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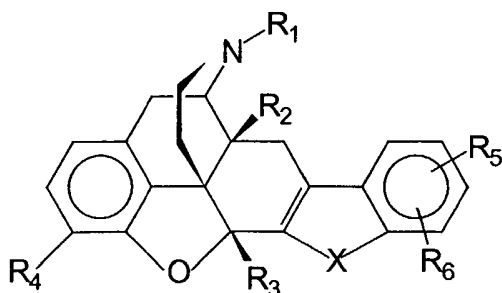
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(54) Title: USE OF OPIOID RECEPTOR ANTAGONIST COMPOUNDS FOR THE PREVENTION AND/OR TREATMENT OF DISEASES ASSOCIATED WITH THE TARGET CALCINEURIN



(I)

(57) Abstract: Morphinane derivatives of the formula
(I) their pharmaceutically acceptable salts are provided
for use as medicaments for the treatment and/or preven-
tion of disorders associated with the target calcineurin.

USE OF OPIOID RECEPTOR ANTAGONIST COMPOUNDS FOR THE PREVENTION AND/OR TREATMENT OF DISEASES ASSOCIATED WITH THE TARGET CALCINEURIN

Field of the invention

The present invention is related to the use of opioid receptor antagonists as well as their pharmaceutically acceptable salts in the treatment of disorders influenced by the target calcineurin.

Background of the invention

The further advance in medicinal research has yielded over the last decades a broad variety of powerful medicaments useful in a broad variety of indications. One important class of such compounds are opioid antagonists which are being used in the treatment of drug addiction and opioid induced constipation. Great improvements have been achieved, including the preparation of selective and long-lasting medicaments, showing furthermore a reduced tendency towards undesirable side-effects. However, other fields still require improvements, in particular chronic disorders and disorders affecting large parts of a given population. In this respect much attention has been focused on the developments of new classes of compounds showing a desired profile of activity concerning selected disorders.

However, the development of the understanding of the mechanisms of disorders on a molecular level has also greatly improved the knowledge as regards biological targets which appear to provide great promise concerning the treatment of larger groups of disorders, which all are interrelated with a given biological target.

In this respect the target calcineurin is an important target offering great promise for the treatments of a broad variety of disorders, including inflammatory disorders, skin disorders, neurodegenerative disorders, ischemic disorders, allergic diseases, nerve injuries, cancer, disorders of the intestine tract, pruritus, heart diseases,

cardiovascular diseases, stroke, psychic disorders, addiction and drug abuse, overweight and obesity, ileus and side-effects associated with opioid analgesics.

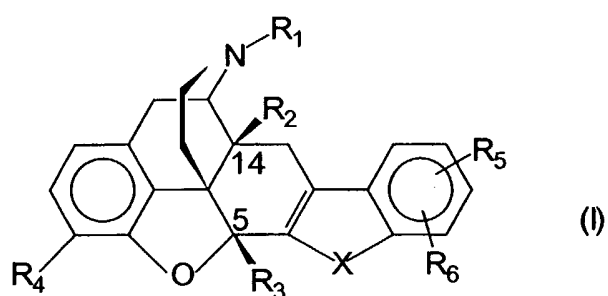
Object of the present invention

Accordingly it is the object of the present invention to provide a group of compounds enabling the treatment of disorders as listed above by means of interaction with the target calcineurin. A further object of the present invention is to enable the prevention and/or treatments of disorders such as inflammatory disorders, skin disorders, neurodegenerative disorders, ischemic disorders, allergic diseases, nerve injuries, cancer, disorders of the intestine tract, pruritus, heart diseases, cardiovascular diseases, stroke, psychic disorders, addiction and drug abuse, overweight and obesity, ileus and side-effects associated with opioid analgesics.

Outline of the invention

Accordingly the present invention provides the use of compounds of the formula (I) as defined below for the purposes as defined in the claims. Preferred embodiments are given below and defined in the subclaims.

COMPOUNDS OF FORMULA (I):



wherein

R₁ represents C₁-C₁₀ alkenyl; C₄-C₁₀ cycloalkylalkyl wherein the cycloalkyl is C₃-C₆ cycloalkyl and the alkyl is C₁-C₄ alkyl; C₄-C₁₀ cykloalkenylalkyl wherein the cycloalkenyl is C₃-C₆ cykloalkenyl and the alkyl is C₁-C₄ alkyl; C₇-C₁₆ arylalkyl wherein

the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl; C₈-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₂-C₆ alkenyl;

R₂ represents hydrogen, hydroxy, C₁-C₆ alkoxy; C₁-C₆ alkenyloxy; C₇-C₁₆ arylalkyloxy wherein the aryl is C₆-C₁₀ aryl and the alkyloxy is C₁-C₆ alkyloxy; C₇-C₁₆ arylalkenyloxy wherein the aryl is C₆-C₁₀ aryl and the alkenyloxy is C₁-C₆ alkenyloxy; C₁-C₆ alkanoyloxy; C₇-C₁₆ arylalkanoyloxy wherein the aryl is C₆-C₁₀ aryl and the alkylaroyloxy is C₁-C₆ alkylaroyloxy;

