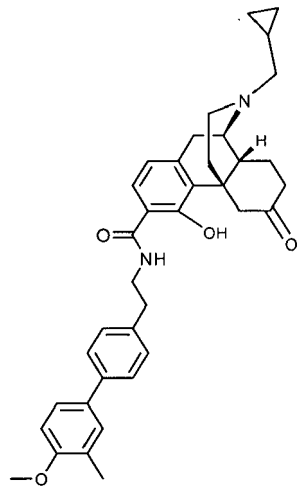
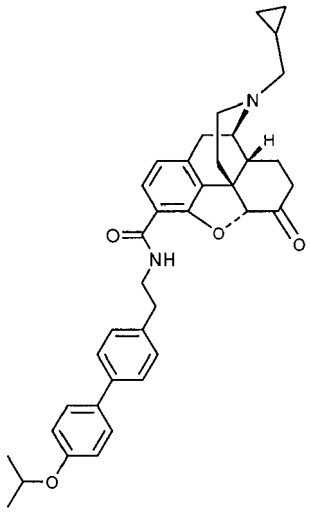
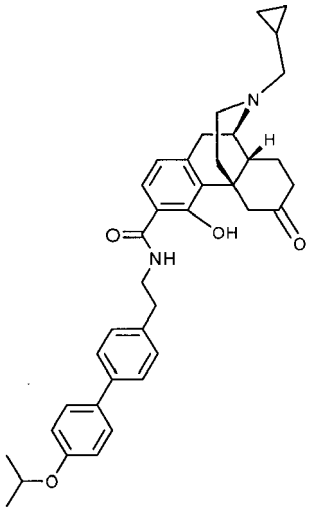
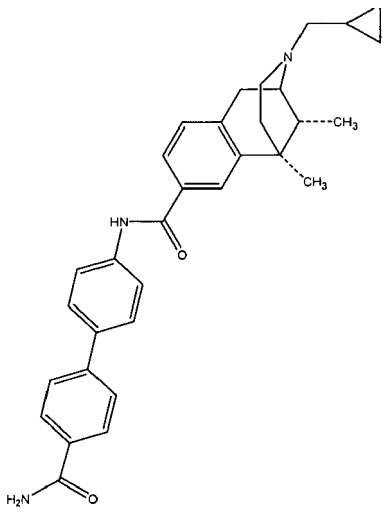
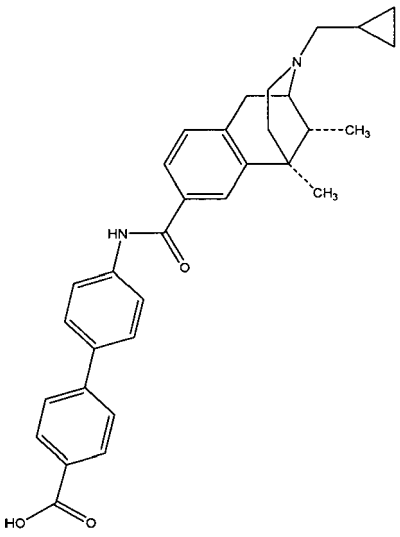
27	 (not claimed)	28	 (not claimed)
29	 (not claimed)	30	 (not claimed)
31		32	

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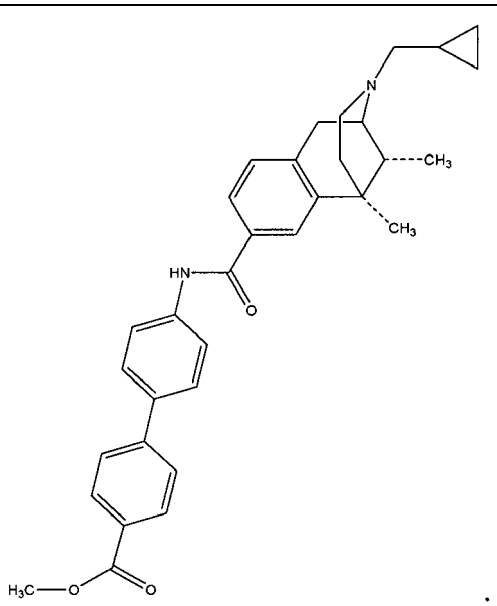
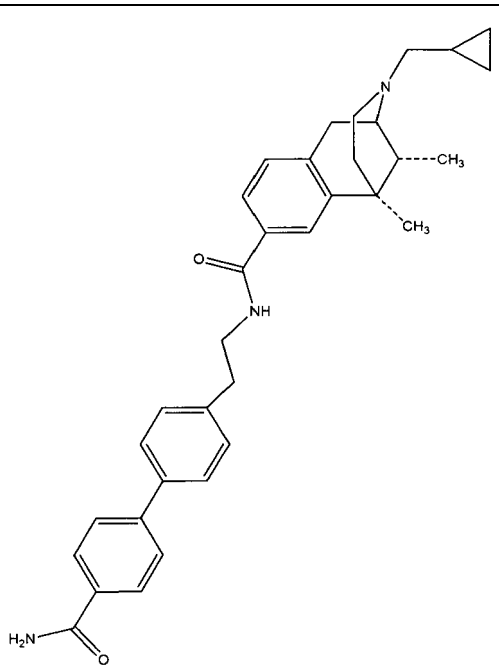
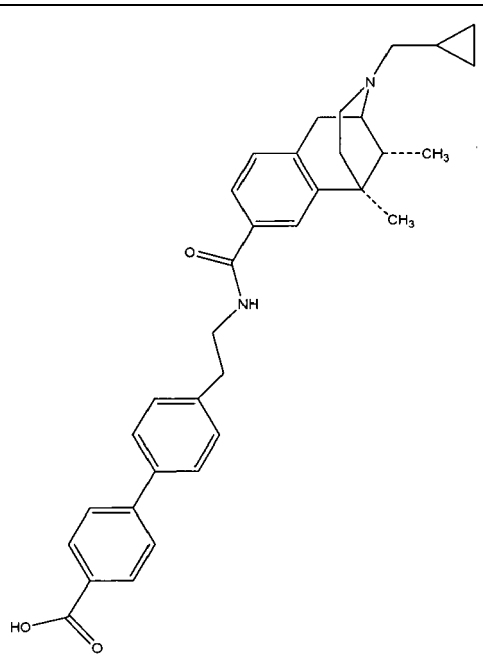
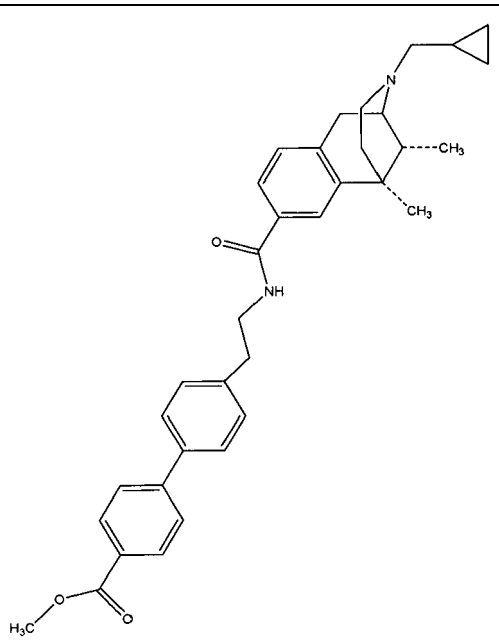
33		34	
35		36	

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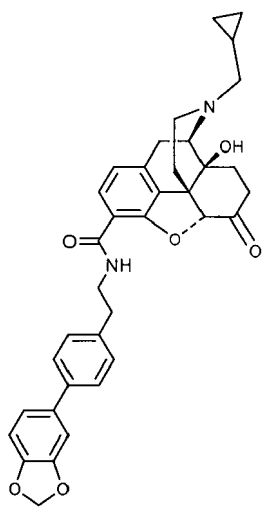
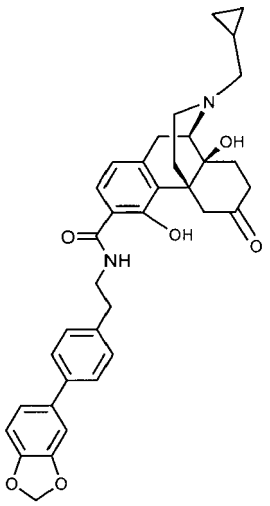
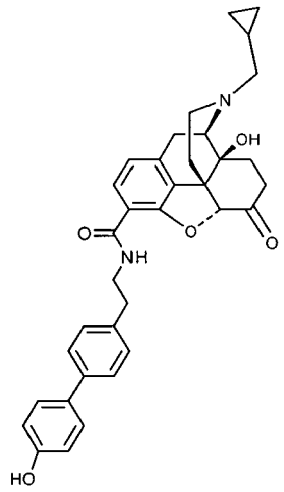
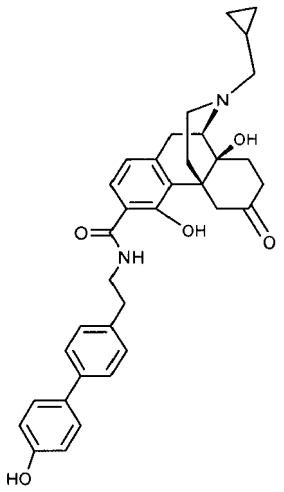
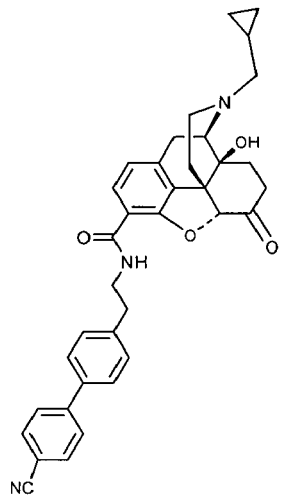
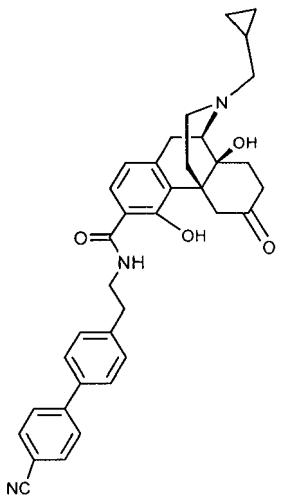
37		38	
39		40	
41		42	

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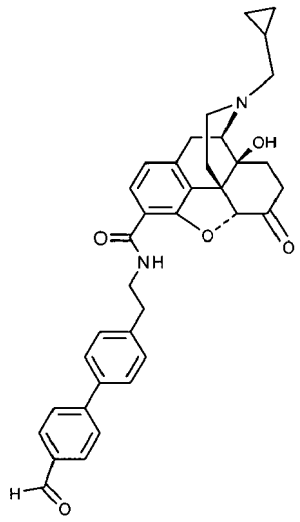
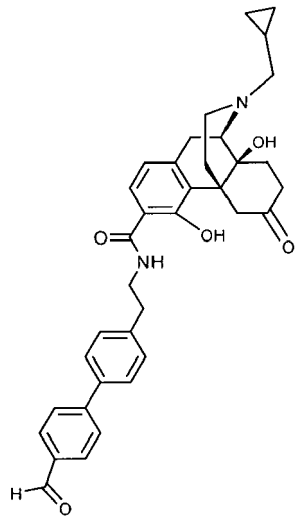
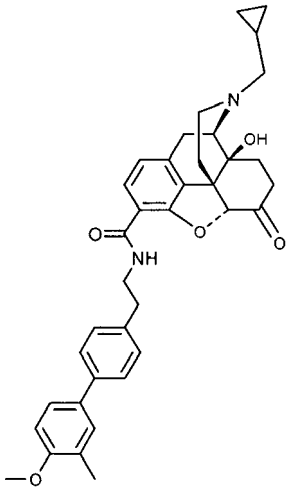
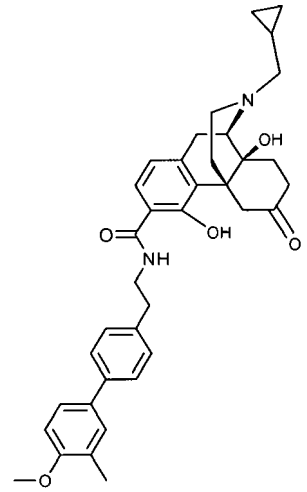
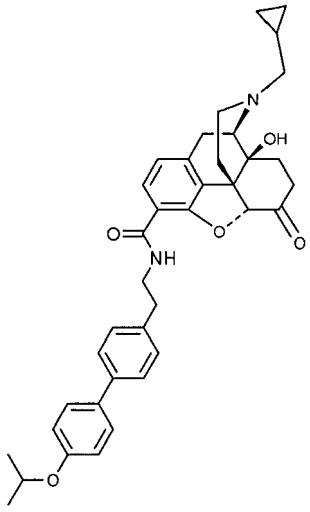
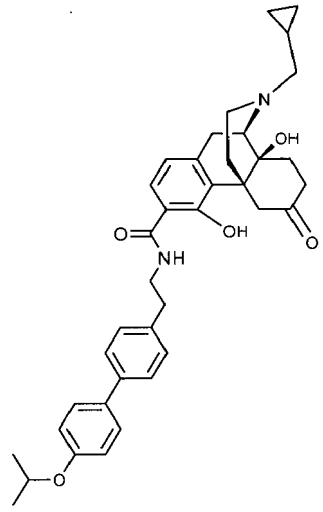
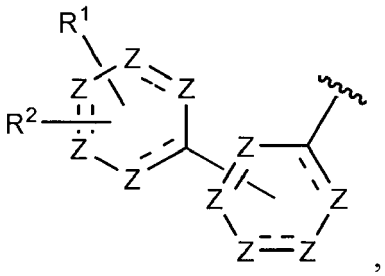
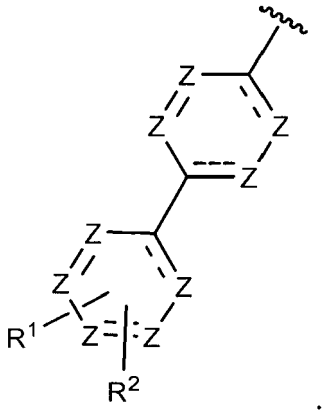
43		44	
45	 (not claimed)	46	 (not claimed)
47	 (not claimed)	48	 (not claimed)

[0046] In some embodiments of the invention, Cy-R^1R^2 is of formula



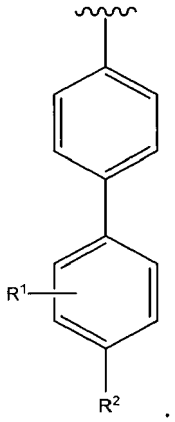
wherein Z is CR^{10} (with R^{10} defined as above) or N. In these instances, Z must be C at the point of attachment of the distal ring to the proximal ring. Additionally, at the points of attachment of R^1 and R^2, Z will be CR^1 and CR^2, respectively. In some embodiments, Cy-R^1R^2 will have the structure:



[0047] In some of these embodiments, one of R^1 and R^2 is in the para position relative to B (the point of attachment of the distal ring to the proximal ring) and the other of R^1 and R^2 is hydrogen.

[0048] In some embodiments of the invention, Ar^2 is phenyl and one of R^1 or R^2 is in the para position relative to B.

[0049] In some embodiments of the invention, Cy-R^1R^2 has the structure:



[0050] The phenolic hydroxyls of benzomorphans and morphinans can be chemically converted to carboxamides by a simple, flexible and convenient route described in Patent Publications 6,784,187, 7,057,035, US 20070021457, and WO 2010/011619.

[0051] It is known in the art that compounds that are μ, δ and κ agonists exhibit analgesic activity; compounds that are selective μ agonists exhibit anti-diarrheal activity and are useful in treating dyskinesia; μ antagonists and κ agonists are useful in treating heroin, cocaine, alcohol and nicotine addiction; κ agonists are also anti-pruritic agents and are useful in treating hyperalgesia. Recently it has been found [Peterson et al. Biochem. Pharmacol. 61, 1141-1151 (2001)]

that κ agonists are also useful in treating retroviral infections. In general, the dextrorotatory isomers of morphinans of type III above are useful as antitussives and anticonvulsants. Opiate binding is also related to the treatment of arthritis. (Keates et al., Anesth Analg 1999;89:409-15). Furthermore it has been reported that in patients suffering from osteoarthritis, μ- and δ-opioid receptors are synthesized and located in synovial lining cells, lymphocytes, and macrophages surrounding the vessels in synovial tissues, and may play a role in the regulation and modulation of inflammation. (Tanaka et al., Modern Rheumatology, 2003, 13(4) 326-332).

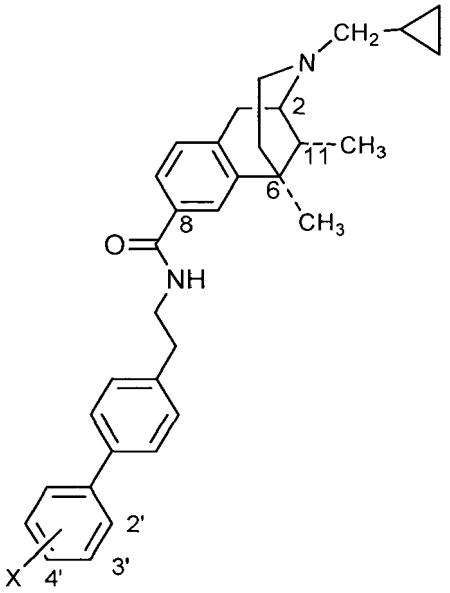
[0052] Opioid receptor ligands having known high affinity are shown in charts 1-3. Replacement of the phenolic OH with the -C(O)N(R_9)LCy(R_1)(R_2) residue in these compounds produces compounds that exhibit similar activity and better bioavailability.

[0053] Binding assays used to screen compounds are similar to those previously reported by Neumeyer et al., Design and Synthesis of Novel Dimeric Morphinan Ligands for κ and μ Opioid Receptors. J. Med. Chem. 2003, 46, 5162. Membrane protein from CHO cells that stably expressed one type of the human opioid receptor were incubated with 12 different concentrations of the compound in the presence of either 1 nM [^{3}H]U69,593[10] (κ), 0.25 nM [^{3}H]DAMGO[11] (μ) or 0.2 nM [^{3}H]naltrindole[12] (δ) in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5 at 25°C. Incubation times of 60 min were used for [^{3}H]U69,593 and [^{3}H]DAMGO. Because of a slower association of [^{3}H]naltrindole with the receptor, a 3 h incubation was used with this radioligand. Samples incubated with [^{3}H]naltrindole also contained 10 mM $MgCl_2$ and 0.5 mM phenylmethylsulfonyl fluoride. Nonspecific binding was measured by inclusion of 10 μM naloxone. The binding was terminated by filtering the samples through Schleicher & Schuell No. 32 glass fiber filters using a Brandel 48-well cell harvester. The filters were subsequently washed three times with 3 mL of cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL Ecoscint A scintillation fluid. For [^{3}H]naltrindole and [^{3}H]U69,593 binding, the filters were soaked in 0.1% polyethylenimine for at least 60 min before use. IC_{50} values were-calculated by least squares fit to a logarithm-probit analysis. K_i values of unlabeled compounds were calculated from the equation $K_i = (IC_{50})/1+S$ where S = (concentration of radioligand)/(K_d of radioligand).[13] Data are the mean ± SEM from at least three experiments performed in triplicate.

[0054] [^{35}S]GTPγS Binding Assays. In a final volume of 0.5 mL, 12 different concentrations of each test compound were incubated with 15 μg (κ), 10 μg (δ) or 7.5 μg (μ) of CHO cell membranes that stably expressed either the human κ, δ or μ opioid receptor. The assay buffer consisted of 50 mM Tris-HCl, pH 7.4, 3 mM $MgCl_2$, 0.2 mM EGTA, 3 μM GDP, and 100 mM NaCl. The final concentration of [^{35}S]GTPγS was 0.080 nM. Nonspecific binding was measured by inclusion of 10 μM GTPγS. Binding was initiated by the addition of the membranes. After an incubation of 60 min at 30°C, the samples were filtered through Schleicher & Schuell No. 32 glass fiber filters. The filters were washed three times with cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL of Ecoscint scintillation fluid. Data are the mean E_{max} and EC_{50} values ± S.E.M. from at least three separate experiments, performed in triplicate. For calculation of the E_{max} values, the basal [^{35}S]GTPγS binding was set at 0%. To determine antagonist activity of a compound at the μ opioid receptors, CHO membranes expressing the μ opioid receptor, were incubated with 12 different concentrations of the compound in the presence of 200 nM of the μ agonist DAMGO. To determine antagonist activity of a compound at the κ opioid receptors, CHO membranes expressing the κ opioid receptor, were incubated with the compound in the presence of 100 nM of the κ agonist U50,488. To determine if a compound was an antagonist at δ receptors, CHO membranes expressing the δ receptor were incubated with 12 different concentrations of the test compound in the presence of 10 nM of the δ -selective agonist SNC 80.

Examples - Cyclazocine subseries

[0055]



K_i (nM ± S.E.)

Compound No.		X	[^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	[^{3}H]U69,593 (κ)
Reference	(±)	H	0.30 ± 0.02	0.74 ± 0.019	1.8 ± 0.19
Reference	(-)	H	0.25 ± 0.031	0.24 ± 0.014	0.35 ± 0.009
Reference	(+)	H	6.4 ± 0.50	9.9 ± 0.44	8.5 ± 1.07
1	(±)	4'-OH	0.0056 ± 0.00073	0.81 ± 0.12	0.49 ± 0.011
1A	(-)	4'-OH	0.0049 ± 0.001	0.78 ± 0.05	0.36 ± 0.018
2	(±)	3'-CH_3-4'-OCH_3	0.059 ± 0.0050	1.5 ± 0.14	1.7 ± 0.14
3	(±)	2'CH_3-4'-OCH_3	0.23 ± 0.0056	1.1 ± 0.18	1.3 ± 0.11
4	(±)	4'-OCH_2CH_3	0.64 ± 0.058	3.4 ± .039	3.3 ± 0.32
5	(±)	4'-$OCH(CH_3)_2$	0.23 ± 0.041	1.9 ± 0.21	1.6 ± 0.11
6	(±)	3'-$OCH(CH_3)_2$	0.43 ± 0.041	3.9 ± 1.4	2.4 ± 0.25
7	(±)	2'-$OCH(CH_3)_2$	0.12 ± 0.0018	0.55 ± 0.025	1.8 ± 0.17
8	(±)	3',4'-OCH_2O-	0.0016 ± 0.0034	1.0 ± 0.12	0.73 ± 0.049
9	(±)	4'-CN	0.017 ± 0.00075	3.0 ± 0.11	1.0 ± 0.095
10	(±)	4'-CHO	0.0020 ± 0.00029	2.5 ± 0.12	1.8 ± 0.038
34	(±)	4'-$CONH_2$	0.0052 ± 0.00055	1.0 ± 0.018	0.91 ± 0.066
35	(±)	4'-CO_2H	2.3 ± 0.16	68 ± 9.0	55 ± 4.1
36	(±)	4'-CO_2CH_3	0.0091 ± 0.00071	1.5 ± 0.062	1.1 ± 0.13

[0056] Antinociceptive activity is evaluated by the method described in Jiang et al. [J. Pharmacol. Exp. Ther. 264, 1021-1027 (1993), page 1022]. The ED_{50}'s of compounds of the invention are expected to be under 100 nmol in the mouse acetic acid writhing test when administered i.c.v., and an increase in the duration of action is expected for compounds of the invention compared to their "parents" when given by i.p. administration.

Definitions

[0057] Throughout this specification the terms and substituents retain their definitions.

[0058] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. A combination would be, for example, cyclopropylmethyl. Lower alkyl refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, s-and t-butyl, cyclobutyl and the like. Preferred alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl and the like.

[0059] Alkoxy or alkoxyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, or cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons.

[0060] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. The aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole. As used herein aryl and heteroaryl refer to residues in which one or more rings are aromatic, but not all need be.

[0061] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like. Heteroarylalkyl means an alkyl residue attached to a heteroaryl ring. Examples include, e.g., pyridinylmethyl, pyrimidinylethyl and the like.

[0062] C_1 to C_{20} hydrocarbon means a linear, branched, or cyclic residue comprised of hydrogen and carbon as the only elemental constituents and includes alkyl, cycloalkyl, polycycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include, e.g., benzyl, phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0063] The term "halogen" means fluorine, chlorine, bromine or iodine. In one embodiment, halogen may be fluorine or chlorine.

[0064] The terms "haloalkyl" and "haloalkoxy" mean alkyl or alkoxy, respectively, substituted with one or more halogen atoms.

[0065] Heterocycle means a cycloalkyl or aryl residue in which one to four of the carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. Heteroaryls form a subset of heterocycles. Examples of heterocycles that fall within the scope of the invention include , e.g., pyrrolidine, pyrazole, pyrrole, indole, quinoline, isoquinoline, tetrahydroisoquinoline, benzofuran, benzodioxan, benzodioxole (commonly referred to as methylenedioxyphenyl, when occurring as a substituent), tetrazole, morpholine, thiazole, pyridine, pyridazine, pyrimidine, thiophene, furan, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like.

[0066] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, alkyl, acyl, alkoxyalkyl, hydroxyloweralkyl, phenyl, heteroaryl, benzenesulfonyl, hydroxy, loweralkoxy, haloalkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), alkoxycarbonylamino, carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, acetoxy, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, sulfonylamino, acylamino, amidino, aryl, benzyl, heterocyclyl, phenoxy, benzyloxy, heteroaryloxy, hydroxyimino, alkoxyimino, oxaalkyl, aminosulfonyl, trityl, amidino, guanidino, ureido, and benzyloxy.

[0067] Virtually all of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. In general it has been found that the levo isomer of morphinans and benzomorphans is the more potent antinociceptive agent, while the dextro isomer may be useful as an antitussive or antispasmodic agent. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0068] Some of the compounds of the invention are quaternary salts, i.e. cationic species. Therefore they will always be presented as salts, and the term "pharmaceutically acceptable salt" refers to salts whose counter ion (anion) derives from pharmaceutically acceptable non-toxic acids including inorganic acids, organic acids and water (which formally furnishes the hydroxide anion). Suitable pharmaceutically acceptable anions for the compounds of the present invention include hydroxide, acetate, benzenesulfonate (besylate), benzoate, bicarbonate, bisulfate, carbonate, camphorsulfonate,

citrate, ethanesulfonate, fumarate, gluconate, glutamate, glycolate, bromide, chloride, isethionate, lactate, maleate, malate, mandelate, methanesulfonate, mucate, nitrate, pamoate, pantothenate, phosphate, succinate, sulfate, tartrate, trifluoroacetate, p-toluenesulfonate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, calcium edetate, camphorate, camsylate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, edetate (EDTA), edisylate, embonate, estolate, esylate, fluoride, formate, gentisate, gluceptate, glucuronate, glycerophosphate, glycolate, glycollylarsanilate, hexylresorcinate, hippurate, hydroxynaphthoate, iodide, lactobionate, malonate, mesylate, napadisylate, napsylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, pidolate, propionate, rhodanide, salicylate, sebacate, stearate, tannate, theoclate, tosylate and the like. The desired salt may be obtained by ion exchange of whatever counter ion is obtained in the synthesis of the quat. These methods are well known to persons of skill. Although pharmaceutically acceptable counter ions will be preferred for preparing pharmaceutical formulations, other anions are quite acceptable as synthetic intermediates. Thus X may be pharmaceutically undesirable anions, such as iodide, oxalate, trifluoromethanesulfonate and the like, when such salts are chemical intermediates. When the compounds of the invention are bisquats, one may employ as counter ions either two monoanionic species (e.g. Cl_2) or a single dianionic species (e.g. fumarate). Similarly, one could employ oligoanionic species and make salts having appropriate ratios of quat to counterion, such as (quat)3 citrates. These would be obvious equivalents. In some embodiments, the nitrogen of the morphinan or benzomorphan core structure is quaternized. Quaternization can be achieved by methylation of a tertiary nitrogen atom. Although this invention is susceptible to embodiment in many different forms, preferred embodiments of the invention are shown. It should be understood, however, that the present disclosure is to be considered as an exemplification of the principles of this invention and is not intended to limit the invention to the embodiments illustrated.

Abbreviations

[0069] The following abbreviations and terms have the indicated meanings throughout:

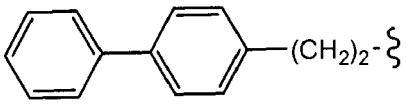
——
------ represents a single or double bond;

Ac = acetyl

BNB = 4-bromomethyl-3-nitrobenzoic acid

Boc = t-butyloxy carbonyl

BPE = 2(4-biphenylyl)ethyl =



Bu = butyl

c- = cyclo

DAMGO = Tyr-ala-Gly-NMePhe-$NHCH_2OH$

DBU = diazabicyclo[5.4.0]undec-7-ene

DCM = dichloromethane = methylene chloride = CH_2Cl_2

DEAD = diethyl azodicarboxylate

DIC = diisopropylcarbodiimide

DIEA = N,N-diisopropylethyl amine

DMAP = 4-N,N-dimethylaminopyridine

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DOR = delta opioid receptor

DPPF = 1,1'-bis(diphenylphosphino)ferrocene

DVB = 1,4-divinylbenzene

EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

Fmoc = 9-fluorenylmethoxycarbonyl

GC = gas chromatography

HATU = O-(7-Azabenzotriazol-l-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HOAc = acetic acid

HOBt = hydroxybenzotriazole

KOR = kappa opioid receptor

Me = methyl

mesyl = methanesulfonyl

MOR = mu opioid receptor

MTBE = methyl t-butyl ether

NMO = N-methylmorpholine oxide

PEG = polyethylene glycol

Ph = phenyl

PhOH = phenol

PfP = pentafluorophenol

PPTS = pyridinium p-toluenesulfonate

PyBroP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate

rt = room temperature

sat'd = saturated

s- = secondary

t- = tertiary

TBDMS = t-butyldimethylsilyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

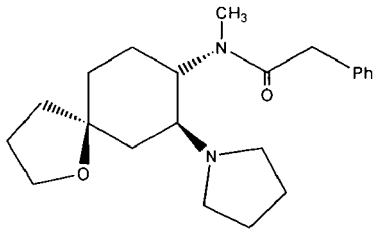
TMOF = trimethyl orthoformate

TMS = trimethylsilyl

tosyl = p-toluenesulfonyl

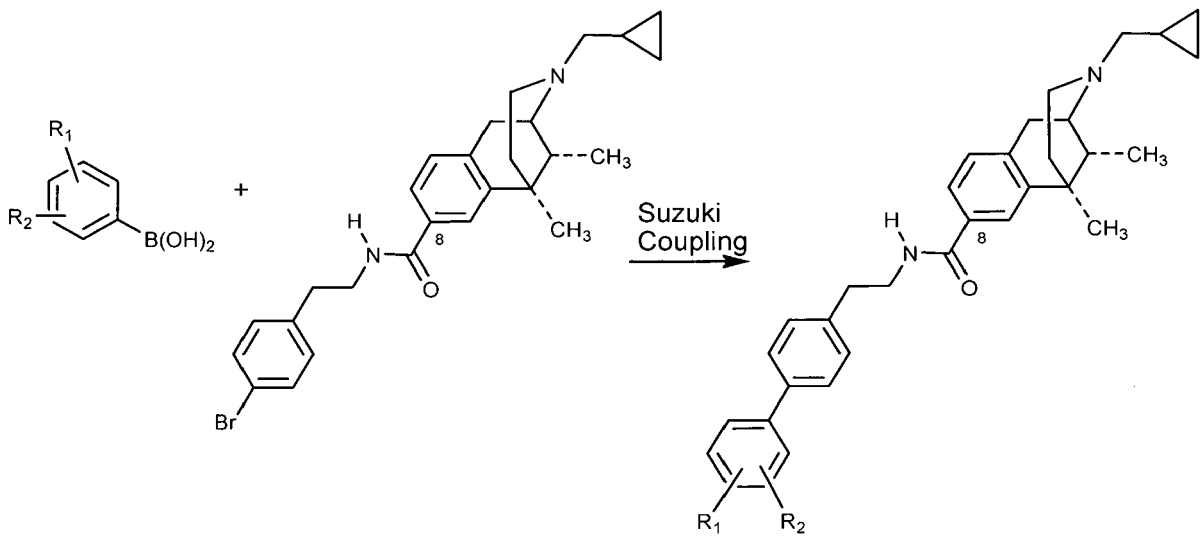
Trt = triphenylmethyl

U69,593 =



[0070] It may happen that residues in the substrate of interest require protection and deprotection during the conversion of the phenol hydroxyl. Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is below, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991].

[0071] The compounds of the invention are synthesized by one of the routes described below: Scheme 1. Synthesis via Suzuki coupling.



[0072] In general, the method of replacing a phenolic -OH with triflate, is described in US patent 6,784,187.

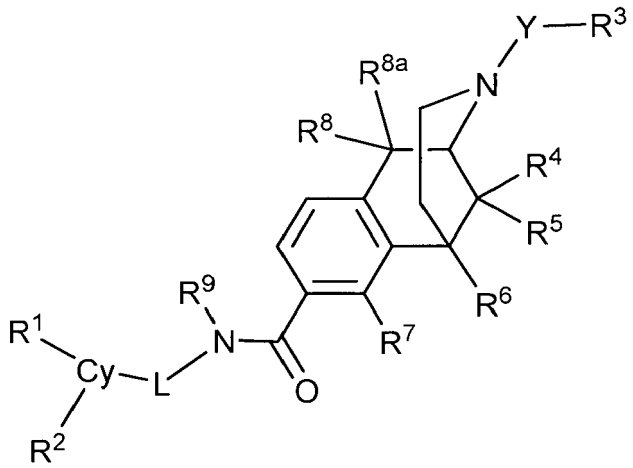
[0073] Proton NMR spectra and in certain cases ^{13}C NMR were obtained on a Varian Unity-300 or 500 NMR spectrometer with tetramethylsilane as an internal reference for samples dissolved in $CDCl_3$. Samples dissolved in CD_3OD and DMSO-d_6 were referenced to the solvent. Proton NMR multiplicity data are denoted by s (singlet), d (doublet), t

(triplet), q (quartet), m (multiplet), dd (doublet of doublets), and br (broad). Coupling constants are in hertz. Direct insertion probe chemical ionization mass spectral data were obtained on a Shimadzu GC-17A GC-MS mass spectrometer. Direct infusion electrospray ionization (in positively charged ion mode) mass spectral data were obtained on an Agilent 1100 series LC/MSD system (Germany). Melting points were determined on a Meltemp capillary melting point apparatus and were uncorrected. Infrared spectral data were obtained on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Optical rotation data was obtained from a Perkin-Elmer 241 polarimeter. The assigned structure of all test compounds and intermediates were consistent with the data. Carbon, hydrogen, and nitrogen elemental analyses for all novel targets were performed by Quantitative Technologies Inc., Whitehouse, NJ, and were within ± 0.4% of theoretical values except as noted; the presence of water or other solvents was confirmed by proton NMR. Reactions were generally performed in an argon or nitrogen atmosphere. Commercially purchased chemicals were used without purification unless otherwise noted. The following reagents were purchased from Aldrich Chemical Company: N-hydroxysuccinimide, phenethylamine, 3-phenyl-1-propylamine, 4-aminobiphenyl, palladium acetate, 4-phenylbenzylamine and benzyl amine. The following reagent was purchased from Trans World Chemicals: 2-(4-biphenyl ethylamine). The following reagents were purchased from Strem Chemicals, Incorporated: 1,1'-bis(diphenyl-phosphino)ferrocene (dppf) and dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct [$PdCl_2$(dppf)]. Pyridine was distilled from KOH. DMF and DMSO were distilled over CaH_2 under reduced pressure. Silica gel (Bodman Industries, ICN SiliTech 2-63 D 60A, 230-400 Mesh) was used for all flash chromatography. Amines were purchased from Aldrich Chemical Company and used as received unless otherwise indicated. Toluene and Et_2O were distilled from sodium metal. THF was distilled from sodium/benzophenone ketyl. Pyridine was distilled from KOH. Methylene chloride was distilled from CaH2. DMF and DMSO were distilled from CaH_2 under reduced pressure. Methanol was dried over 3± molecular sieves prior to use. Silica gel (Bodman Industries, ICN SiliTech 2-63 D 60A, 230-400 Mesh) was used for flash column chromatography.

[0074] In general, the chemistry described above works in the presence of the variety of functional groups found on known core structures. The exceptions would be morphine and congeners having a free 6-OH, which can be protected by a TBDPS (t-butyldiphenylsilyl) group [see Wentland et al., "Selective Protection and Functionalization of Morphine...", J. Med. Chem. 43, 3558-3565 (2000)].

Claims

1. A compound of formula I:



wherein

R^1 is selected from -OH, -CN, -CHO, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONH_2$, $-CSNH_2$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$ and $-C(=NR^{10})R^{11}$;

R^2 is selected from hydrogen, halogen, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$, $-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$. $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $-C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, heterocyclyl, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, and (C_1-C_6)alkylthio; or,

R^1 and R^2 together with the atoms to which they are attached, and a fragment selected from $-OCH_2O$-, or

$-OCH_2CH_2O-$, form a ring,
R^3 is chosen from hydrogen, C_1-C_8 hydrocarbon, heterocyclyl, aryl and hydroxyalkyl;
R^4 is chosen from hydrogen, hydroxyl, amino, C_1-C_4 alkoxy, C_1-C_{20} alkyl and C_1-C_{20} alkyl substituted with hydroxyl or carbonyl;
R^5 is C_1-C_6 alkyl;
R^6 is C_1-C_6 alkyl;
R^7 is chosen from hydrogen, $NR^{10}R^{11}$ and $-OR^{10}$; or
together R^4, R^5, R^6 and R^7 may form from one, two, three, or four rings, said rings having optional additional substitution;
R^8 and R^{8a} are both hydrogen or taken together R^8 and R^{8a} are =O;
R^9 is chosen from hydrogen and C_1-C_6 alkyl;

R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, $-NR^{100}R^{101}$ or optionally substituted C_1-C_4 alkoxy, or
R^{10} and R^{11}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;
t is 0, 1, 2, 3, 4, 5, or 6;
R^{100} and R^{101} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, hydroxyl, or optionally substituted C_1-C_4 alkoxy, or
R^{100} and R^{101}, together with the nitrogen atom to which they are attached, form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S;

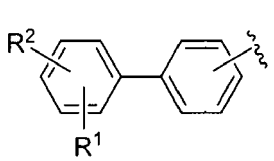
Y is a direct bond or $-(C(R^{10})(R^{11}))_q-$, wherein q is 0, 1, 2, 3, 4 or 5;
L is a direct bond or $-(C(R^{10})(R^{l1}))q-$; and
Cy is Ar^1-B-Ar^2, wherein

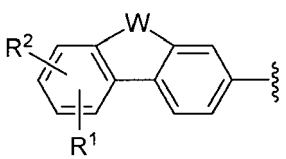
Ar^1 is absent, or an aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ or $-COOR^{10}$;
B is a direct bond, -O-, $-NR^{10}$, $-SO_2$, or $-(C(R^{10})(R^{11})s-$, wherein s is 0, 1, 2, 3, 4 or 5; and
Ar^2 is aryl or heteroaryl radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by halogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ or $-COOR^{10}$.

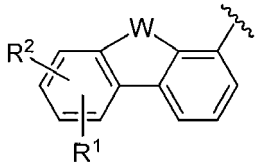
2. A compound according to claim 1, wherein said R^{10} and R^{11} are hydrogen, and/or wherein R_1 is -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, or $-CON(H)CH_2CH_2COOH$; or R^1 and R^2 together with the atoms to which they are attached forms a $-OCH_2O$-fused ring, and/or
wherein R^2 is H.