R₃ represents hydrogen, C₁-C₆ alkyl; C₁-C₆ alkenyl; C₇-C₁₆ arylalkyl wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl; C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₁-C₆ alkenyl; hydroxy(C₁-C₆)alkyl; alkoxyalkyl wherein the alkoxy is C₁-C₆ alkoxy and the alkyl is C₁-C₆ alkyl; CO₂H; CO₂(C₁-C₆ alkyl);

R₄ is hydrogen, hydroxy; C₁-C₆ alkoxy; C₇-C₁₆ arylalkyloxy wherein the aryl is C₆-C₁₀ aryl and the alkyloxy is C₁-C₆ alkyloxy; C₁-C₆ alkenyloxy; C₁-C₆ alkanoyloxy; C₇-C₁₆ arylalkanoyloxy wherein the aryl is C₆-C₁₀ aryl and the alkanoyloxy is C₁-C₆ alkanoyloxy; C₂-C₁₀ alkyloxyalkoxy wherein alkyloxy is C₁-C₄ alkyloxy and alkoxy is C₁-C₆ alkoxy;

R₅ and R₆ each independently represent hydrogen; OH; C₁-C₆ alkoxy; C₁-C₆ alkyl; hydroxyalkyl wherein the alkyl is C₁-C₆ alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO₂H; CO₂(C₁-C₆ alkyl); CONH₂; CONH(C₁-C₆ alkyl); CON(C₁-C₆ alkyl)₂; amino; C₁-C₆ monoalkyl amino; C₁-C₆ dialkyl amino, C₅-C₆ cycloalkylamino; SH; SO₃H; SO₃(C₁-C₆ alkyl); SO₂(C₁-C₆ alkyl); SO₂NH₂; SO₂NH(C₁-C₆ alkyl); SO₂NH(C₇-C₁₆ arylalkyl); SO(C₁-C₆ alkyl); or R₅ and R₆ together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C₁-C₆ alkyl; trifluoromethyl; C₁-C₆ alkoxy, CO₂H, CO(C₁-C₆ alkyl), amino, C₁-C₆ monoalkylamino, C₁-C₆ dialkylamino, SH; SO₃H; SO₃(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), SO(C₁-C₆ alkyl), and

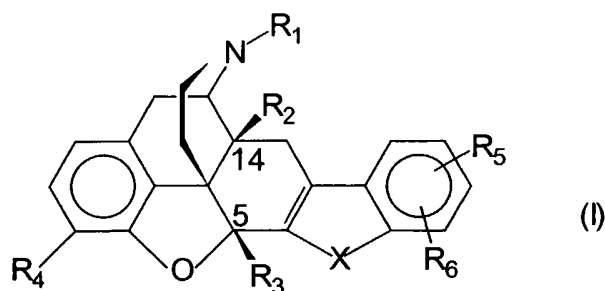
X represents oxygen; sulfur; CH=CH or NR₉ wherein R₉ is H, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₇-C₁₆ arylalkyl wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl, C₇-

C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₁-C₆ alkenyl; C₁-C₆ alkanoyl,

with the proviso that when R₂ is hydroxy R₃ cannot be hydrogen, except when R₄ is hydrogen, OCH₂OCH₃, OCH₂OC₂H₅ or OC(Ph)₃;

and pharmacologically acceptable salts thereof.

Preferred embodiments of compounds of formula (I) are as follows:



wherein

R₁ is: C₁-C₁₀-alkenyl; C₄-C₁₀-cycloalkylalkyl wherein cycloalkyl is C₃-C₆-cycloalkyl and alkyl is C₁-C₄-alkyl; C₄-C₁₀-cycloalkenylalkyl wherein cycloalkenyl is C₃-C₆-cycloalkenyl and alkyl is C₁-C₄-alkyl; C₇-C₁₆-arylalkyl wherein aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₈-C₁₆-arylalkenyl wherein aryl is C₆-C₁₀-aryl and alkenyl is C₂-C₆-alkenyl;

R₂ is: C₁-C₆-alkoxy; C₁-C₆-alkenyloxy; C₇-C₁₆-arylalkyloxy wherein aryl is C₆-C₁₀-aryl and alkyloxy is C₁-C₆-alkyloxy; C₇-C₁₆-arylalkenyloxy wherein aryl is C₆-C₁₀-aryl and alkenyloxy is C₁-C₆-alkenyloxy;

R₃ is: hydrogen, C₁-C₆-alkyl; C₁-C₆-alkenyl; C₇-C₁₆-arylalkyl wherein aryl is C₆-C₁₀-aryl and alkyl is C₁-C₆-alkyl; C₇-C₁₆-arylalkenyl wherein aryl is C₆-C₁₀-aryl and alkenyl is C₁-C₆-alkenyl; hydroxy(C₁-C₆)alkyl; alkoxyalkyl wherein alkoxy is C₁-C₆-alkoxy and alkyl is C₁-C₆-alkyl; CO₂H; CO₂(C₁-C₆ alkyl);

R₄ is: hydroxy, C₁-C₆-alkoxy; C₇-C₁₆-arylalkyloxy wherein aryl is C₆-C₁₀-aryl and alkyloxy is C₁-C₆-alkyloxy; C₁-C₆-alkenyloxy; C₂-C₁₀-alkyloxyalkoxy wherein alkyloxy is C₁-C₄-alkyloxy and alkoxy is C₁-C₆-alkoxy;