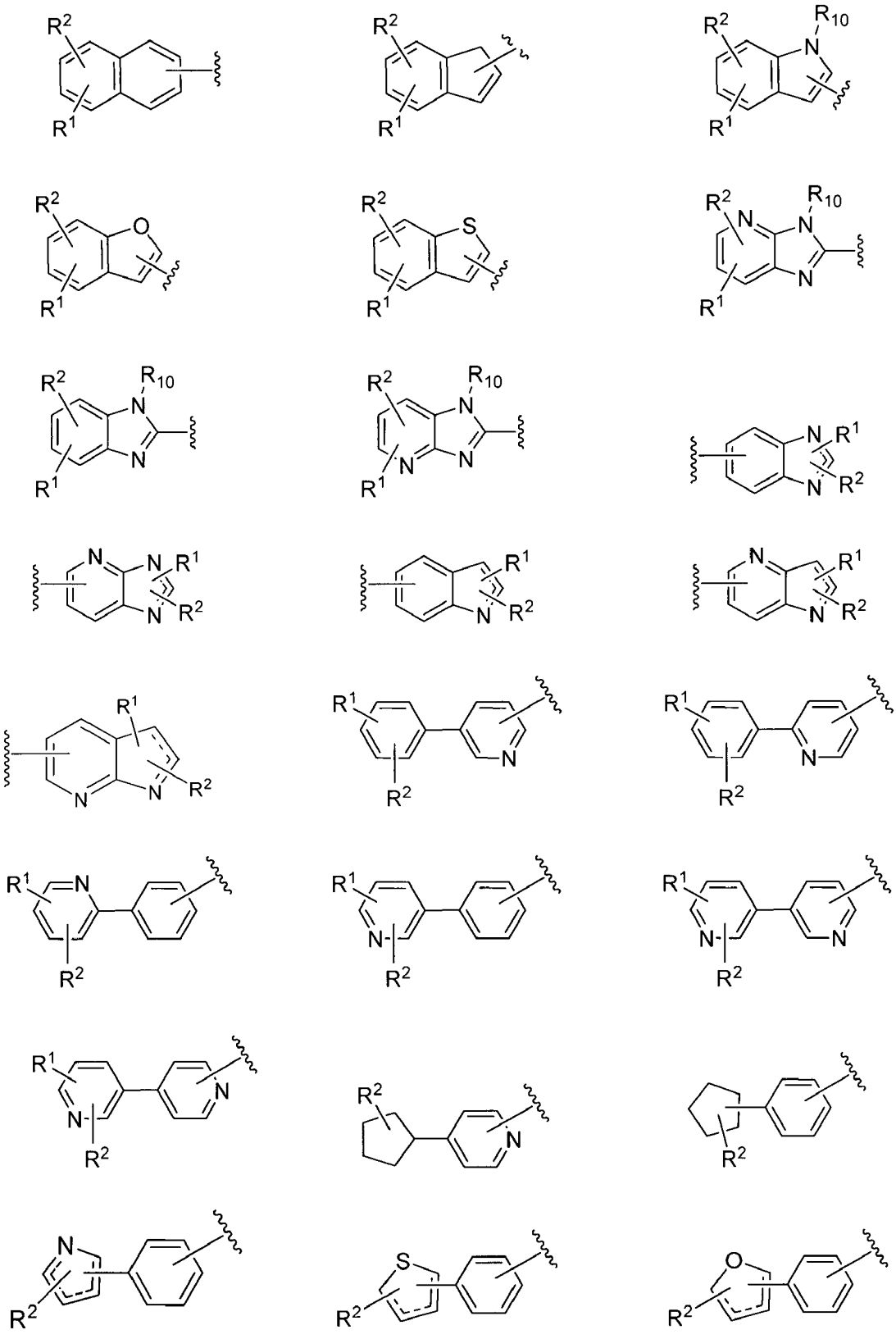
3. A compound according to claim 1, wherein R^1 is selected from -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, or $-CON(H)CH_2CH_2COOH$; or R^1 and R^2 together with the atoms to which they are attached forms a $-OCH_2O$-fused ring, and/or
wherein R^2 is H.

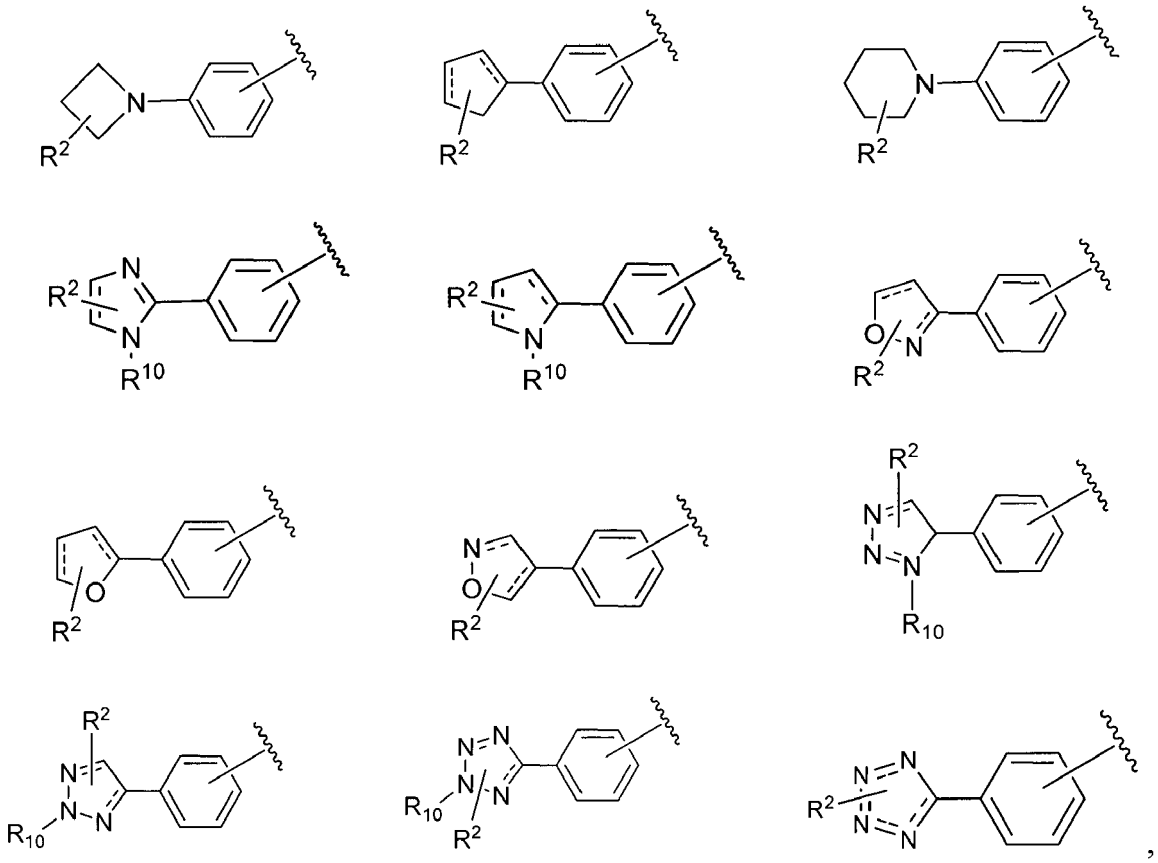
4. A compound of claim 1 wherein Cy is selected from:





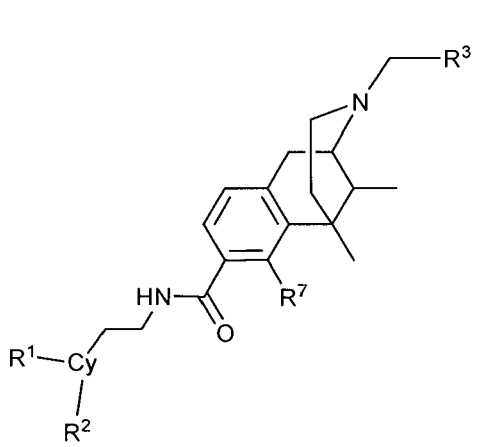




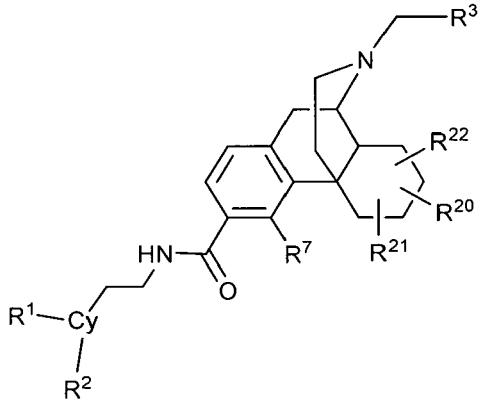


wherein W is selected from $[C(R^9)_2]_n$, CR^8R^{8a}, O, NR^9, S and $CR^9{=}CR^9$; and n is 1, 2, 3, 4 or 5.

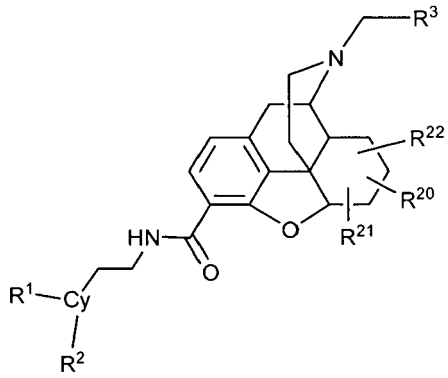
5. A compound of claim 1 of formula III-VI:



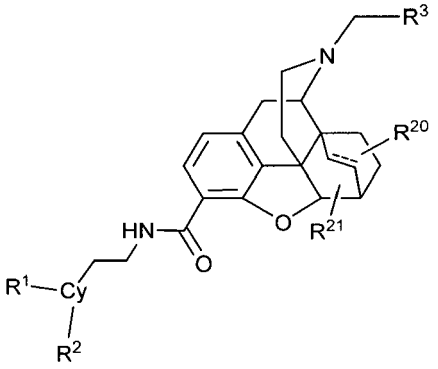
Formula III



Formula IV



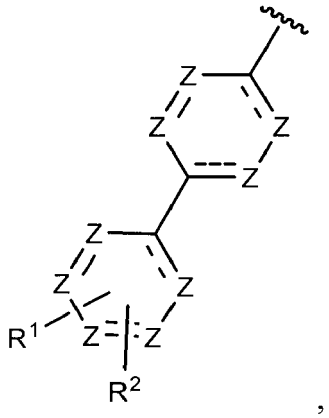
Formula V



Formula VI,

wherein, R^{20}, R^{21} and R^{22} are each chosen from hydrogen, hydroxyl, amino, C_1-C_4 alkoxy, C_1-C_{20} alkyl and C_1-C_{20} alkyl substituted with hydroxyl or carbonyl; or together, R^{20} , and R^{21} with the carbon to which they are attached, form -CO, or -CS; or together, R^{20}, and R^{21} with the carbon(s) to which they are attached, form a ring.

6. A compound according to claim 5, wherein Cy-R^1R^2 is of formula:

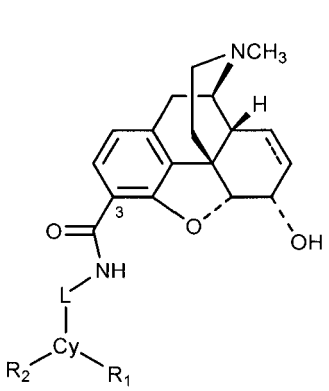
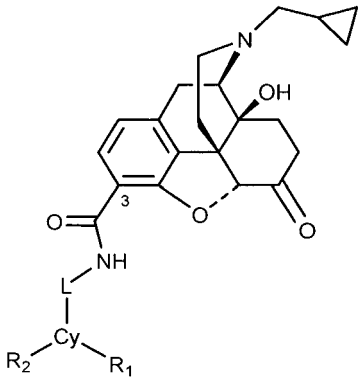
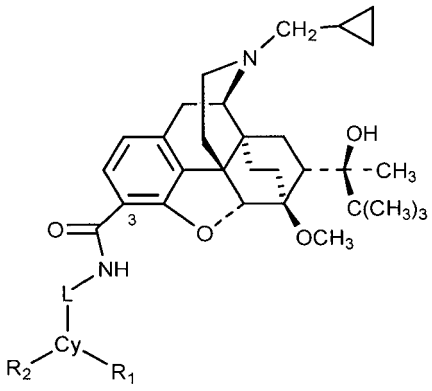
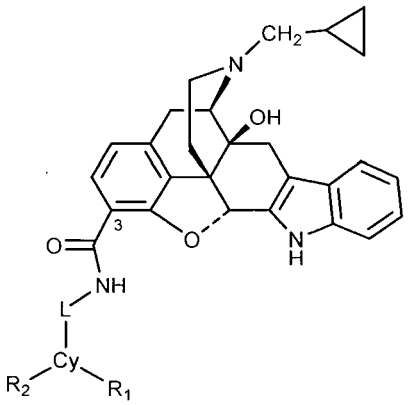
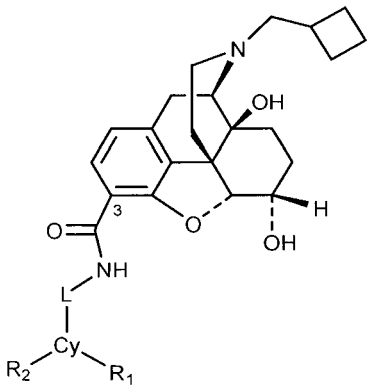
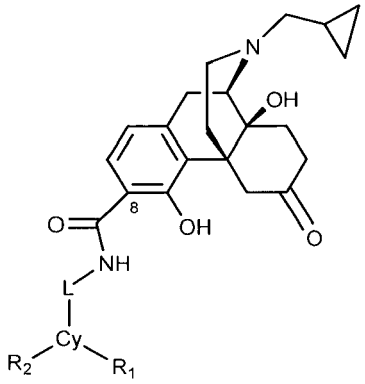
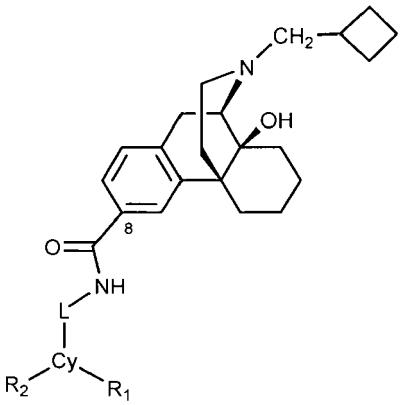
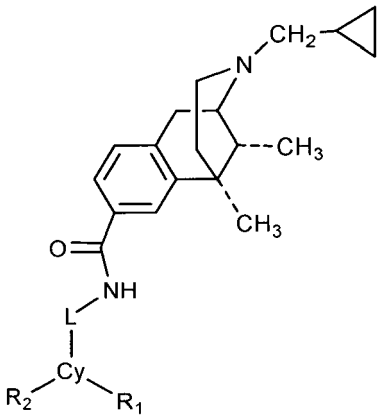
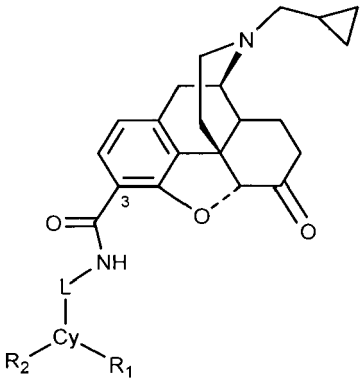
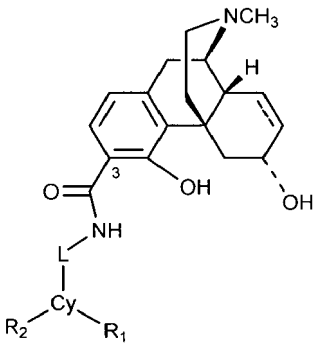


,

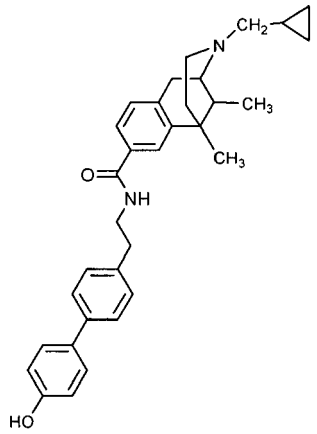
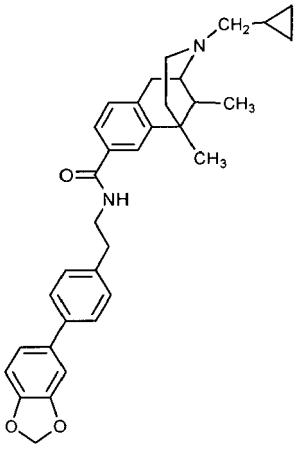
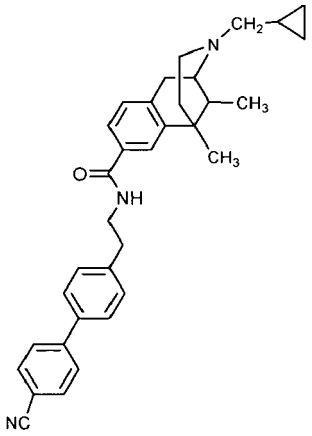
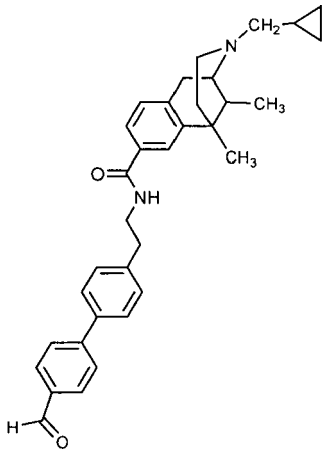
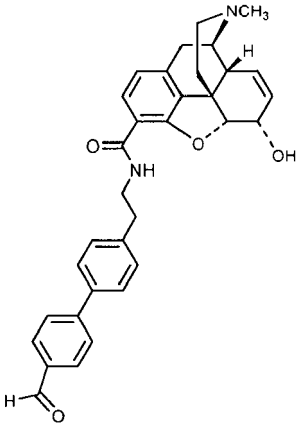
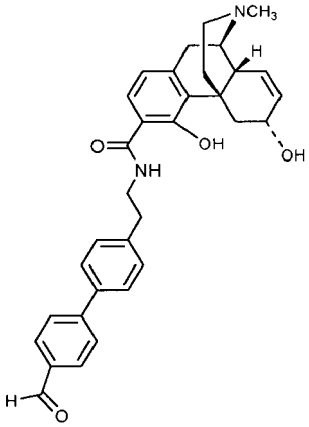
wherein at the points of attachment of R^1 and R^2, Z will be CR^1 and CR^2, respectively.

7. A compound according to claim 6, wherein R^1 is in the para position relative to B and R^2 is hydrogen or methyl; or R^1 and R^2 together with the atoms to which they are attached, and a fragment selected from -OCH_2O- or -OCH_2CH_2O-, form a ring.

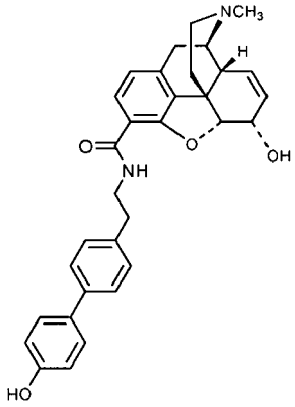
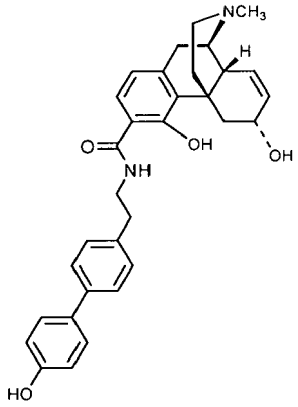
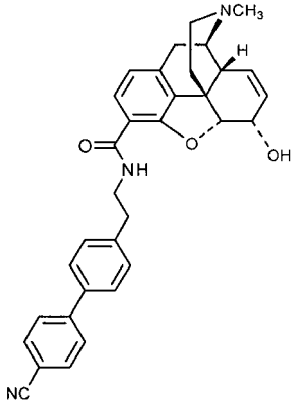
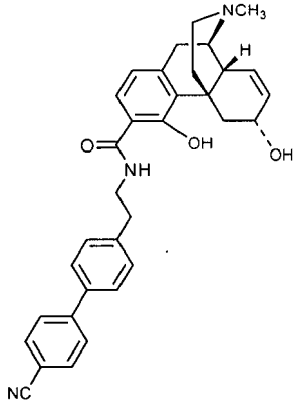
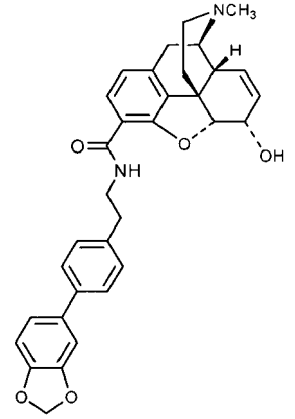
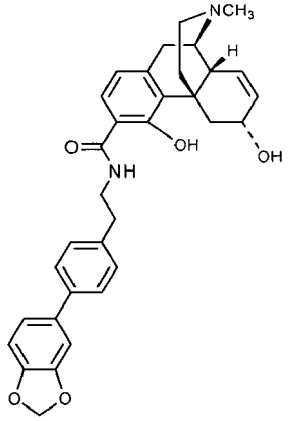
8. A compound according to claim 1 of formula:

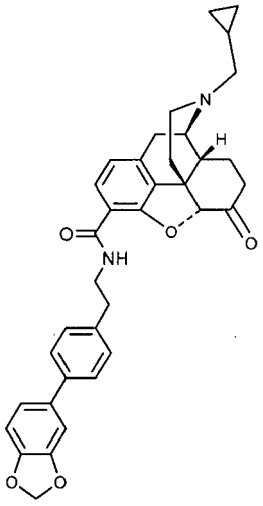
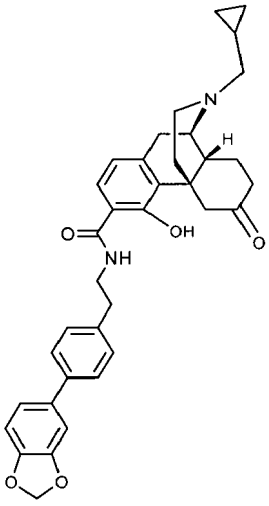
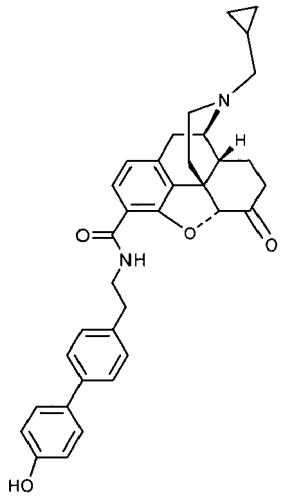
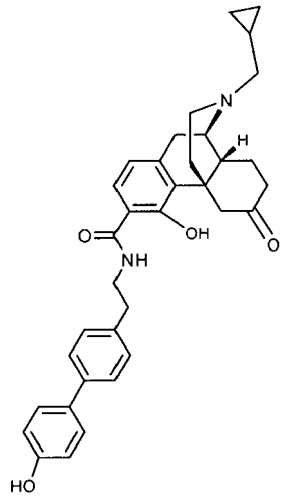
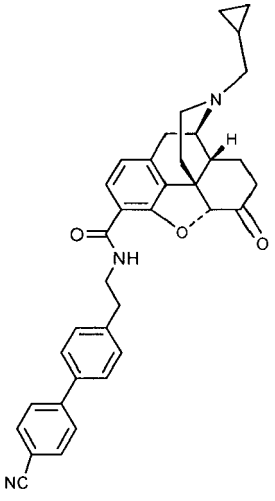
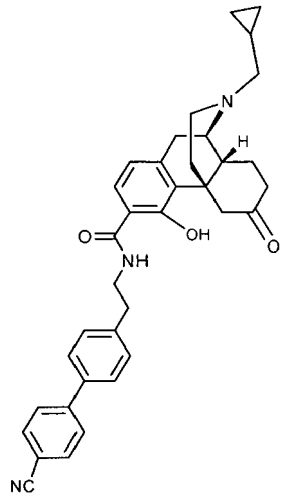
9. A compound according to claim 1 selected from Table 1:

No	Structure	No	Structure
1		8	
9		10	
11		12	

(continued)

No	Structure	No	Structure
13		14	
15		16	
17		18	

(continued)

No	Structure	No	Structure
19		20	
21		22	
23		24	

(continued)

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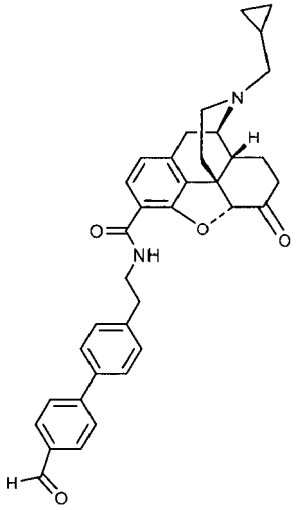
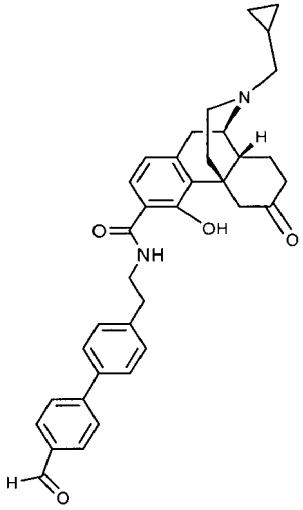
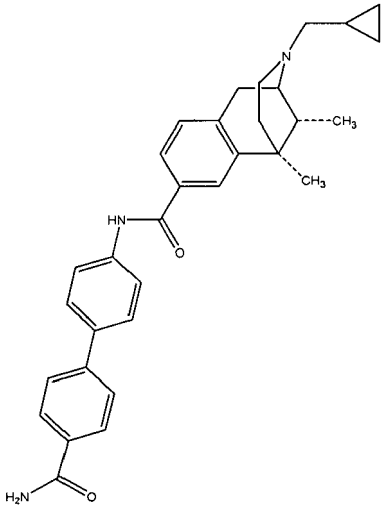
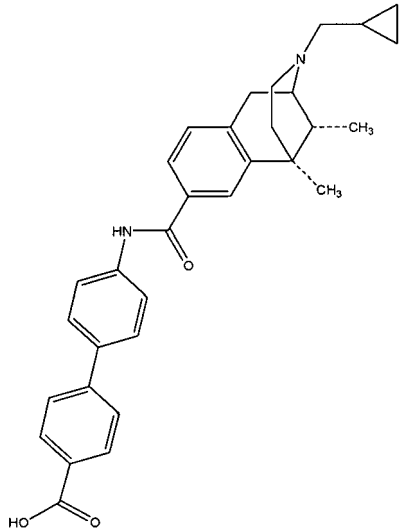
25		26	
31		32	

(continued)

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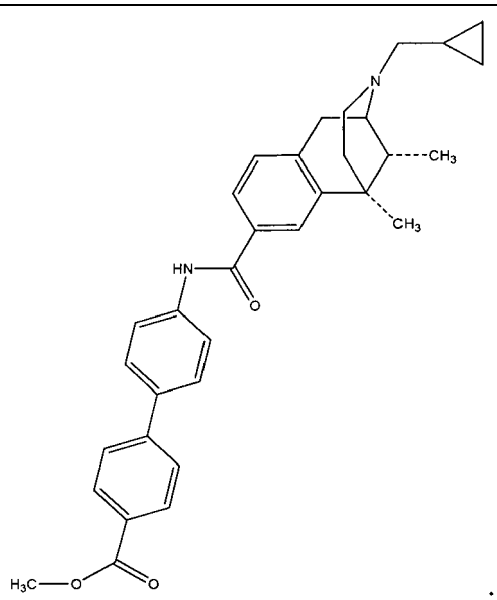
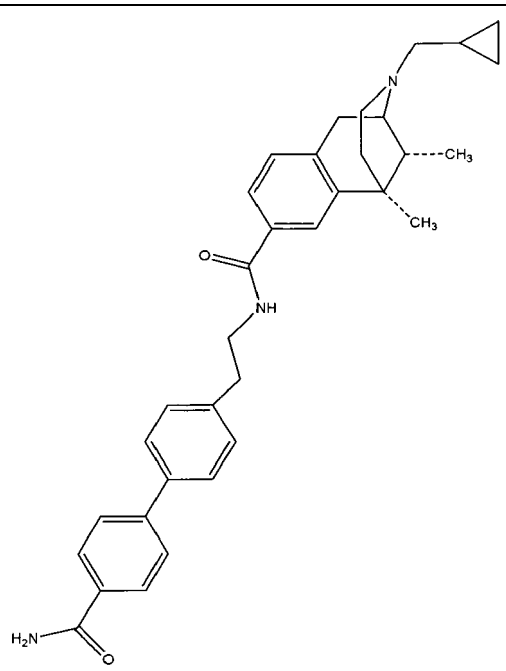
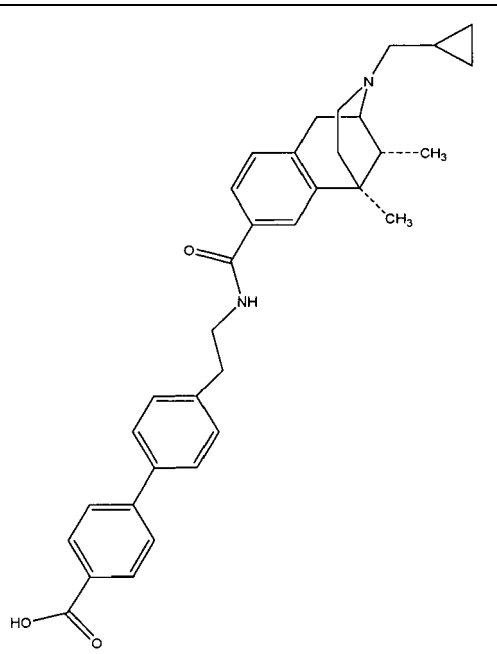
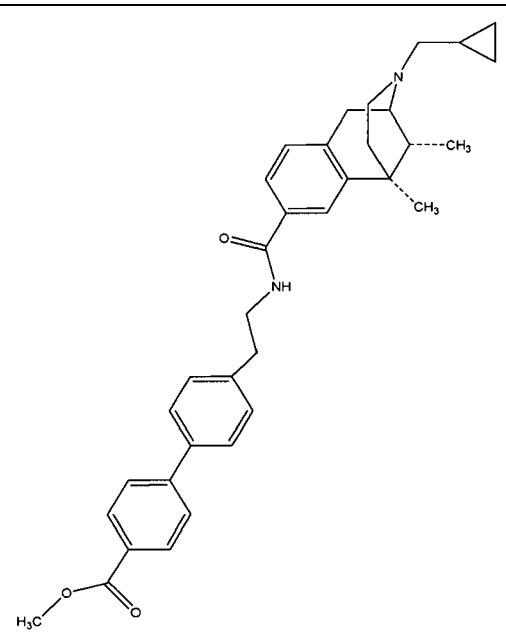
33		34	
35		36	

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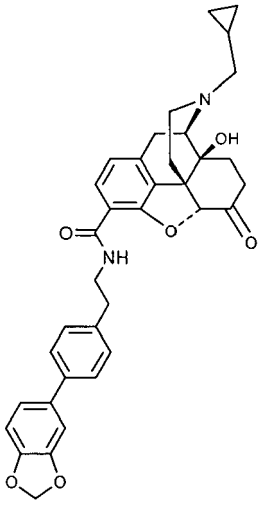
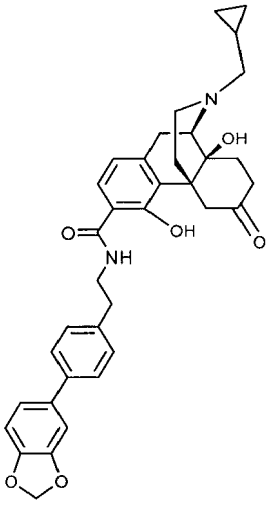
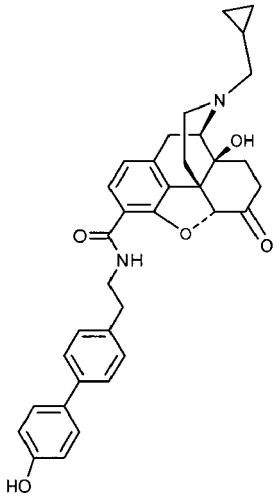
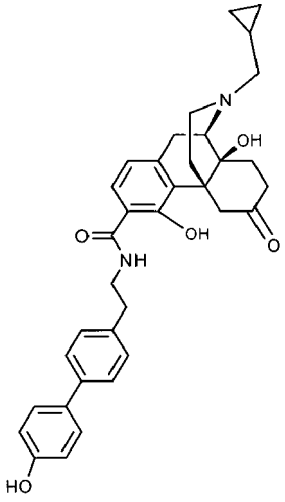
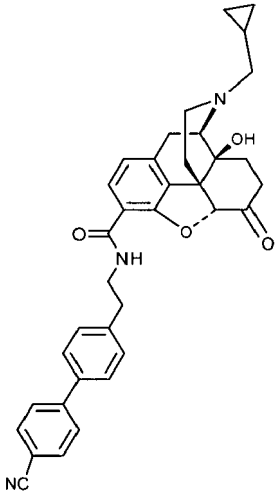
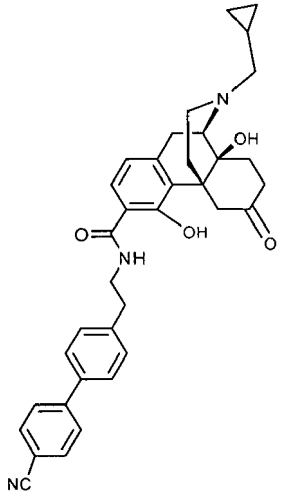
37		38	
39		40	
41		42	

(continued)

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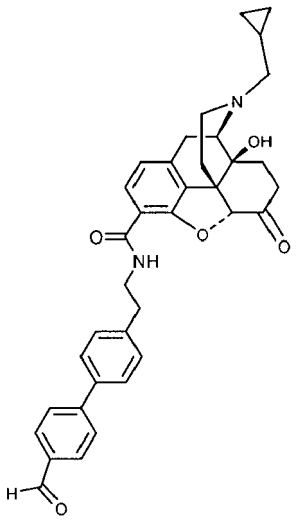
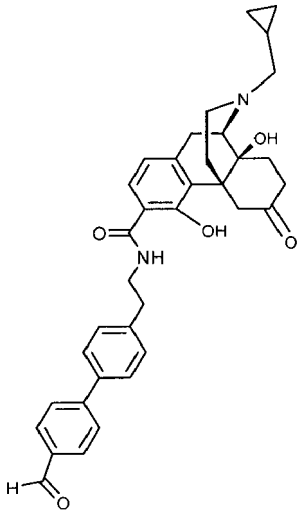
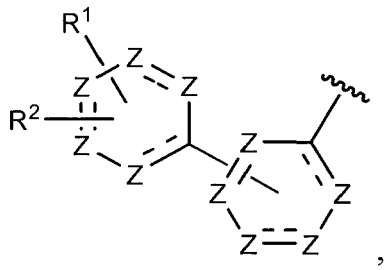
43		44	

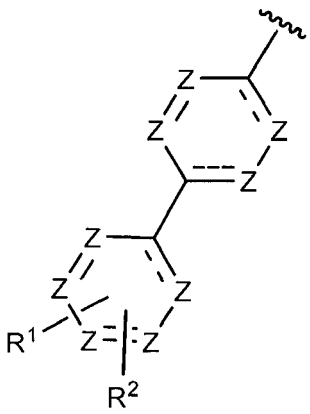
10. A compound according to claim 1 wherein Cy-R^1R^2 is of formula



wherein Z is CR^{10} or N, with the provisos that,

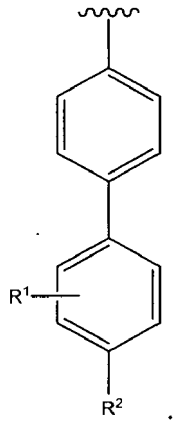
a) at the point of attachment of the distal ring to the proximal ring, Z must be C, and
b) at the points of attachment of R^1 and R^2, Z will be CR^1 and CR^2, respectively.

11. A compound according to claim 10 of formula wherein Cy-R^1R^2 is of formula:



wherein one of R^1 and R^2 is preferably in the para position relative to B and the other of R^1 and R^2 is hydrogen.

12. A compound according to claim 1, wherein Ar^2 is phenyl and one of R^1 or R^2 is in the para position relative to B, wherein Cy-R^1R^2 is preferably of formula:



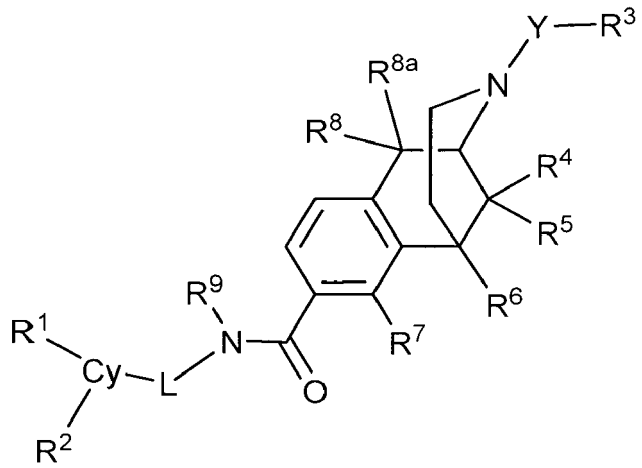
13. A pharmaceutical formulation comprising a compound according to any one of claims 1-12 and a pharmaceutically acceptable carrier.

14. A composition comprising an effective amount of a compound according to any one of claims 1-12 for use in a method of preventing or treating a condition or disease associated with binding opioid receptors in a patient in need thereof,
wherein said disease or condition is preferably chosen from the group consisting of pain, pruritis, diarrhea, irritable bowel syndrome, gastrointestinal motility disorder, obesity, respiratory depression, convulsions, coughing, hyperalgesia, inflammation, osteoarthritis and drug addiction.

15. A composition for use according to claim 14, wherein said drug addiction is selected from heroin, cocaine, nicotine, amphetamine and alcohol addiction, or
wherein the condition is pain and the composition further comprises an effective amount of an opioid, or
wherein the condition is osteoarthritis and the composition further comprises an effective amount of an opioid.

Patentansprüche

1. Verbindung der Formel I:



wobei

R^1 ausgewählt ist aus -OH, -CN, -CHO, -COR^{10}, -$COOR^{10}$, -SO_2R^{10}, -$CONH_2$, -$CSNH_2$, -$CONR^{10}((C(R^{12})(R^{13})_tCONR^{10}R^{11}$, -$CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, -$C(=S)R^{10}$ und -$C(=NR^{10})R^{11}$;

R^2 ausgewählt ist aus Wasserstoff, Halogen, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$, $-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $-C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, Heterocyclyl, optional substituiertem C_1-C_6-Alkyl, optional substituiertem Alkenyl, optional substituiertem Alkynyl, optional substituiertem Aryl, Halogen-C_1-C_6-Alkyl, Halogen-C_1-C_6-Alkoxy, und C_1-C_6-Alkylthio; oder,
R^1 und R^2 zusammen mit den Atomen, an die sie gebunden sind, und einem Fragment, ausgewählt aus $-OCH_2O-$ oder $-OCH_2CH_2O-$, einen Ring bilden,
R^3 ausgewählt ist aus Wasserstoff, C_1-C_8-Kohlenwasserstoff, Heterocyclyl, Aryl und Hydroxyalkyl;
R^4 ausgewählt ist aus Wasserstoff, Hydroxyl, Amino, C_1-C_4-Alkoxy, C_1-C_{20}-Alkyl und C_1-C_{20}-Alkyl substituiert mit Hydroxyl oder Carbonyl;
R^5 C_1-C_6 Alkyl ist;
R^6 C_1-C_6 Alkyl ist;
R^7 ausgewählt ist aus Wasserstoff, $NR^{10}R^{11}$ und $-OR^{10}$; oder

R^4, R^5, R^6 und R^7 können zusammen einen, zwei, drei oder vier Ringe bilden, wobei die genannten Ringe optional zusätzliche Substitution aufweisen;

R^8 und R^{8a} beide Wasserstoff sind oder R^8 und R^{8a} sind zusammengenommen =O;
R^9 ausgewählt ist aus Wasserstoff und C_1-C_6-Alkyl;

R^{10}, R^{11}, R^{12} und R^{13} jeweils unabhängig voneinander Wasserstoff, optional substituiertes C_1-C_6-Alkyl, optional substituiertes Alkenyl, optional substituiertes Alkynyl, optional substituiertes Aryl, Hydroxyl, $-NR^{100}R^{101}$ oder optional substituiertes C_1-C_4-Alkoxy sind, oder
R^{10} und R^{11} bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen optional substituierten fusionierten carbocyclischen oder heterocyclischen Ring mit 5 bis 7 Ringgliedern, von denen bis zu 3 Heteroatome, ausgewählt aus N, O und S, sein können;
t 0, 1, 2, 3, 4, 5, oder 6 ist;
R^{100} und R^{101} jeweils unabhängig voneinander Wasserstoff, optional substituiertes C_1-C_6-Alkyl, optional substituiertes Alkenyl, optional substituiertes Alkynyl, optional substituiertes Aryl, Hydroxyl, oder optional substituiertes C_1-C_4-Alkoxy sind, oder
R^{100} und R^{101} bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen optional substituierten fusionierten carbocyclischen oder heterocyclischen Ring mit 5 bis 7 Ringgliedern, von denen bis zu 3 Heteroatome, ausgewählt aus N, O und S, sein können;