R₅ and R₆ each independently represent: hydrogen; OH; C₁-C₆-alkoxy; C₁-C₆-alkyl; hydroxyalkyl wherein alkyl is C₁-C₆-alkyl; halogen; nitro; cyano; thiocyanato; trifluoromethyl; CO₂H; CO₂(C₁-C₆-alkyl); CONH₂; CONH(C₁-C₆-alkyl); CON(C₁-C₆-alkyl)₂; amino; C₁-C₆-monoalkylamino; C₁-C₆-dialkylamino; C₅-C₆-cycloalkylamino; SH; SO₃H; SO₃(C₁-C₆-alkyl); SO₂(C₁-C₆-alkyl); SO₂NH₂; SO₂NH(C₁-C₆-alkyl); SO₂NH (C₇-C₂₀-arylalkyl); SO(C₁-C₆-alkyl); or R₅ and R₆ together form a phenyl ring, which may be unsubstituted or substituted with halogen, nitro, cyano, thiocyanato; C₁-C₆-alkyl; trifluoromethyl; C₁-C₆-alkoxy, CO₂H, CO(C₁-C₆-alkyl), amino, C₁-C₆-monoalkylamino, C₁-C₆-dialkylamino, SH; SO₃H; H; SO₃(C₁-C₆-alkyl), SO₂(C₁-C₆-alkyl), SO(C₁-C₆-alkyl), and

pharmacologically acceptable salts thereof.

By aryl the following definitions are intended throughout the whole patent application.

Aryl may be unsubstituted or mono-, di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C₁-C₃ alkyl, C₁-C₃ alkoxy, CO₂H, CO₂ (C₁-C₃)alkyl, CONH₂, CONH(C₁-C₃ alkyl), CON(C₁-C₃ alkyl)₂, CO(C₁-C₃ alkyl), amino, (C₁-C₃ monoalkyl)amino, (C₁-C₃ dialkyl)amino, C₅-C₆ cycloalkylamino, (C₁-C₃ alkanoyl)amino, SH, SO₃H, SO₃ (C₁-C₃ alkyl), SO₂ (C₁-C₃ alkyl), SO(C₁-C₃ alkyl), C₁-C₃ alkylthio or C₁-C₃ alkanoylthio.

In all of the above mentioned substitution patterns it is preferred when R₁ to R₆ and X are selected as defined below, wherein these preferred definitions are preferred individually as well as in any conceivable combination, i.e. it is preferred that R₁ alone is as defined below, or that R₁ and R₂ are as defined below, or that R₁ and R₃ are as defined below, etc., i.e. including all possible combinations:

R₁: alkenyl, arylalkenyl, cycloalkylalkyl, all as defined above;

R₂: alkoxy, arylalkoxy, alkenyloxy, arylalkenyloxy, all as defined above;

R₃: alkyl, arylalkyl, alkenyl, all as defined above;

R₄: alkoxy, alkyloxyalkoxy, alkenyloxy, all as defined above;

R₅ and R₆: independently selected from hydrogen, nitro, cyano, chloro, fluoro, bromo, trifluoromethyl; CO₂H; CO₂ CH₃, CONH₂; CONH CH₃, CH₃, SH; SO₂NH₂; N(CH₃)₂, SO₂ CH₃;

X: O, NH, N CH₃, N-benzyl, N-allyl.

In a preferred embodiment

R₁ is selected from allyl, cinnamyl, cyclopropylmethyl or cyclobutylmethyl;

R₂ is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO₂, CN, CF₃, CH₃ or OCH₃; allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R₃ is selected from hydrogen, methyl, ethyl, benzyl or allyl;

R₄ is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R₅ and R₆ are each and independently selected from hydrogen, nitro, cyano, chloro, fluoro, bromo, trifluoromethyl; CO₂H; CO₂ CH₃, CONH₂; CONH CH₃, CH₃, SH; SO₂NH₂; N(CH₃)₂, SO₂ CH₃; and

X is selected from O, NH, N CH₃, N-benzyl, N-allyl.

In an especially preferred embodiment R₁ is allyl or cyclopropylmethyl;

R₂ is selected from methoxy, ethoxy, n-propyloxy, benzyloxy substituted in the aromatic ring with chlorine;

R₃ is selected from hydrogen or CH₃;

R₄ is hydroxy

R₅ and R₆ are each independently selected from hydrogen, CO₂H, CONH₂, SO₂NH₂ or SO₂CH₃; and

X is selected from O or NH.

The best mode known at present is to use the compounds of Examples 1, 6, 8, 18, 24, 41 and 42.

The novel compounds according to the invention are useful as agents for the treatment and/or prevention of disorders associated with the target calcineurin. The compounds as defined herein are in particular suitable for the preparation of a medicament for the treatment and/or prevention of disorders such as inflammatory disorders, skin disorders, in particular neurodermatitis and psoriasis, neurodegenerative disorders, ischemic disorders, allergic diseases, nerve injuries, cancer, disorders of the intestine tract, pruritus, heart diseases, cardiovascular diseases, stroke, psychic disorders, addiction and drug abuse, overweight and obesity, ileus and side-effects associated with the treatment with opioid analgesics.