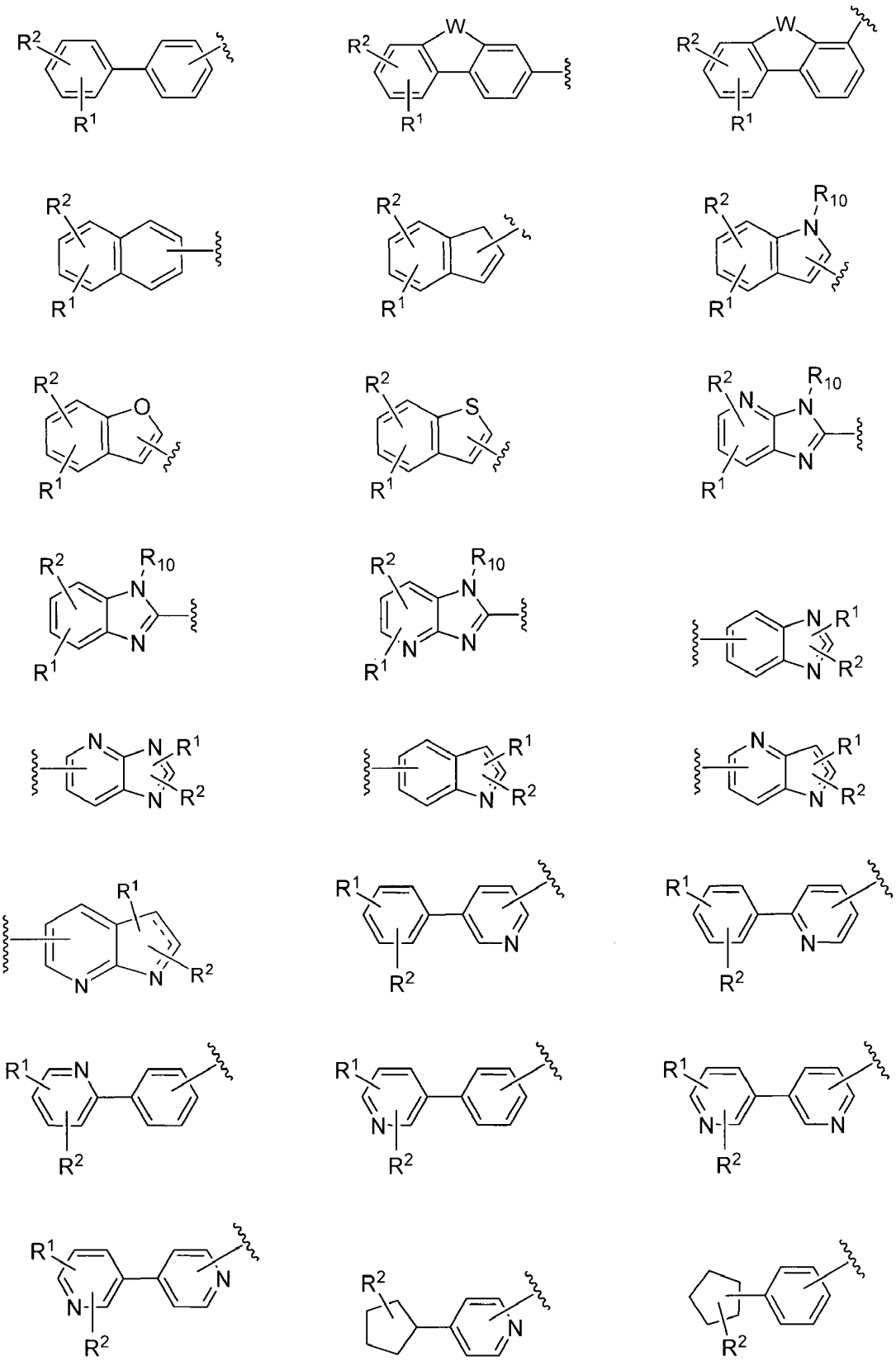
Y eine direkte Bindung oder $-(C(R^{10})(R^{11}))_q-$ ist, wobei q 0, 1, 2, 3, 4 oder 5 ist;
L eine direkte Bindung oder $-(C(R^{10})(R^{11}))_q-$ ist; und
Cy Ar^1-B-Ar^2 ist, wobei

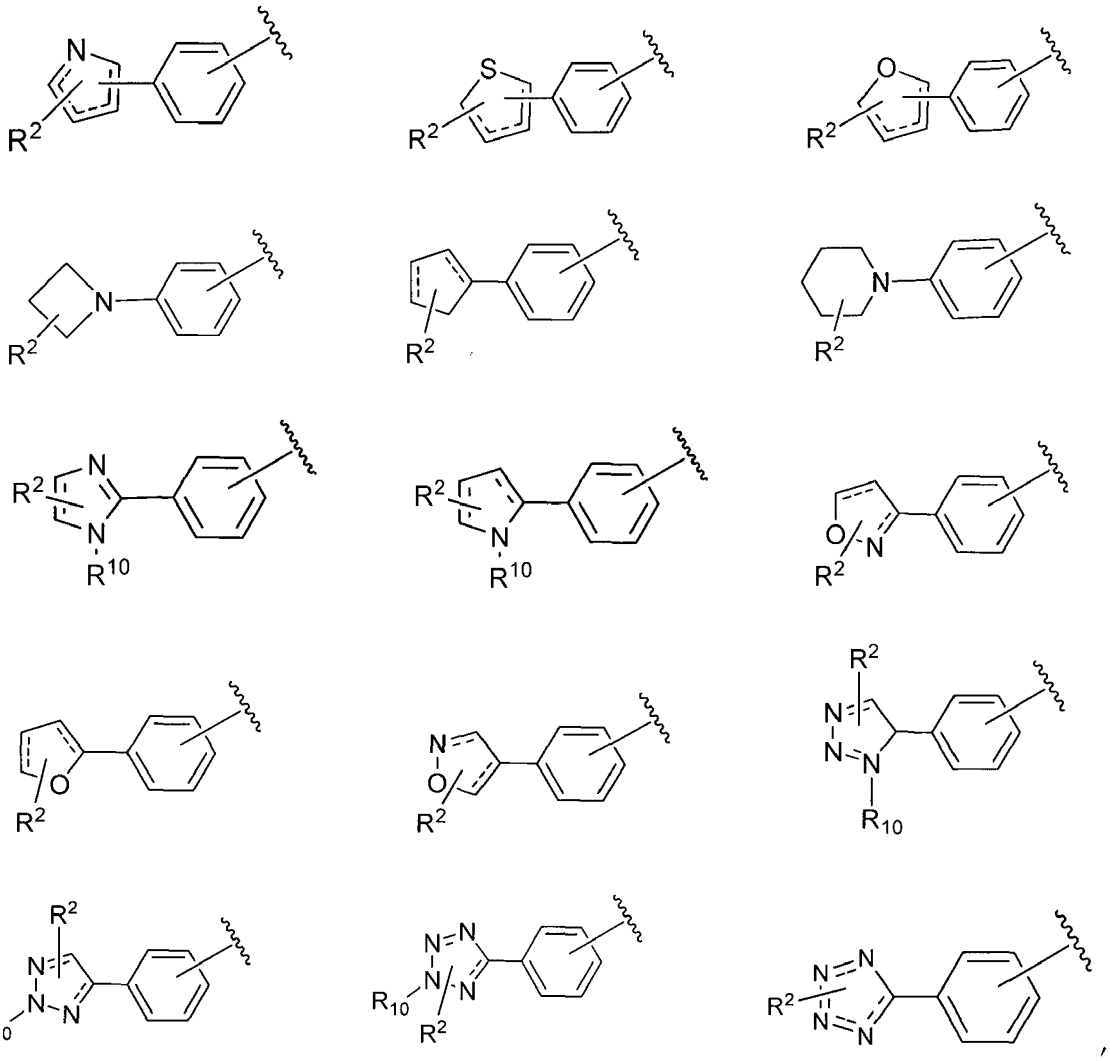
Ar^1 fehlt oder ein Aryl oder Heteroarylradikal mit 1 bis 4 N, O und/oder S Atomen ist, welche unsubstituiert oder mono-, di- oder trisubstituiert mit Halogen, C_1-C_6 Alkyl, Alkenyl, Alkynyl, Cycloalkyl, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ oder $-COOR^{10}$ sein können;
B eine direkte Bindung, -O-, $-NR^{10}$, $-SO_2$, oder $-(C(R^{10})(R^{11})s-$ ist, wobei s 0, 1, 2, 3, 4 oder 5 ist; und
Ar^2 Aryl- oder Heteroarylradikal mit 1 bis 4 N, O und/oder S Atomen ist, welche unsubstituiert oder mono-, di- oder trisubstituiert mit Halogen, C_1-C_6-Alkyl, Alkenyl, Alkynyl, Cycloalkyl, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ oder $-COOR^{10}$ sein können.

2. Verbindung nach Anspruch 1, wobei R^{10} und R^{11} Wasserstoff sind, und/oder wobei R_1 -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, oder $-CON(H)CH_2CH_2COOH$ ist; oder R^1 und R^2 zusammen mit den Atomen, an die sie gebunden sind, einen $-OCH_2O-$fusionierten Ring bilden, und/oder wobei R^2 H ist.

3. Verbindung nach Anspruch 1, wobei R^1 ausgewählt ist aus -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$, oder $-CON(H)CH_2CH_2COOH$; oder R^1 und R^2 zusammen mit den Atomen, an die sie gebunden sind, einen $-OCH_2O-$fusionierten Ring bilden, und/oder wobei R^2 H ist.

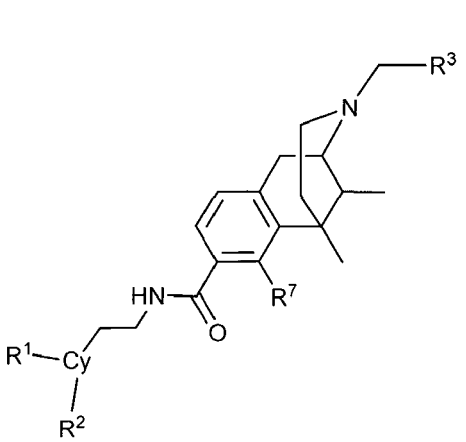
4. Verbindung nach Anspruch 1, wobei Cy ausgewählt ist aus:



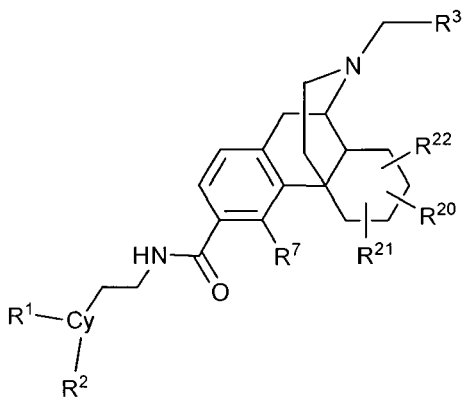


wobei W ausgewählt ist aus $[C(R^9)_2]_n$, CR^8R^{8a}, O, NR^9, S und $CR^9=CR^9$; und n 1, 2, 3, 4 oder 5 ist.

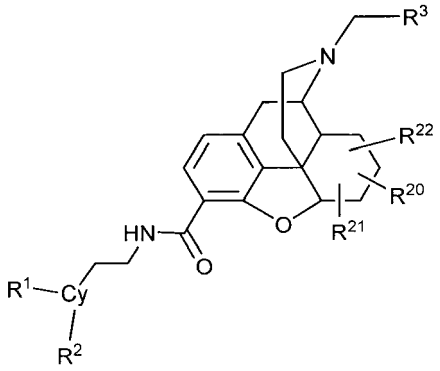
5. Verbindung nach Anspruch 1 der Formel III-VI:



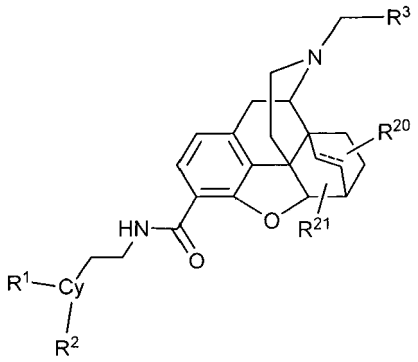
Formel III



Formel IV



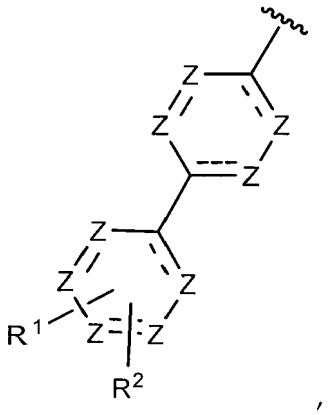
Formel V



Formel VI,

wobei, R^{20}, R^{21} und R^{22} jeweils ausgewählt sind aus Wasserstoff, Hydroxyl, Amino, C_1-C_4 Alkoxy, C_1-C_{20} Alkyl und C_1-C_{20} Alkyl substituiert mit Hydroxyl oder Carbonyl; oder R^{20} und R^{21} bilden zusammen mit dem Kohlenstoff, an den sie gebunden sind, -CO oder -CS; oder R^{20} und R^{21} bilden zusammen mit dem Kohlenstoff/den Kohlenstoffen, an das/die sie gebunden sind, einen Ring.

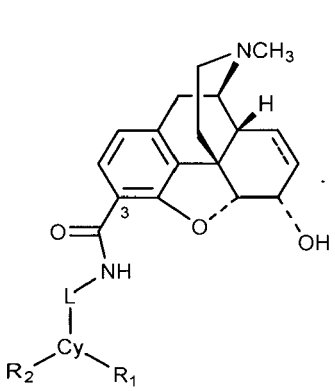
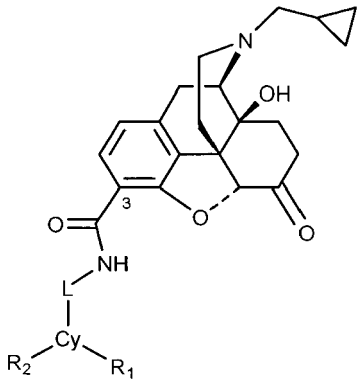
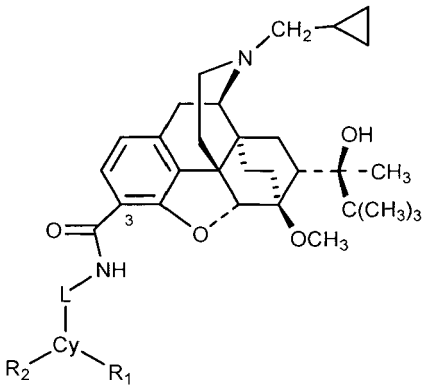
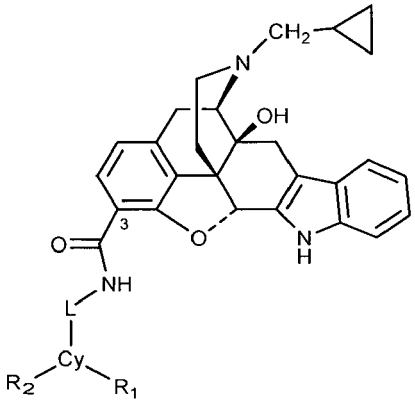
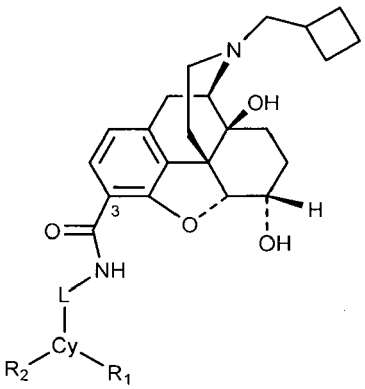
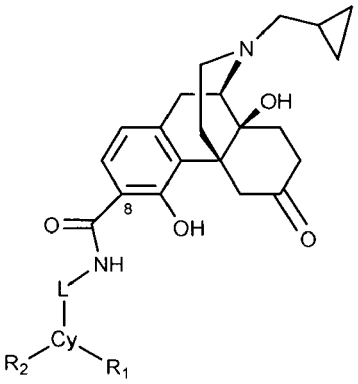
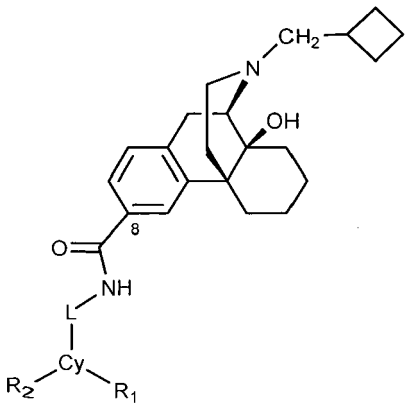
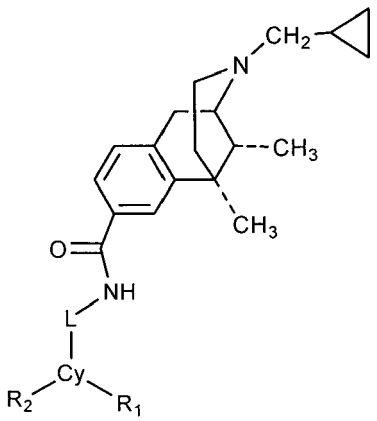
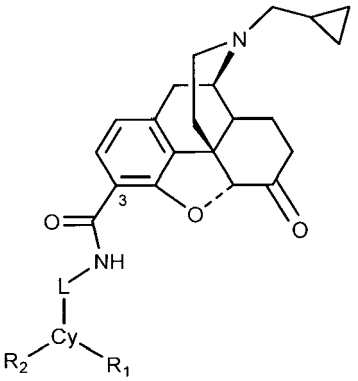
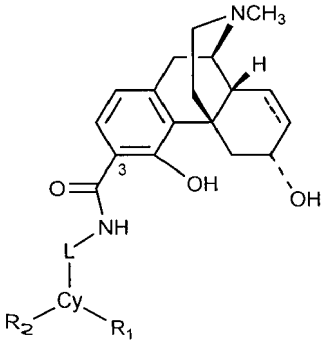
6. Verbindung nach Anspruch 5, wobei Cy-R^1R^2 die Formel aufweist:



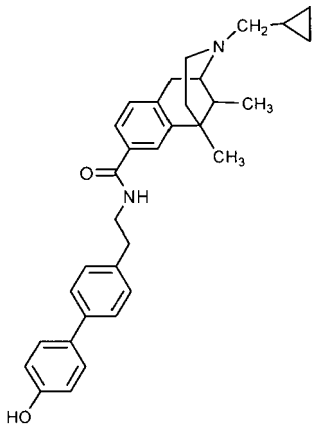
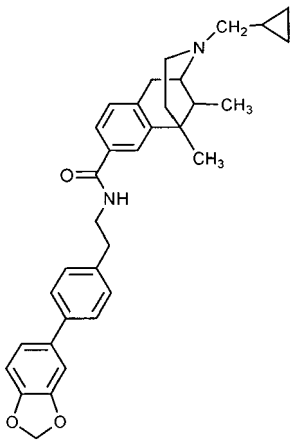
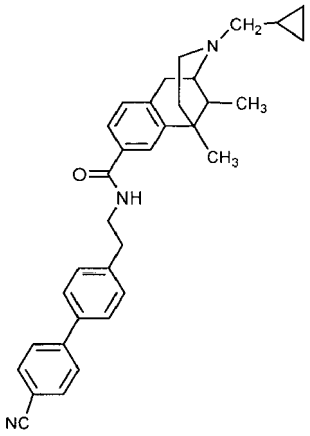
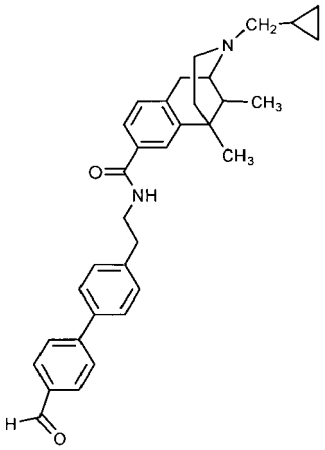
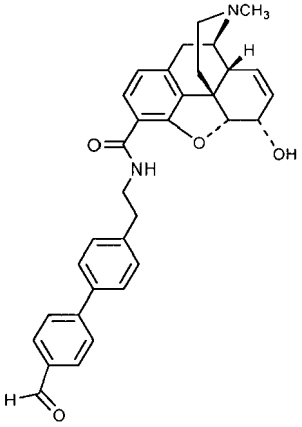
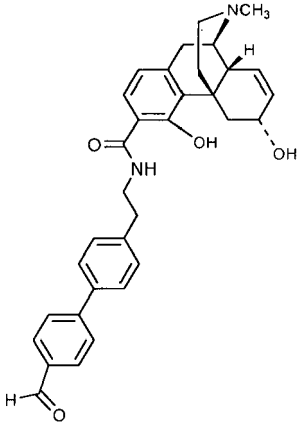
wobei an den Bindungspunkten von R^1 und R^2, Z jeweils CR^1 und CR^2 ist.

7. Verbindung nach Anspruch 6, wobei R^1 in Bezug auf B in der para-Position ist, und R^2 Wasserstoff oder Methyl ist; oder R^1 und R^2 zusammen mit den Atomen, an die sie gebunden sind, und einem Fragment ausgewählt aus -OCH_2O- oder -OCH_2CH_2O-, einen Ring bilden.