Pharmaceutically and pharmacologically acceptable salts of the compounds of formula I are also comprised in the invention. Suitable salts are inorganic salts such as HCl salt, HBr salt, sulfuric acid salt, phosphoric acid salt. Organic acid salts such as methanesulfonic acid salt, salicylic acid salt, fumaric acid salt, maleic acid salt, succinic acid salt, aspartic acid salt, citric acid salt, oxalic acid salt, orotic acid salt, although the salts are not restricted thereto, can also be used according to the invention.

The present invention is related to new possibilities for the therapeutic use of compounds known as δ -opioid receptor antagonists.

The new possibilities for the therapeutic use of δ -opioid receptor antagonists are related in part on the basis of the surprising identification of a second target – beside the target δ -opioid receptors – namely calcineurin. Calcineurin inhibition was proved with several of the δ -opioid receptor antagonists disclosed herein.

The present invention is related to the use of the δ -opioid receptor antagonists and their pharmaceutically acceptable salts as disclosed here for the prevention and/or treatment of the following groups of medicinal indications:

1. side effects of use of opioids

pruritus, ileus, vomiting, nausea, sedation, dizziness, confusion, addiction,

constipation, respiratory depression

2. addiction

opioid addicts, alcohol addicts, cocaine addicts, drug addicts, drug abuse

3. inflammatory disorders

Intestinal diseases, such as colon irritable, Crohn's disease, colitis ulcerosa; epithelial diseases, such as bronchial asthma, uveitis; blepharitis; inflammatory myopathies; rosacea; erythema; lichen; inflammatory disorders; atopic dermatitis; neurodermatitis; allergic contact dermatitis; psoriasis; ischemic disorders, such as stroke, cardiac infarction; pruritus; multiple sclerosis; phlebitis; ascites; glaucoma; scleroderma; systemic sclerosis

4. disorders associated with the metabolism and/or the level of tryptophan

bulimia, anorexia, depression, phobia, panic disorders, cataplexy, hallucination, sleeping disorders, narcolepsy, schizophrenia, dysphoria, gluttony, craving for food, bulimia, Alzheimer's disease, neurodegenerative disorders, Huntington's disease, Parkinson's disease, disorders of the central nervous system, Lyme borelliosis, Tourette syndrome, systemic sclerosis, scleroderma, multiple sclerosis, systemic lupus erythematosus, colon carcinoma, anxiety disorders, migraine, increased algaesthesia, sleeping disorders, narcolepsy

5. psychic disorders

multiple sclerosis, mood changes, confusion, insomnia, tinnitus, dysphoria, depression, schizophrenia, overweight, gluttony, craving for food, bulimia, sedation, dizziness, confusion, addiction, Tourette syndrome, anxiety disorders, increased algaesthesia, hallucination, sleeping disorders, narcolepsy

6. immunological impairments

Alopecia, diabetes mellitus, neurodermatitis, atopic dermatitis, lichen, vitiligo, autoimmune diseases, allergic contact dermatitis, psoriasis, allergic disorders, pernicious anemia, struma lymphomatosa hashimoto, diabetes mellitus, systemic

lupus erythematosus, scleroderma, dermatomyositis, multiple sclerosis, hepatitis, colitis ulcerosa, glaucoma, modulating the activity of cells in the immune system

7. disorders of the intestine tract

colon irritabile, colitis ulcerosa, Crohn's disease, ileus, postoperative ileus, postpartum ileus, colon carcinoma

8. cardiovascular disorders

cardiac infarction, heart disorders, phlebitis, stroke, heart enlargement, edema, ascites

9. infections with pathogens

blepharitis, rosacea, Lyme borelliosis, gangrenous pyoderma, infections, virus infections, bacterial infections, protozoa infections, metazoa infections

10. to minimize side effects of classical calcineurin inhibitors

diabetes mellitus, kidney disorders, liver disorders, hypertrichosis, tremor, fatigue, tiredness, headache, gingivitis hypertrophicans, anorexia, nausea, vomiting, diarrhea/diarrhoea, gastritis, paresthesia, constipation, dizziness, dyspepsia, tinnitus, high blood pressure, heart enlargement, hyperglycemia, edema, oliguria, thrombocytopenia, lymphomas, cancers, mood changes, depression, confusion, insomnia, anemia, pain, backpain, backache, muscle cramps, ascites

11. skin disorders

neurodermatitis, atopic dermatitis, blepharitis, gangrenous pyoderma, rosacea, lichen, erythema, alopecia, ichthyosis, vitiligo, scleroderma, dermatomyositis, allergic contact dermatitis, pruritus, psoriasis, paresthesia, systemic sclerosis, scleroderma, seborrheic dermatitis

12. neurological disorders

neurodegenerative disorders, disorders of the central nervous system, Alzheimer's

disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injuries, spinal cord injuries, nerve injuries, tinnitus, muscle cramps, Tourette syndrome, migraine, increased algaesthesia, cataplexy, sleeping disorders, narcolepsy

13. eating disorders

bulimia, anorexia, obesity, overweight, gluttony, craving for food

14. malignant disorders

malignant cells, cancer, colon cancer, malignant tumors, lymphomas

Without being bound to any particular theory it is believed that the above mentioned groups of indications can be treated with the compounds disclosed and claimed in view of the particular activity disclosed and shown later in the application and the therewith associated biochemical pathways. Regarding groups 1 and 10 it is apparent that the desired effect can be obtained since the compounds and the associated activity as disclosed here enable to reduce the amount of opioids or other cacineurin inhibitors to be used in view of the activity shown by the compounds as employed in the present invention. In this connection it has to be emphasized that in relation with group 1 the present invention allows to prevent, treat or suppress the side effects without sacrificing the desired analgetic activity of the opioid analgesics.

Of particular importance are the disorders as defined in the claims. Further important disorders which may be treated in accordance with the teaching of the present invention are the following:

high blood pressure, Alzheimer's disease, Parkinson's disease, allergic diseases, cancer, heart disorders, tinnitus, headache, diabetes mellitus, pain, gastritis, obesity, heart enlargement

Others are as follows:

skin disorders, seborrheic dermatitis, gangrenous pyoderma, lichen, alopecia, ichthyosis, vitiligo, allergic contact dermatitis, pruritus, neurodegenerative disorders, disorders of the central nervous system, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injuries, spinal cord injuries, nerve injuries, malignant tumors, disorders of the intestine tract, cardiovascular disorders, phlebitis, kidney disorders, liver disorders, hypertrichosis, tremor, fatigue, tiredness, gingivitis hypertrophicans, paresthesia, constipation, dyspepsia, hyperglycemia, edema, oliguria, hyperkalemia, thrombocytopenia, lymphomas, mood changes, confusion, anemia, muscle cramps, ascites, backpain, backache, glaucoma, psychic disorders, dysphoria, depression, schizophrenia, addiction, opioid addicts, cocaine addicts, alcohol addicts, drug addicts, drug abuse, overweight, gluttony, craving for food, ileus, postoperative ileus, postpartum ileus, Lyme borreliosis, Tourette syndrome, systemic lupus erythematosus, advanced colon carcinoma, anxiety disorders, migraine, increased algaesthesia, phobia, anorexia, bulimia, cataplexy, hallucination, sleeping disorders, narcolepsy, pernicious anemia, struma lymphomatosa hashimoto, dermatomyositis, infections, virus infection, bacterial infections, protozoa infections, metazoa infections, modulating the activity of cells in the immune system

Prefreably the present invention is related to the use of the opioid receptor antagonists and their pharmaceutically acceptable salts disclosed in this application for the treatment and/or prevention of inflammatory diseases (e.g. inflammatory intestinal diseases like colon irritabile, colitis ulcerosa or Crohn's disease; inflammatory myopathies, inflammatory epithelial diseases like bronchial asthma; uveitis), skin diseases (e.g. neurodermatitis, atopic dermatitis, seborrheic dermatitis, blepharitis, gangrenous pyoderma, rosacea, psoriasis, lichen, erythema, alopecia, ichthyosis, vitiligo, allergic contact dermatitis, pruritus), neurodegenerative disorders (e.g. Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis), CNS disorders (e.g. traumatic brain injuries, stroke, spinal cord injuries), nerve injuries, cancer, disorders of the intestine tract, heart diseases, cardiovascular diseases, ischemic disorders, allergic diseases.

In this connection the experimental results presented below show a further activity of the compounds defined herein. According to the test results an inhibition of the generation of interleukin-2 could be achieved with the compounds defined in the

present invention, enabling the treatment and or prophylaxis of disorders requiring such an inhibition.

A further possible use of the compounds as defined herein is the treatment of malignant tumors, since an antiproliferative activity of the compounds was surprisingly detected. This activity furthermore shows a highly desirable selectivity, i.e. the antiproliferative activity is displayed towards cancer cells but not towards healthy cells. As mechanism it is assumed that apoptosis occurs.

The compounds as defined herein may also be used for the treatment and/or prevention of postoperative ileus, postpartum ileus. Furthermore they may be used for the treatment of addicts, for example opioid addicts, cocaine addicts, alcohol addicts as well as for the treatment of obesity or psychic disorders, such as dysphoria, depression or schizophrenia. Furthermore side effects of opioid-analgesics such as morphine, fentanyl or oxycodone (e.g. vomiting, nausea, sedation, dizziness, confusion, addiction, constipation, respiratory depression) may be prevented, treated or suppressed, without sacrificing the analgesic activity of these agents.

The compounds according to formula (I) or their pharmaceutically acceptable salts may be administered orally, intravenously, intraarterially, intramuscularly, intrathecally, intralumbarily, intraperitoneally, intranasally, intradermally, subcutaneously, epicutaneously, topically, transdermally, rectally, pulmonarily, conjunctivally, buccally, lingually or sublingually in a pharmaceutical formulation such as a solution, capsule, tablet, spray, suppository, ointment, cream, paste, plaster, patch or the like.

The suitability of the compounds to be used in accordance with the present invention was evaluated using the following test methods.