8. Verbindung nach Anspruch 1 der Formel:

9. Verbindung nach Anspruch 1, ausgewählt aus Tabelle 1:

Nr.	Struktur	Nr.	Struktur
1		8	
9		10	
11		12	

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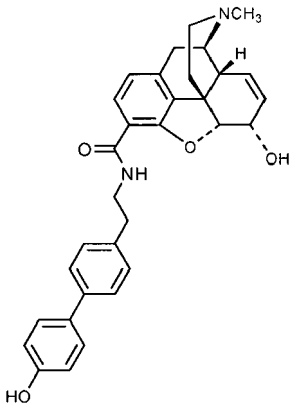
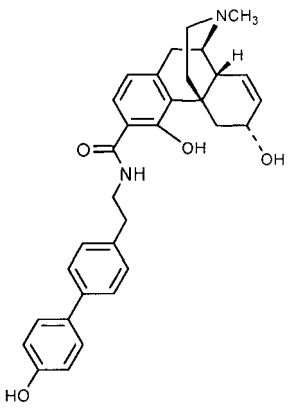
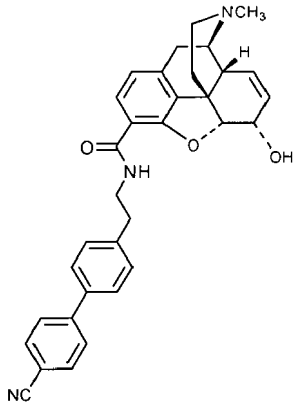
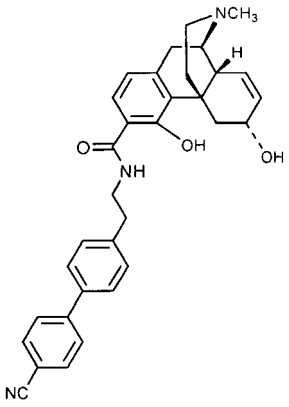
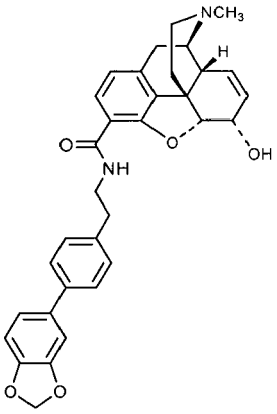
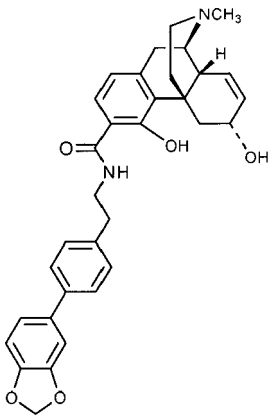
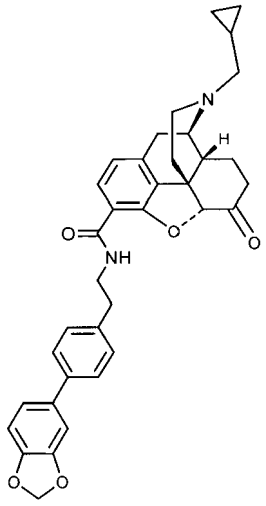
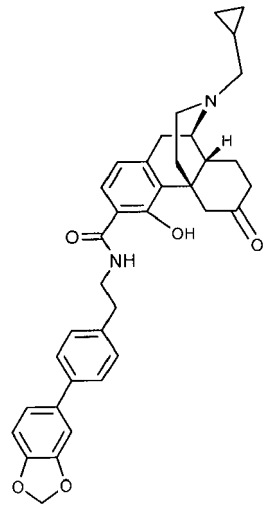
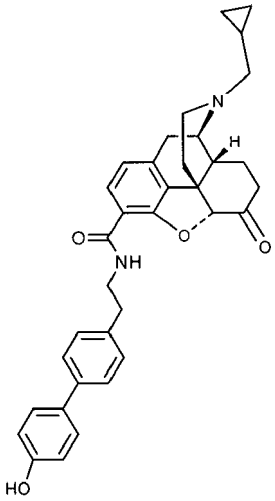
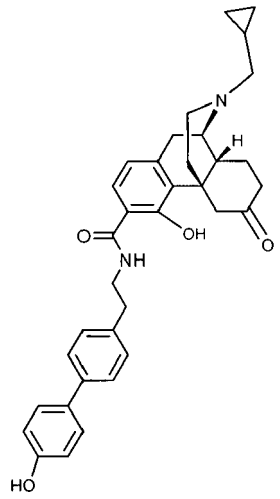
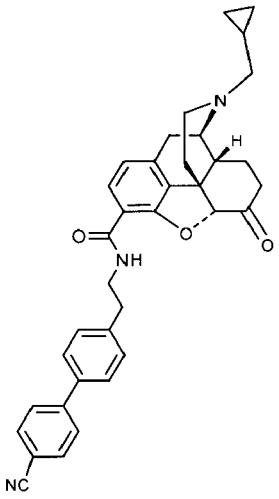
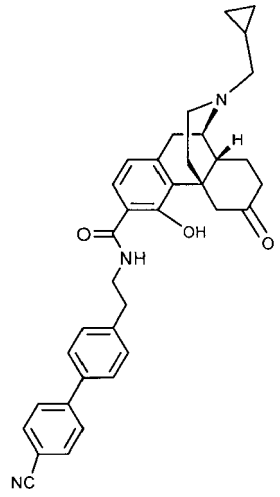
Nr.	Struktur	Nr.	Struktur
13		14	
15		16	
17		18	

(fortgesetzt)

Nr.	Struktur	Nr.	Struktur
19		20	
21		22	
23		24	

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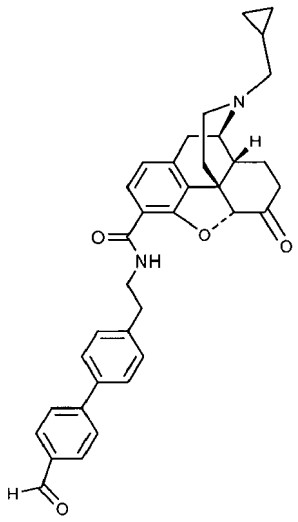
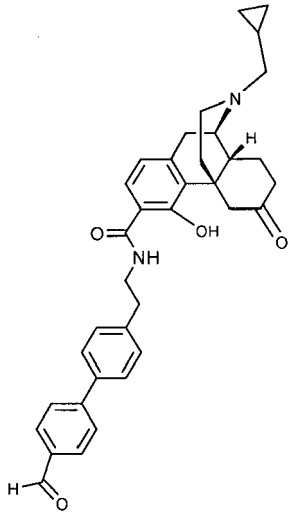
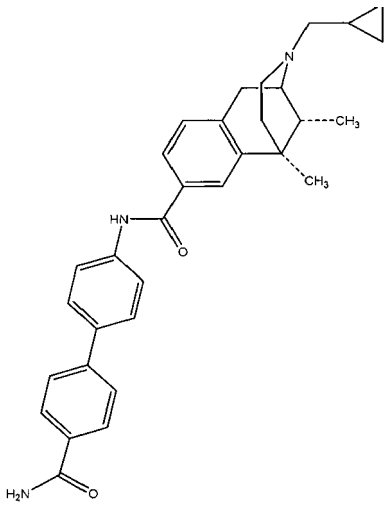
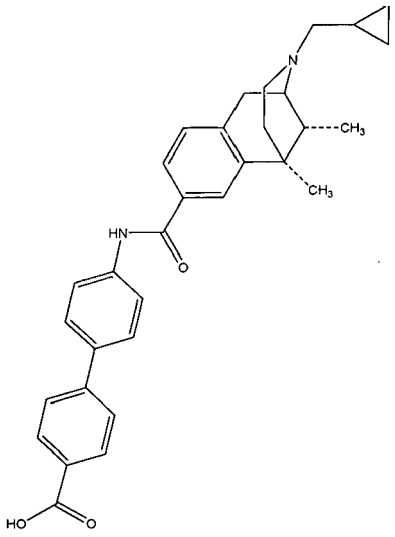
Nr.	Struktur	Nr.	Struktur
25		26	
31		32	

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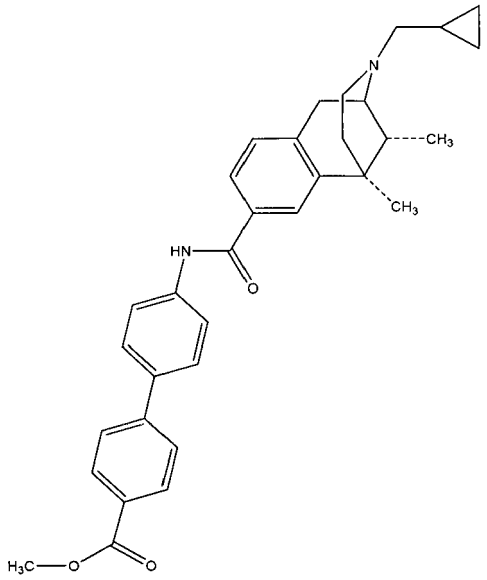
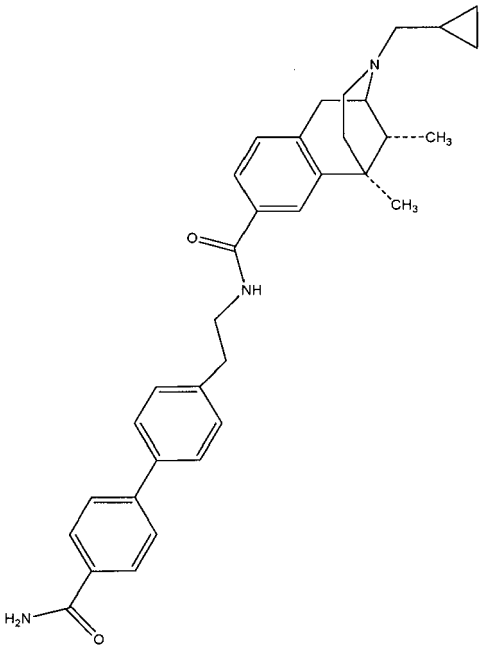
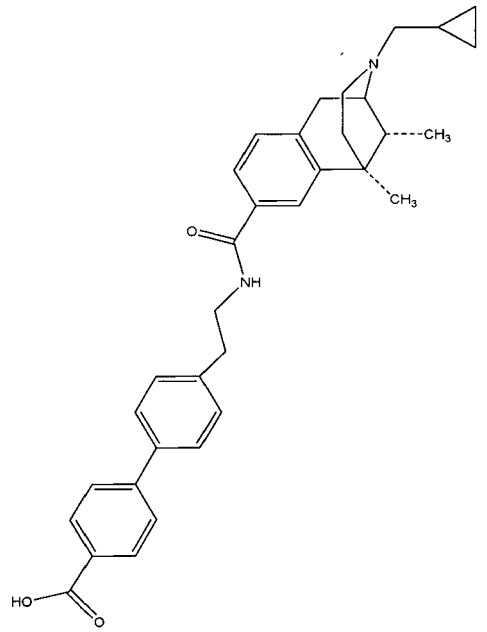
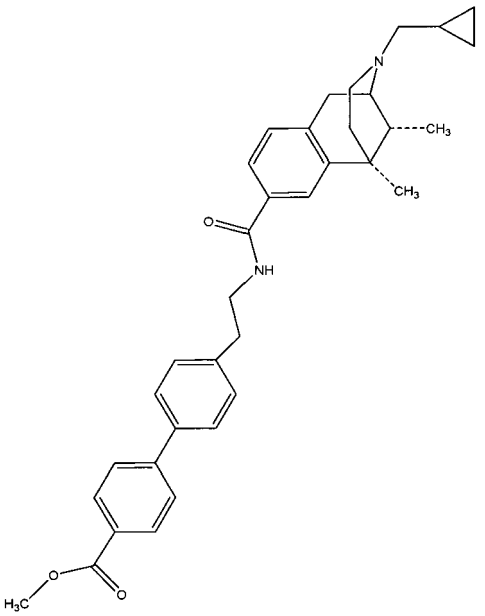
Nr.	Struktur	Nr.	Struktur
33		34	
35		36	

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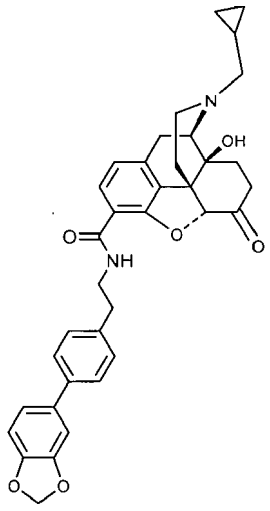
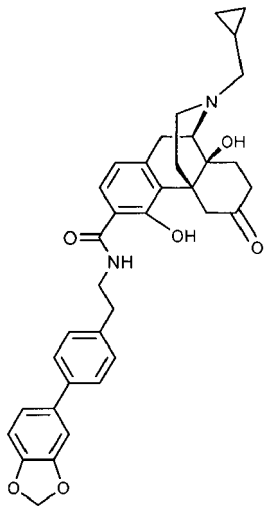
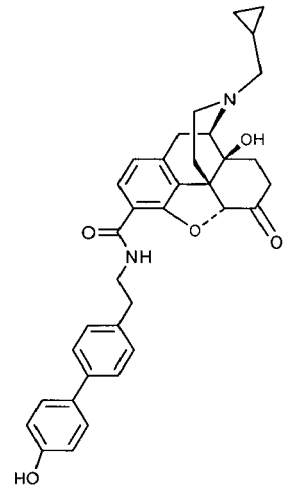
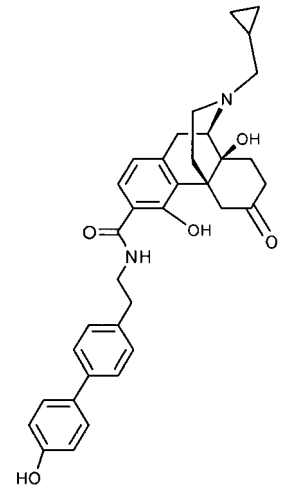
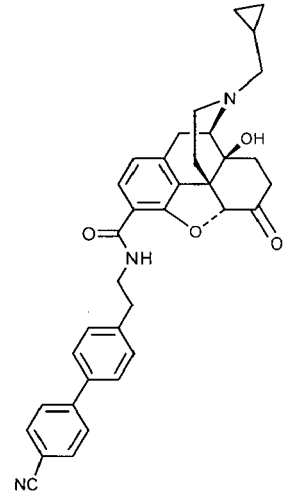
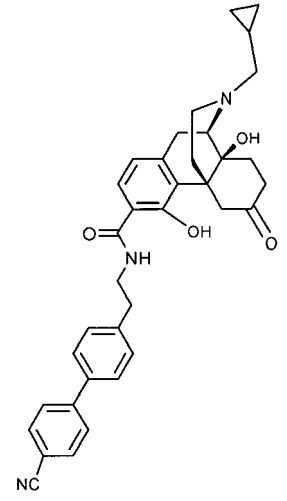
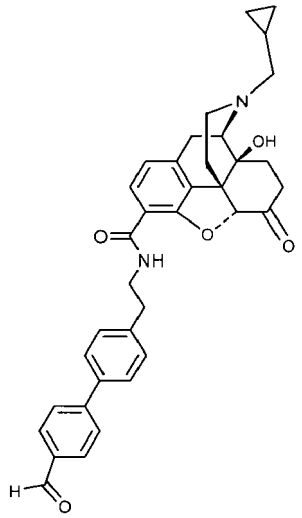
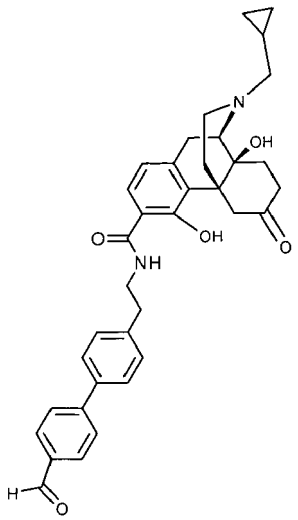
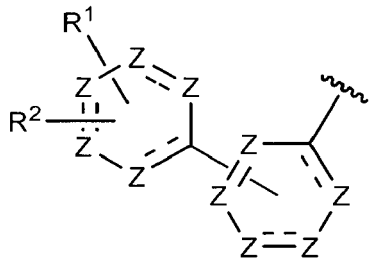
Nr.	Struktur	Nr.	Struktur
37		38	
39		40	
41		42	

(fortgesetzt)

Nr.	Struktur	Nr.	Struktur
43		44	

10. Verbindung nach Anspruch 1, wobei Cy-R^1R^2 die Formel

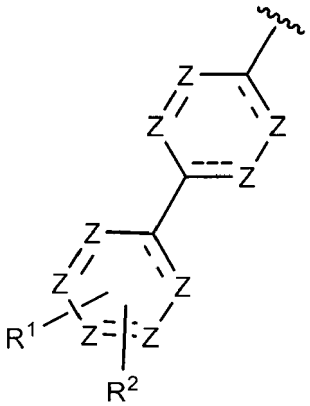


aufweist,

wobei Z, CR^{10} oder N ist, unter den Voraussetzungen, dass

a) am Bindungspunkt des distalen Rings an den proximalen Ring, Z C sein muss, und
b) an den Bindungspunkten von R^1 und R^2, Z jeweils CR^1 bzw. CR^2 ist.

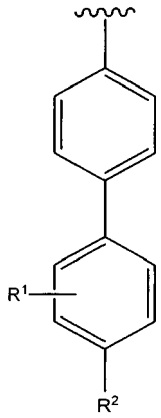
11. Verbindung nach Anspruch 10, wobei Cy-R^1R^2 die Formel:



aufweist,

wobei einer von R^1 und R^2 vorzugsweise in der para-Position in Bezug auf B ist, und der andere von R^1 und R^2 Wasserstoff ist.

12. Verbindung nach Anspruch 1, wobei Ar^2 Phenyl ist, und einer von R^1 oder R^2 in der para-Position in Bezug auf B ist, wobei Cy-R^1R^2 vorzugsweise die Formel:



aufweist.

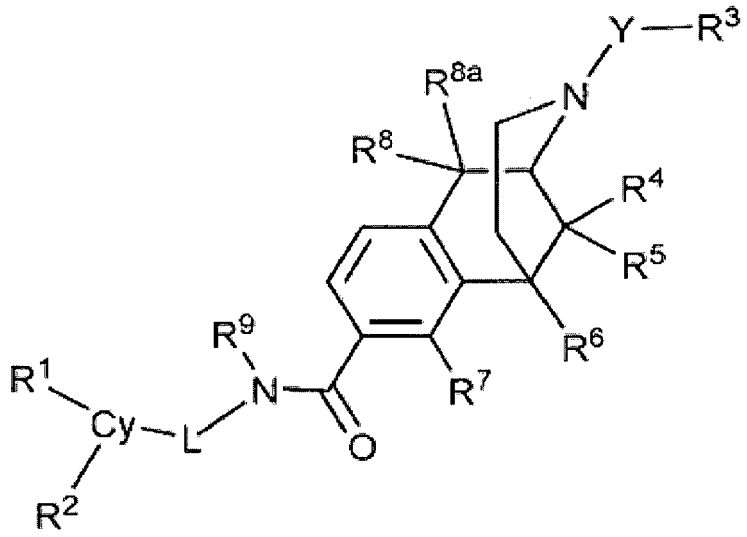
13. Pharmazeutische Formulierung umfassend eine Verbindung nach einem der Ansprüche 1-12 und einen pharmazeutisch akzeptablen Träger.

14. Zusammensetzung umfassend eine wirksame Menge einer Verbindung nach einem der Ansprüche 1-12 zur Verwendung in einem Verfahren zur Prävention oder Behandlung eines Zustandes oder einer Erkrankung, der/die mit dem Binden von Opioidrezeptoren bei einem Patienten, der dessen bedarf, assoziiert ist,
wobei die Erkrankung oder der Zustand vorzugsweise ausgewählt ist aus der Gruppe bestehend aus Schmerz, Pruritis, Diarrhoe, Reizdarmsyndrom, gastrointestinaler Motilitätsstörung, Adipositas, Atemdepression, Krämpfen, Husten, Hyperalgesie, Entzündung, Osteoarthritis und Drogenabhängigkeit.

15. Zusammensetzung zur Verwendung nach Anspruch 14, wobei die Drogenabhängigkeit ausgewählt ist aus Abhängigkeit von Heroin, Kokain, Nicotin, Amphetamin und Alkohol, oder
wobei der Zustand Schmerz ist und die Zusammensetzung ferner eine wirksame Menge eines Opioids umfasst, oder
wobei der Zustand Osteoarthritis ist und die Zusammensetzung ferner eine wirksame Menge eines Opioids umfasst.