METHOD

Calcineurin inhibition assays

Calcineurin inhibition assay was performed according to a described procedure (R. Baumgrass et al., J. Biol. Chem. 276, 47914, 2001).

Calcineurin inhibition was measured in a concentration range of 1-50 μM of the test compound at optimal Ca^{2+} and calmoduline concentrations. The calcineurin/compound mixtures were equilibrated in the assay buffer (40 mM Tris-HCl, pH 7.5, 100 mM NaCl, 6 mM MgCl_2 , 0.5 mM dithiothreitol, 1 mM CaCl_2 , 0.1 mg/ml bovine serum albumin) at 22°C for 30 min. Calcineurin activity was referenced to the assay lacking the test compounds. The data were computed with the SigmaPlot program.

RESULTS

Direct inhibition of calcineurin

Inhibitory potency of calcineurin by δ -opioid receptor antagonists

Compound	IC_{50} (μM)
HS 881	10
HS 879	12
HS 573	44
HS 378	59
Naltrindole	>100

Inhibition of calcineurin mediated by δ -opioid receptor antagonists at a concentration of 20 μM

Compound	Calcineurin activity (% of control)
Naltrindole	93
HS 378	92
HS 573	76
HS 884	65
HS 882	49
HS 881	37
HS 894	30

HS 879	29
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Unlike cyclosporin and FK506 (tacrolimus) which require prior binding to matchmaker proteins to inhibit calcineurin, the δ -opioid receptor antagonists produce a direct inhibition of the phosphatase activity of calcineurin.

Further studies were performed to confirm the calcineurin inhibitory action of the δ -opioid receptor antagonists. It is known that inhibition of calcineurin leads to an inhibition in the expression of interleukin-2.

METHOD

Measurement of interleukin-2 production in concanavalin A stimulated lymphocytes

Lymph nodes from collagen injected Dark-Agouti rats were used 10 days post-immunization to prepare individual single cell suspensions according to the described procedure (Kleinau et al., Journal of Autoimmunity 4, 871, 1991).

Cells were incubated with 5 $\mu\text{g/ml}$ ConA (concanavaline A) and increasing concentrations of the δ -opioid receptor antagonists or cyclosporine A (0.01-10 μM). Cells were harvested 48 h after addition of the test compound and supernatants were collected and used for quantification of interleukin-2 by ELISA (Enzyme-linked immunoabsorbant assay technique). Absorbance at 405 nm was measured. The data were computed with the GraphPad program. Results are expressed as inhibition percentage from the control, in the absence of the test compound.

RESULTS

Effect of δ -opioid receptor antagonists in interleukine-2 production in supernatants of ConA-stimulated lymphocytes

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Measurement of interleukin-2 production in MLR (Mixed Lymphocyte Reaction)

Measurement of interleukin-2 production in MLR was performed according to the described procedure (Gaveriaux-Ruff et al., J. Pharmacol. Exper. Ther. 298, 1193, 2001).

Splenocytes from mice were cultured with allogeneic stimulators (mitomycin treated BALB/c spleen cells). Mixed lymphocyte reaction was performed in the absence or presence of δ -opioid receptor antagonists and cyclosporin A. Interleukin-2 was measured in cell supernatant after 48 h of culture using ELISA.

RESULTS

Effect of opioid compounds on interleukin-2 (IL-2) production on spleen cells in the
MLR

Naltrindole	HS 378	Cyclosporin A	IL-2
μM	μM	nM	pg/ml
			84 \pm 18
3			66 \pm 18
10			29 \pm 6
30			19 \pm 5
	2		49 \pm 7
	10		31 \pm 3
	20		22 \pm 2
		3	76 \pm 27
		10	41 \pm 11
		30	26 \pm 2

Cyclosporin A suppressed interleukin-2 production. The δ -opioid receptor antagonists also were found to inhibit interleukin-2 production, indicating that such compounds suppress lymphocyte proliferation via an interleukin-2-dependent mechanism, thus directing towards a calcineurin pathway.

HS 378 is compound 1 as obtained in example 1

HS 573 is 17-(Cyclobutylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -ethoxy-5 β -methylindolo[2',3':6,7]morphinan-3-ol Hydrochloride

HS 879 is 14 β -(Benzyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol

HS 881 is 14 β -[(4-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride

HS 882 is 17-(Cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -[(2-phenylbenzyl)oxy]indolo[2',3':6,7]morphinan-3-ol Hydrochloride

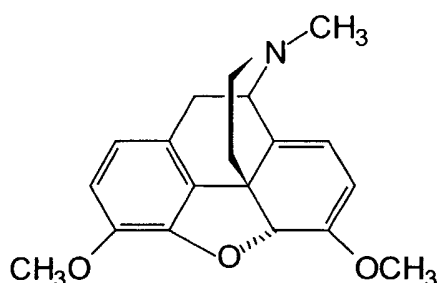
HS 884 is 14 β -[(4-tert.-Butylbenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride

HS 894 is 17-(Cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol

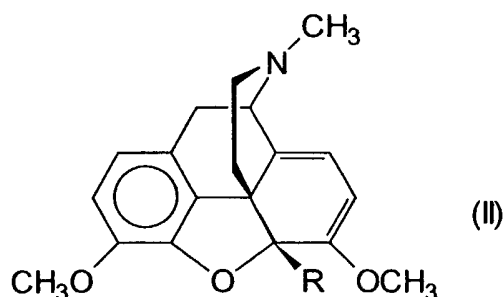
Preparation

The compounds represented by formula (I) may be obtained by the following methods:

Thebaine of the formula



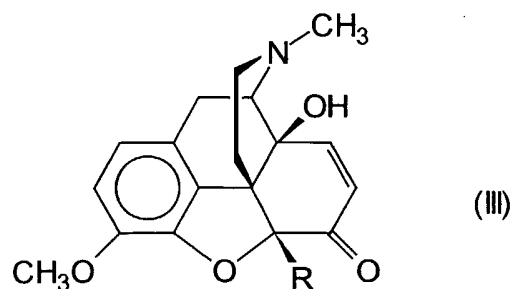
is being treated with dialkylsulfates, fluorosulfonic acid alkyl esters, alkylsulfonic acid alkyl esters, arylsulfonic acid alkylesters, alkyl halides, aralkyl halides, alkylsulfonic acid aralkyl esters, arylsulfonic acid aralkyl, arylalkenyl halides, chloroformates, in solvents such as tetrahydrofurane or diethyl ether using a strong base such as n-butyl lithium, lithium diethyl amide or lithium diisopropyl amide at low temperatures (-20 to -80 °C) (s. Boden et al., J.Org.Chem., Vol. 47: 1347-1349, 1982; Schmidhammer et al., Helv.Chim.Acta, Vol.71:642-647, 1988), giving compounds of the formula II



wherein

R is C₁-C₆ alkyl; C₁-C₆ alkenyl; C₇-C₁₆ aralkyl wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl; C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is

C₁-C₆ alkenyl; alkoxyalkyl wherein the alkoxy is C₁-C₆ alkoxy and the alkyl is C₁-C₆ alkyl; CO₂ (C₁-C₆ alkyl); The substituted thebaine derivatives (formula (II)) or thebaine are converted into the corresponding 14-hydroxycodeinones according to formula III



wherein

R is as defined above or being hydrogen,

by reaction with performic acid (s. Schmidhammer et al., *Helv.Chim.Acta*, Vol.

71:1801-1804, 1988) or m-chloroperbenzoic acid at a temperature between 0 and 60

°C. The preferred procedure is the reaction with performic acid at 0-10 °C (H.

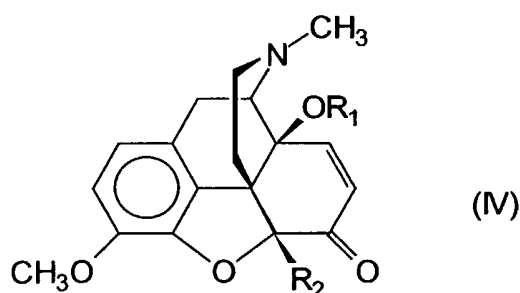
Schmidhammer et al., *Helv.Chim.Acta*, Vol. 71:1801-1804, 1988). These 14-

hydroxycodeinones being treated with dialkyl sulfates, alkyl halides, alkenyl halides,

aralkyl halides, arylalkenyl halides, chloroformates, in solvents such as N,N-dimethyl

formamide or tetrahydrofurane using a strong base such as sodium hydride,

potassium hydride or sodium amide giving compounds of formula (IV),



wherein

R₁ is C₁-C₆ alkyl, C₁-C₆ alkenyl, C₇-C₁₆ arylalkyl wherein the aryl is C₆-C₁₀ aryl and the

alkyl is C₁-C₆ alkyl, C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is

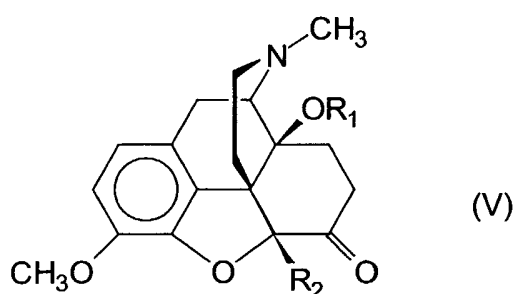
C₁-C₆ alkenyl, C₁-C₆ alkanoyl, C₇-C₂₀ arylalkanoyl wherein the aryl is C₆-C₁₄ aryl and

the alkyl is C₁-C₆ alkyl, C₇-C₂₀ arylalkenoyl wherein the aryl is C₆-C₁₄ aryl and the alkyl

is C₁-C₆ alkenoyl;

R_2 is hydrogen; C_1 - C_6 alkyl; C_1 - C_6 alkenyl C_7 - C_{16} arylalkyl wherein the aryl is C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkyl; C_7 - C_{16} arylalkenyl wherein the aryl is C_6 - C_{10} aryl and the alkenyl is C_1 - C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1 - C_6 alkoxy and the alkyl is C_1 - C_6 alkyl; $CO_2(C_1$ - C_6 alkyl);

which in turn are reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal and solvents such as methanol, ethanol or glacial acetic acid to give compounds of formula (V)