Revendications

1. Composé de formule I :



dans laquelle

R^1 est choisi parmi -OH, -CN, -CHO, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONH_2$, $-CSNH_2$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$ et $-C(=NR^{10})R^{11}$;

R^2 est choisi parmi un hydrogène, un halogène, -OH, -CN, -CHO, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-NO_2$, $-COR^{10}$, $-COOR^{10}$, $-SO_2R^{10}$, $-CONR^{10}R^{11}$, $-CSNR^{10}R^{11}$, $-CONR^{10}NR^{11}R^{12}$, $-CONR^{10}OR^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCONR^{10}R^{11}$, $-CONR^{10}((C(R^{12})(R^{13}))_tCOOR^{11}$, $-C(=S)R^{10}$, $-C(=NOR^{11})R^{10}$, $C(=NR^{10})R^{11}$, $-SO_2NR^{10}R^{11}$, un hétérocycle, un alkyle en C_1 à C_6 facultativement substitué, un alcényle facultativement substitué, un alcynyle facultativement substitué, un aryle facultativement substitué, un haloalkyle en C_1 à C_6, un haloalcoxy en C_1 à C_6 et un alkylthio en C_1 à C_6 ; ou

R^1 et R^2 ensemble avec les atomes auxquels ils sont liés, et un fragment choisi parmi $-OCH_2O-$ ou $-OCH_2CH_2O-$, forment un cycle,

R^3 est choisi parmi un hydrogène, un hydrocarbure en C_1 à C_8, un hétérocycle, un aryle et un hydroxyalkyle ;

R^4 est choisi parmi un hydrogène, un hydroxyle, un amino, un alcoxy en Ci à C_4, un alkyle en C_1 à C_{20} et un alkyle en C_1 à C_{20} substitué avec un hydroxyle ou un carbonyle ;

R^5 est un alkyle en C_1 à C_6 ;

R^6 est un alkyle en C_1 à C_6 ;

R^7 est choisi parmi un hydrogène, $NR^{10}R^{11}$ et $-OR^{10}$; ou

ensemble R^4, R^5, R^6 et R^7 peuvent former un, deux, trois ou quatre cycles, lesdits cycles ayant une substitution supplémentaire facultative ;

R^8 et R^{8a} sont tous les deux un hydrogène ou, pris ensemble, R^8 et R^{8a} sont =O ;

R^9 est choisi parmi un hydrogène et un alkyle en C_1 à C_6 ;

R^{10}, R^{11}, R^{12} et R^{13} sont chacun indépendamment un hydrogène, un alkyle en C_1 à C_6 facultativement substitué, un alcényle facultativement substitué, un alcynyle facultativement substitué, un aryle facultativement substitué, un hydroxyle, $-NR^{100}R^{101}$ ou un alcoxy en C_1 à C_4 facultativement substitué, ou R^{10} et R^{11}, conjointement avec l'atome d'azote auquel ils sont liés, forment un cycle carbocyclique ou hétérocyclique condensé facultativement substitué contenant 5 à 7 éléments de cycle parmi lesquels 3 peuvent être des hétéroatomes choisis parmi N, O et S ;

test 0, 1, 2, 3, 4, 5 ou 6 ;

R^{100} et R^{101} sont chacun indépendamment un hydrogène, un alkyle en C_1 à C_6 facultativement substitué, un alcényle facultativement substitué, un alcynyle facultativement substitué, un aryle facultativement substitué, un hydroxyle ou un alcoxy en C_1 à C_4 facultativement substitué, ou

R^{100} et R^{101}, conjointement avec l'atome d'azote auquel ils sont liés, forment un cycle carbocyclique ou hétérocyclique condensé facultativement substitué contenant 5 à 7 éléments de cycle parmi lesquels 3 peuvent être des hétéroatomes choisis parmi N, O et S ;

Y est une liaison directe ou $-(C(R^{10})(R^{11}))_q-$, dans lequel q est 0, 1, 2, 3, 4 ou 5 ;

L est une liaison directe ou $-(C(R^{10})(R^{11}))_q-$; et

Cy est Ar^1-B-Ar^2, dans lequel

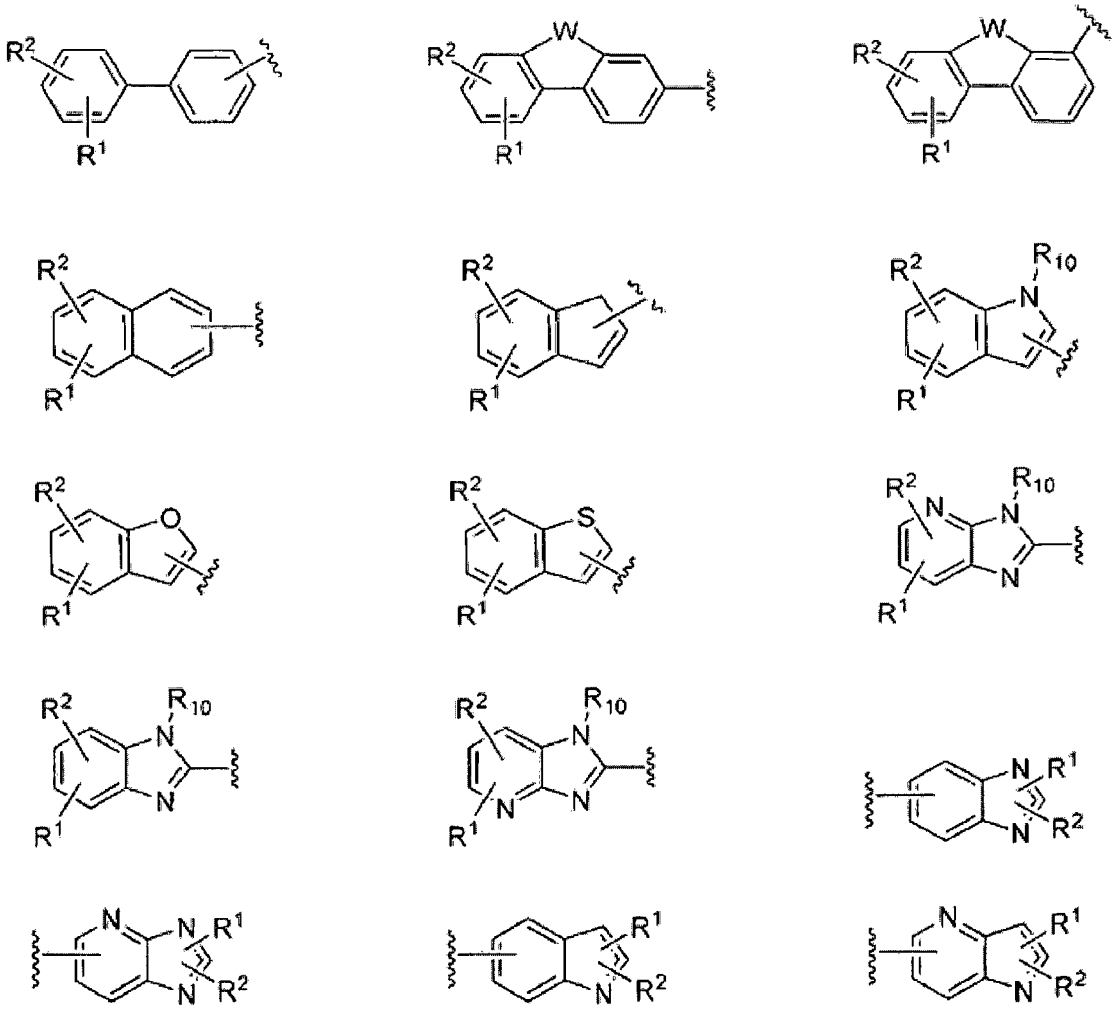
AR^1 est absent, ou est un radical aryle ou hétéroaryle contenant 1 to 4 atomes N, O et/ou S, qui peut être non

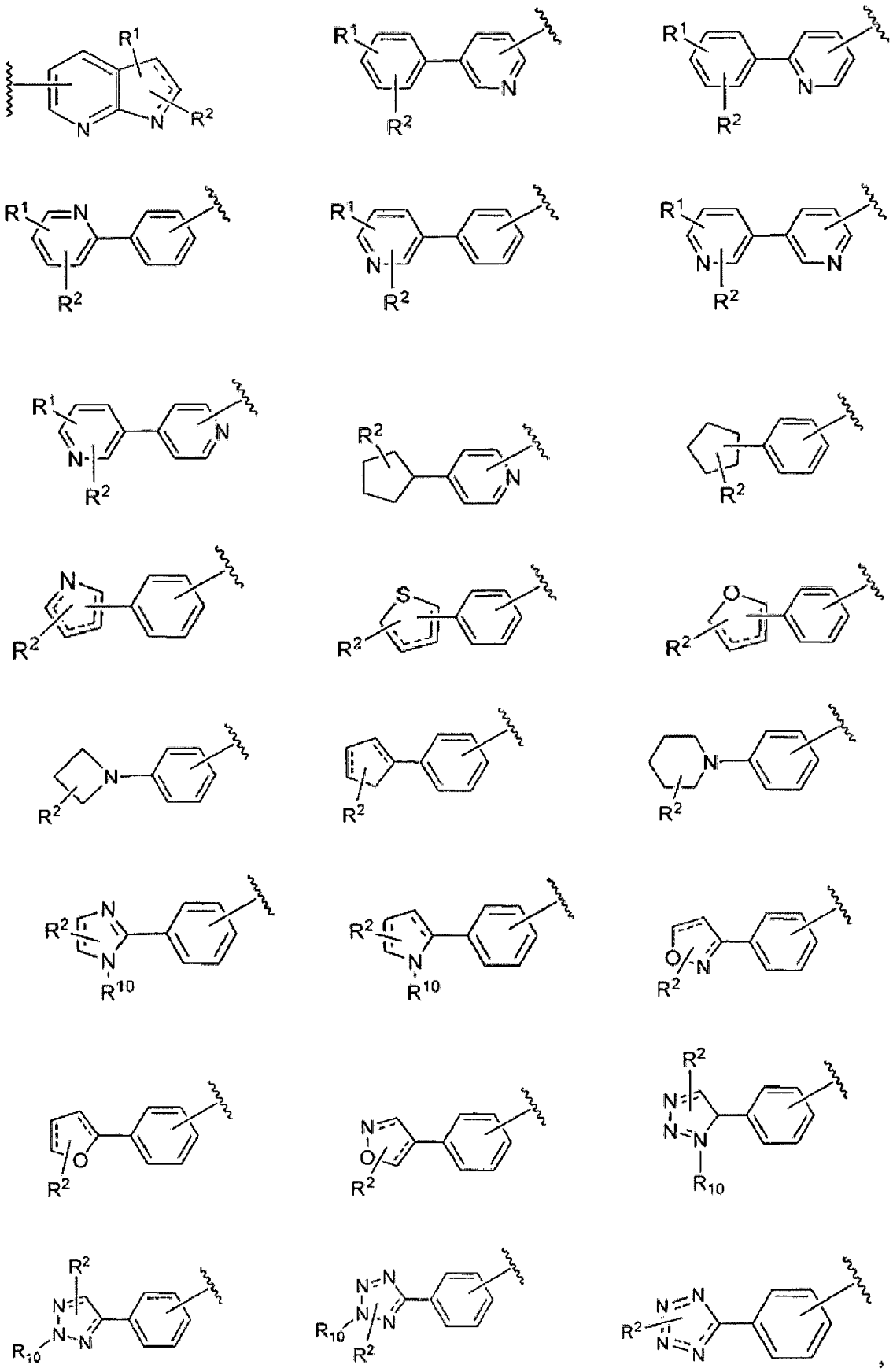
substitué ou mono-, di- ou tri-substitué avec un halogène, un alkyle en Ci à C_6, un alcényle, un alcynyle, un cycloalkyle, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ ou $-COOR^{10}$;
B est une liaison directe, -O-, $-NR^{10}$, $-SO_2$ ou $-(C(R^{10})(R^{11})s-$, dans lequel s est 0, 1, 2, 3, 4 ou 5 ; et
Ar^2 est un radical aryle ou hétéroaryle contenant 1 to 4 atomes N, O et/ou S, qui peut être non substitué ou mono-, di- ou tri-substitué avec un halogène, un alkyle en C_1 à C_6, un alcényle, un alcynyle, un cycloalkyle, $-OR^{10}$, $-NR^{10}R^{11}$, -CN, $-COR^{10}$ ou $-COOR^{10}$.

2. Composé selon la revendication 1, dans lequel lesdits R^{10} et R^{11} sont des hydrogènes, et/ou dans lequel R_1 est -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$ ou $-CON(H)CH_2CH_2COOH$; ou R^1 et R^2 ensemble avec les atomes auxquels ils sont liés forment un cycle condensé à $-OCH_2O-$, et/ou
dans lequel R_2 est H.

3. Composé selon la revendication 1, dans lequel R^1 est choisi parmi -OH, -CHO, $-CONH_2$, $-CON(H)CH_2CONH_2$, $-CON(H)CH_2CH_2CONH_2$, $-CON(H)CH_2COOH$ ou $-CON(H)CH_2CH_2COOH$; ou R^1 et R^2 ensemble avec les atomes auxquels ils sont liés forment un cycle condensé à $-OCH_2O-$, et/ou
dans lequel R^2 est H.

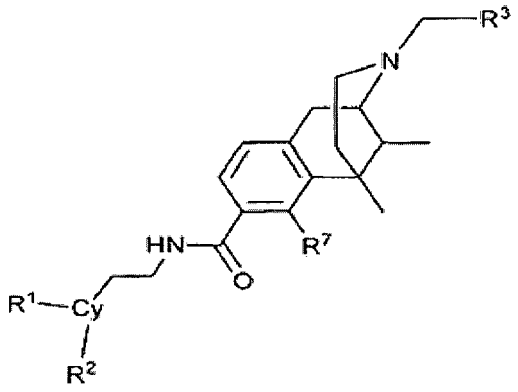
4. Composé selon la revendication 1, dans lequel Cy est choisi parmi :



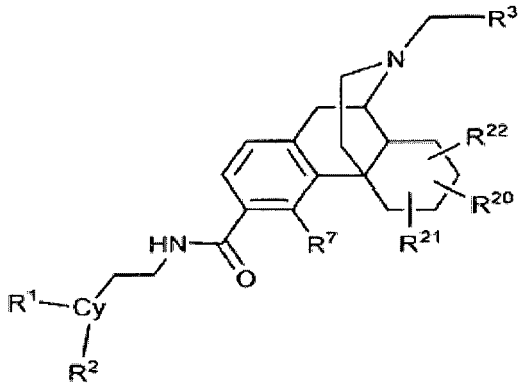


où W est choisi parmi $[C(R^9)_2]_n$, CR^8R^{8a}, O, NR^9, S et $CR^9=CR^9$; et n est 1, 2, 3, 4 ou 5.

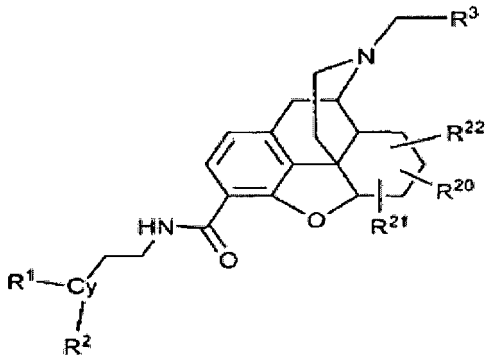
5. Composé selon la revendication 1 de formules III à VI :



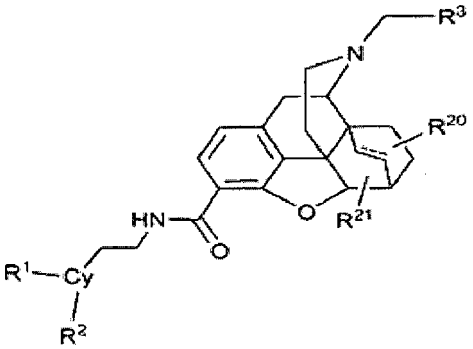
Formule III



Formule IV



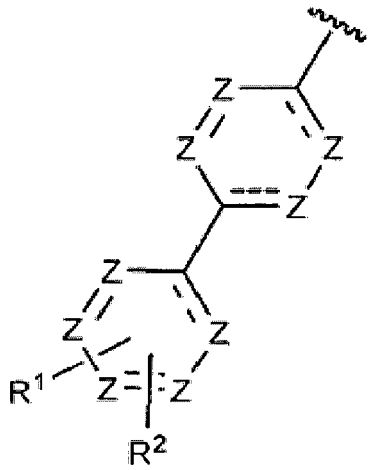
Formule V



Formule VI,

dans lesquelles R^{20}, R^{21} et R^{22} sont chacun choisis parmi un hydrogène, un hydroxyle, un amino, un alcoxy en C_1 à C_4, un alkyle en C_1 à C_{20} et un alkyle en C_1 à C_{20} substitué avec un hydroxyle ou un carbonyle ; ou ensemble, R^{20} et R^{21} avec le carbone auquel ils sont liés, forment -CO, ou -CS ; ou ensemble, R^{20} et R^{21} avec le ou les carbones auxquels ils sont liés, forment un cycle.

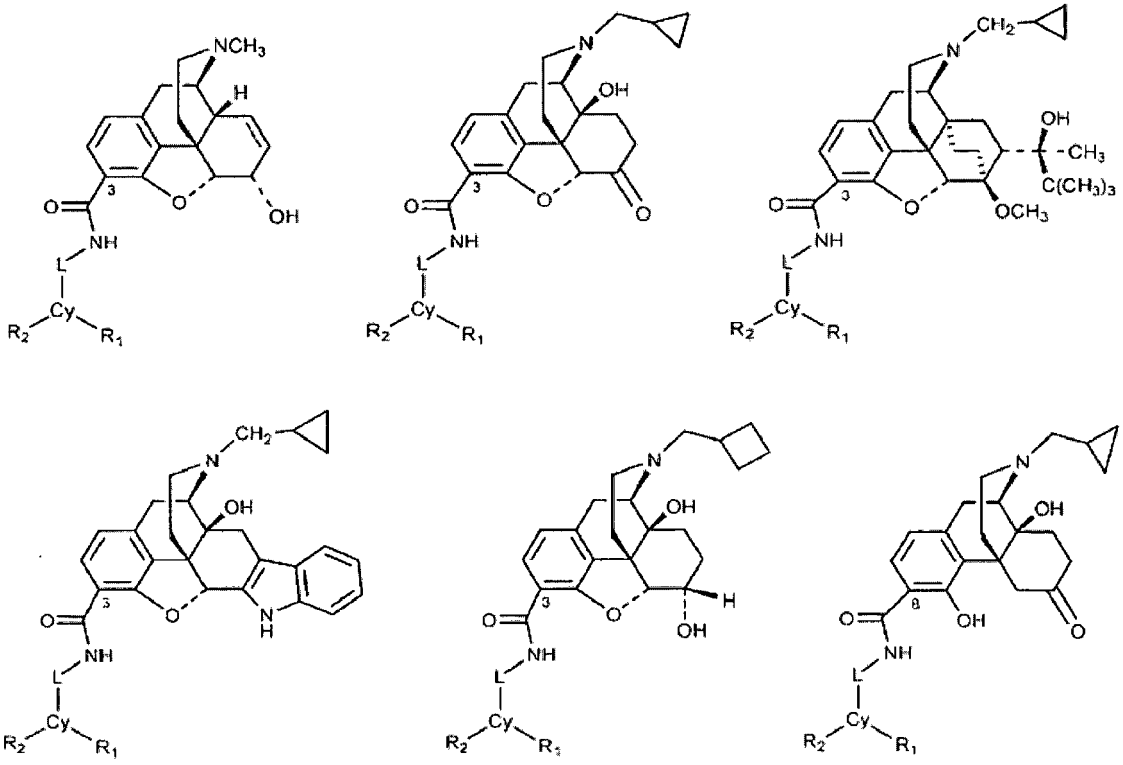
6. Composé selon la revendication 5, dans laquelle Cy-R^1R^2 est de formule :

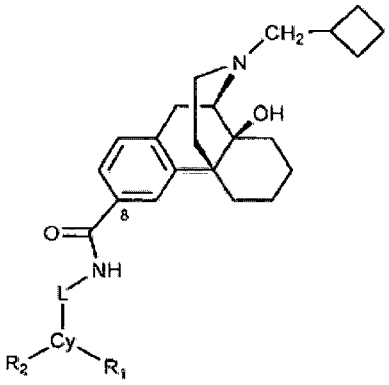


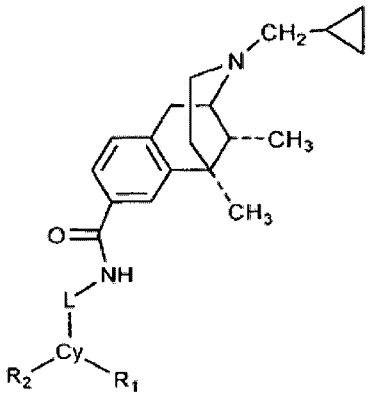
dans laquelle, au niveau des points de fixation de R^1 et R^2, Z sera CR^1 et CR^2, respectivement.

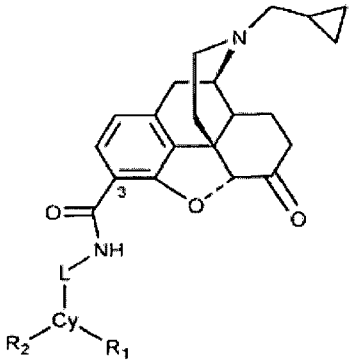
7. Composé selon la revendication 6, dans lequel R^1 est en position para par rapport à B et R^2 est un hydrogène ou un méthyle ; ou R^1 et R^2 conjointement avec les atomes auxquels ils sont liés, et un fragment choisi parmi $-OCH_2O-$ ou $-OCH_2CH_2O-$, forment un cycle.

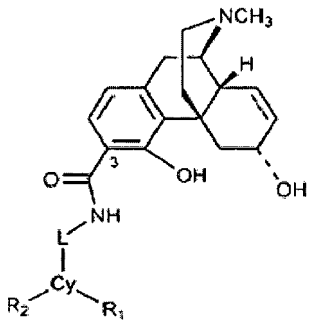
8. Composé selon la revendication 1 de formule :



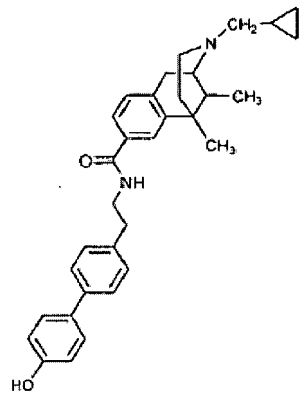
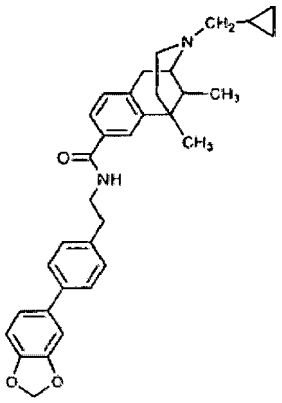




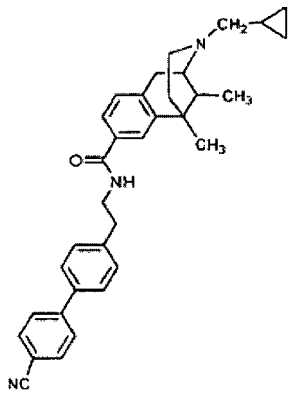
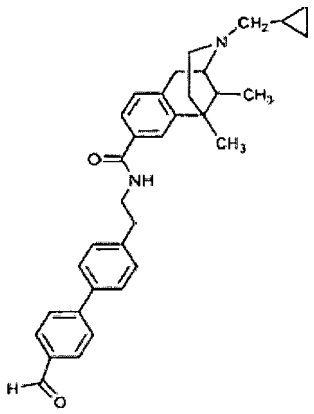
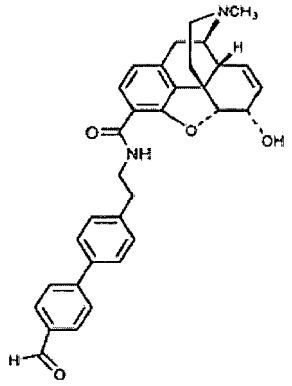
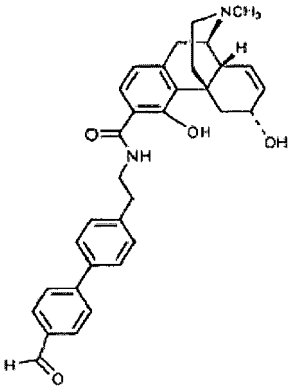
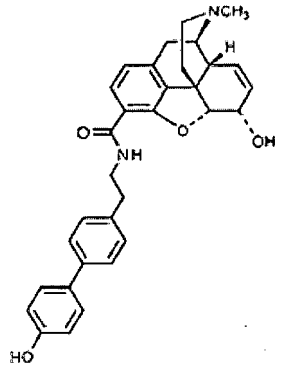
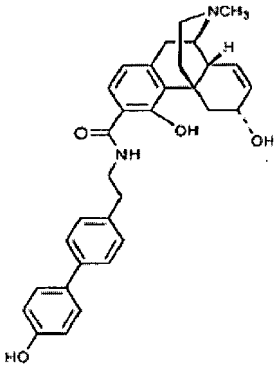
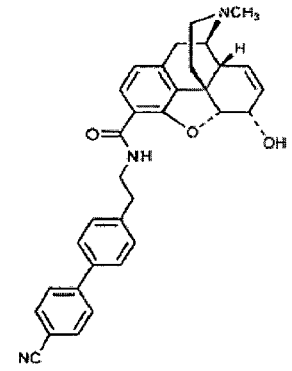
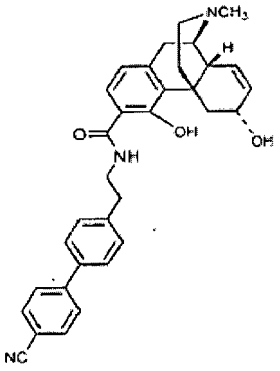




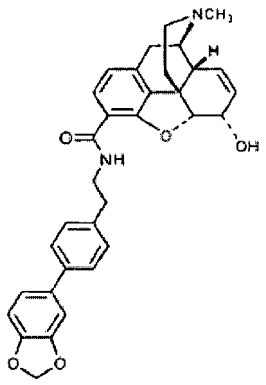
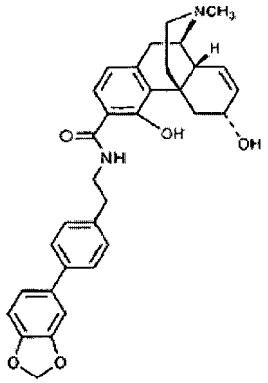
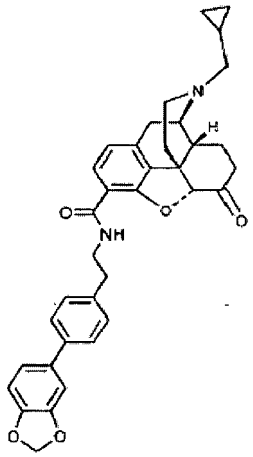
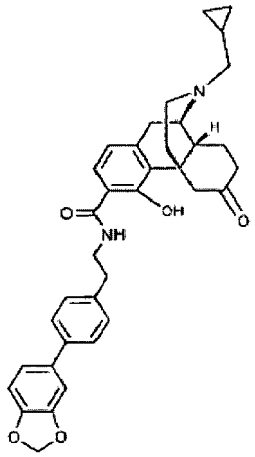
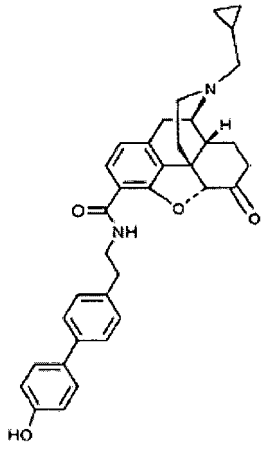
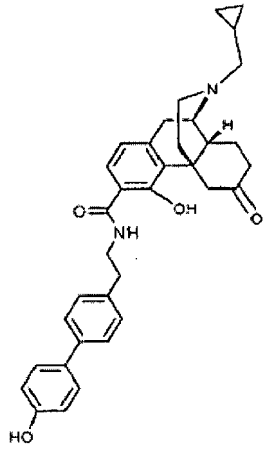
9. Composé selon la revendication 1, choisi dans le tableau 1 :

No	Structure	No	Structure
1		8	

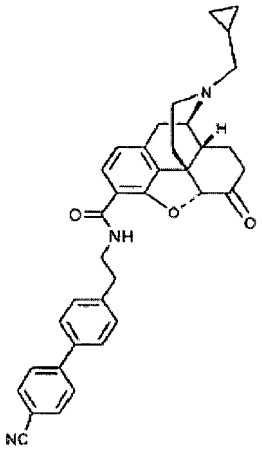
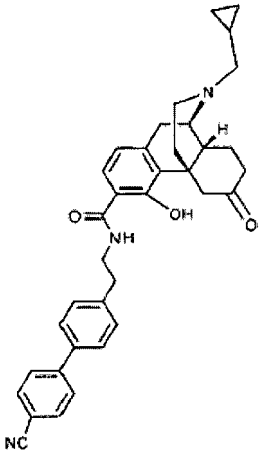
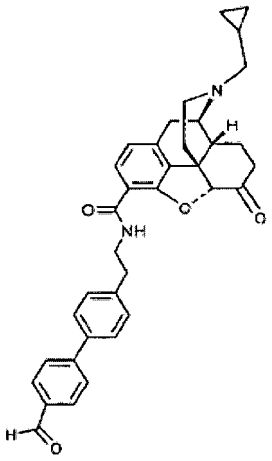
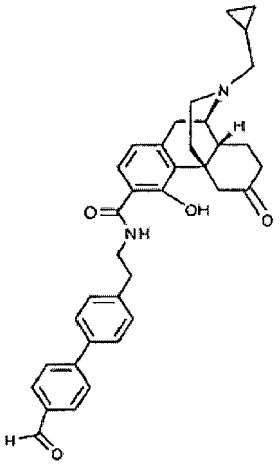
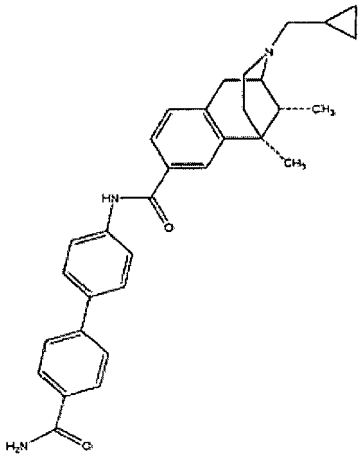
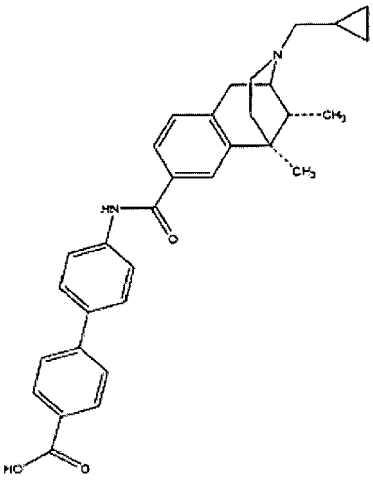
(suite)

No	Structure	No	Structure
9		10	
11		12	
13		14	
15		16	

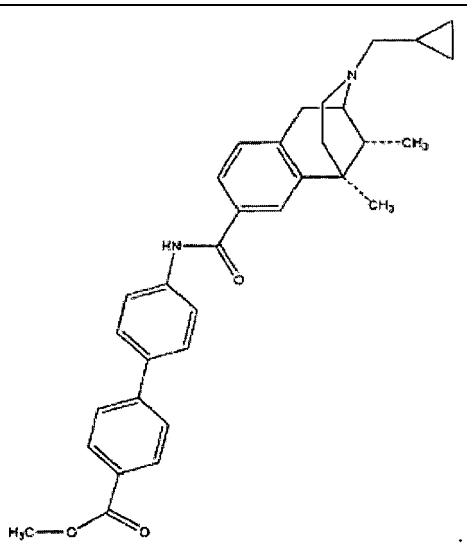
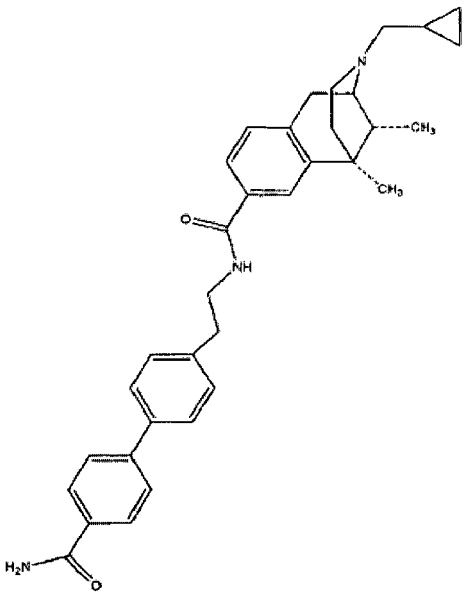
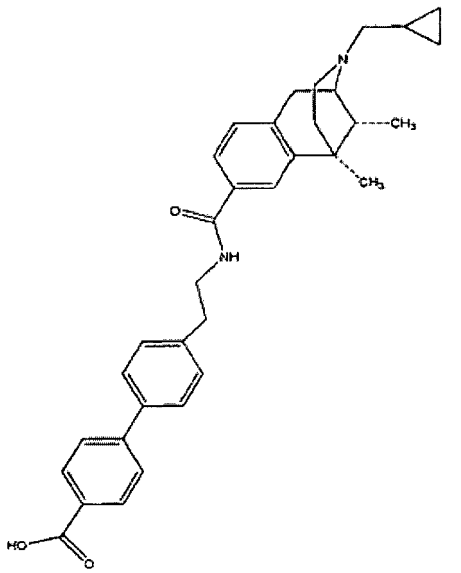
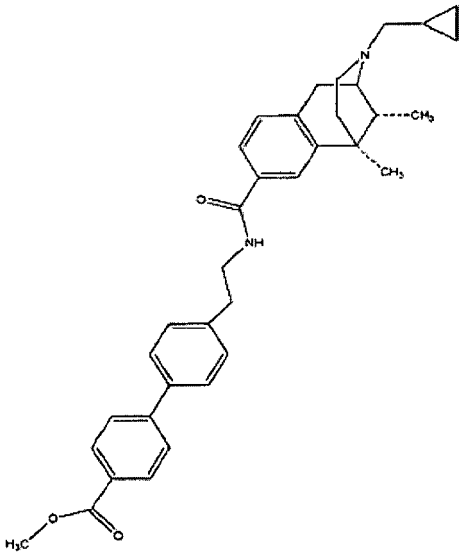
(suite)

No	Structure	No	Structure
17		18	
19		20	
21		22	

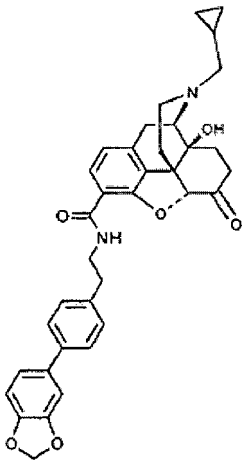
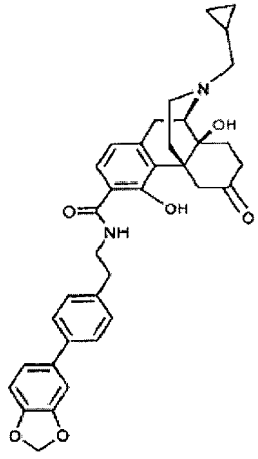
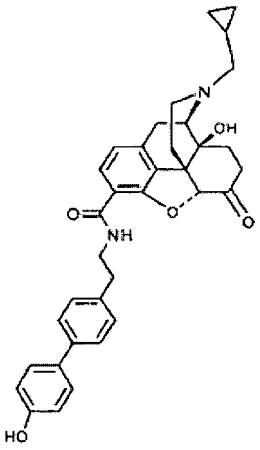
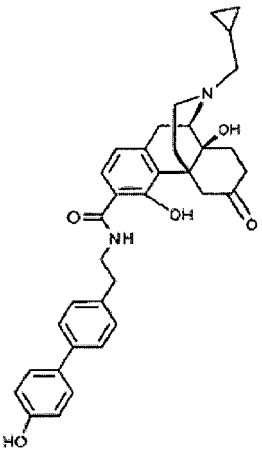
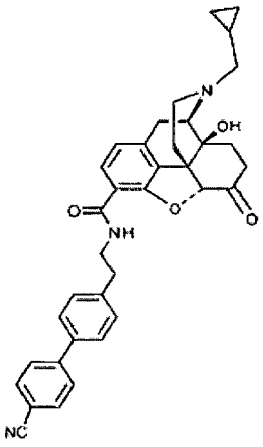
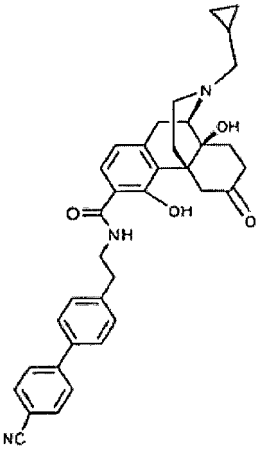
(suite)

No	Structure	No	Structure
23		24	
25		26	
31		32	

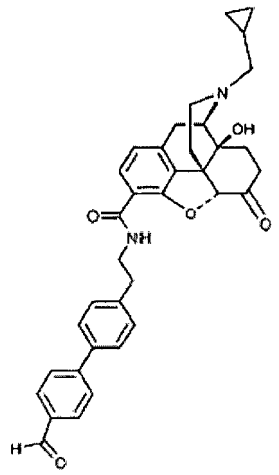
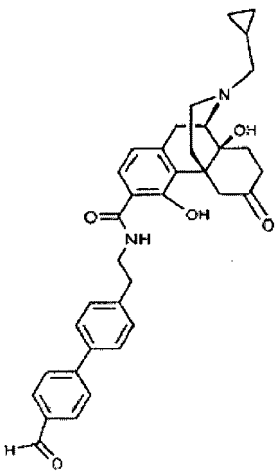
(suite)

No	Structure	No	Structure
33		34	
35		36	

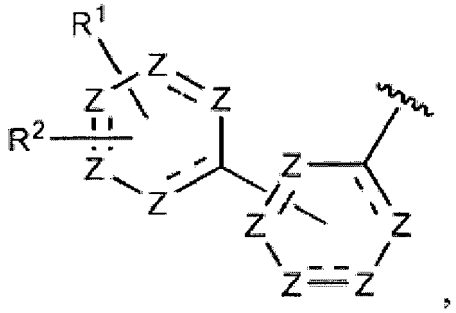
(suite)

No	Structure	No	Structure
37		38	
39		40	
41		42	

(suite)

No	Structure	No	Structure
43		44	

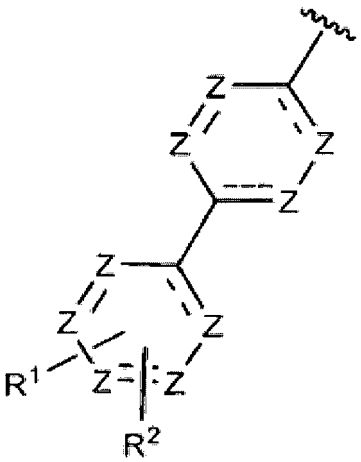
10. Composé selon la revendication 1, dans lequel Cy-R^1R^2 est de formule



dans laquelle Z est CR^{10} ou N, à condition que

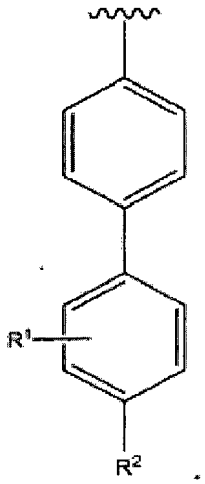
a) au niveau du point de fixation du cycle distal au cycle proximal, Z soit C, et
b) au niveau des points de fixation de R^1 et R^2, Z soit CR^1 et CR^2, respectivement.

11. Composé selon la revendication 10 de formule dans laquelle Cy-R^1R^2 est de formule :



dans laquelle un parmi R^1 et R^2 est de préférence en position para par rapport à B et l'autre parmi R^1 et R^2 est un hydrogène.

12. Composé selon la revendication 1, dans lequel Ar^2 est un phényle et un parmi R^1 et R^2 est en position para par rapport à B,
dans laquelle Cy-R^1R^2 est de préférence de formule :



13. Formulation pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 12 et un support pharmaceutiquement acceptable.

14. Composition comprenant une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 12, pour son utilisation dans un procédé de prévention ou de traitement d'une affection ou d'une maladie associée à la liaison aux récepteurs opioïdes chez un patient ayant besoin,
dans laquelle ladite maladie ou affection est choisie de préférence dans le groupe constitué d'une douleur, d'un prurit, d'une diarrhée, du syndrome du côlon irritable, d'un trouble de la motilité gastro-intestinale, de l'obésité, de la dépression respiratoire, des convulsions, de la toux, de l'hyperalgie, d'une inflammation, de l'arthrose et d'une pharmacodépendance.

15. Composition pour son utilisation selon la revendication 14, dans laquelle ladite pharmacodépendance est choisie parmi une dépendance à l'héroïne, à la cocaïne, à la nicotine, à l'amphétamine et à l'alcool, ou
dans laquelle l'affection est une douleur et la composition comprend en outre une quantité efficace d'un opioïde, ou
dans laquelle l'affection est l'arthrose et la composition comprend en outre une quantité efficace d'un opioïde.

REFERENCES CITED IN THE DESCRIPTION

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