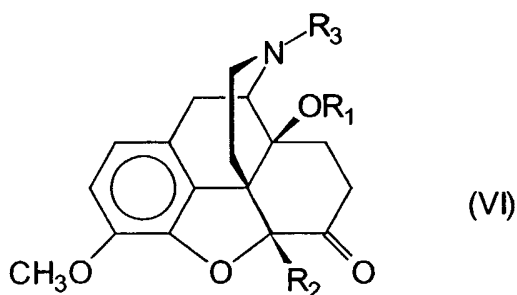


wherein

R_1 is C_1 - C_6 alkyl, C_7 - C_{16} arylalkyl wherein the aryl is C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_7 - C_{16} arylalkanoyl wherein the aryl is C_6 - C_{10} aryl and the alkanoyl is C_1 - C_6 alkanoyl; and

R_2 is hydrogen; C_1 - C_6 alkyl, C_1 - C_6 alkenyl C_7 - C_{16} arylalkyl wherein the aryl C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkyl; C_7 - C_{16} arylalkenyl wherein the aryl is C_6 - C_{10} aryl and alkenyl is C_1 - C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1 - C_6 alkyl; $CO_2(C_1$ - C_6 alkyl);

Thereafter N-demethylation can be carried out using chloroformates or cyanogen bromide to give intermediates of formula (VI)

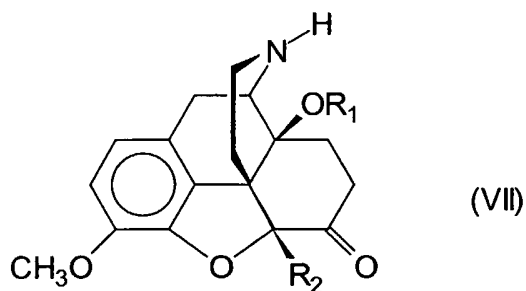


wherein

R_1 and R_2 are as defined above in formula (IV); and

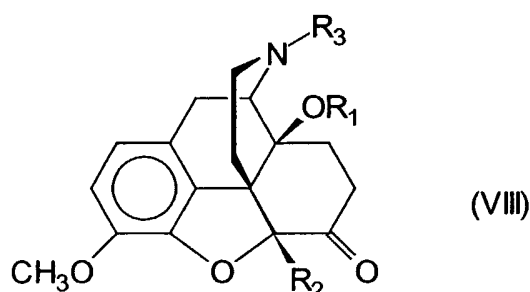
R_3 is $\text{CO}_2\text{CHClCH}_3$, $\text{CO}_2\text{CH}=\text{CH}_2$, $\text{CO}_2\text{CH}_2\text{CCl}_3$, $\text{CO}_2\text{CH}_2\text{CH}_3$, CO_2Ph , CN or the like.

The intermediate carbamates of formula (VI) can be cleaved by refluxing in alcohols (in the case of 1-chloroethyl carbamates), by addition of hydrogen halides or halogen and subsequent refluxing in alcohols (in the case of vinyl carbamates), or by reductive cleavage using zinc in glacial acetic acid or methanol (in the case of 2,2,2-trichloroethyl carbamates). Other carbonates may be cleaved using aqueous acid, alkali or hydrazine. The intermediate cyanamides of formula (VI) can be cleaved by acid hydrolysis. Alkylation of the corresponding N-nor derivatives of formula (VII)



wherein

R_1 and R_2 are as defined above in formula (V), can be accomplished with alkenyl halides, cycloalkylalkyl halides, cycloalkenylalkyl halides, aralkyl halides, arylalkenyl halides, in solvents such as dichloromethane, chloroform, or *N,N*-dimethyl formamide in the presence of a base such as sodium hydrogen carbonate or potassium carbonate to yield derivatives of formula (VIII)

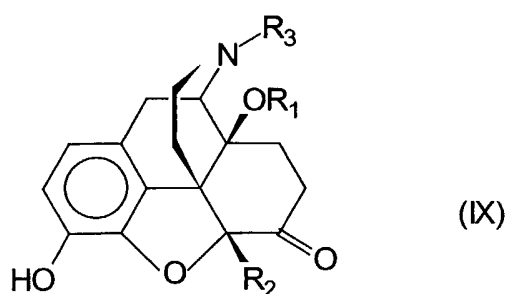


wherein

R_1 and R_2 are as defined above in formula (V); and

R₃ represents C₁-C₆ alkenyl; C₇-C₁₆ arylalkyl wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl; C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₁-C₆ alkenyl; C₄-C₁₀ cycloalkylalkyl wherein the cycloalkyl is C₃-C₆ cycloalkyl and the alkyl is C₁-C₄ alkyl; C₄-C₁₀ cycloalkylalkenyl wherein the cycloalkenyl is C₃-C₆ cycloalkenyl and the alkyl is C₁-C₄ alkyl;

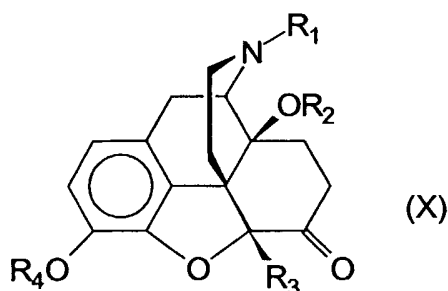
Ether cleavage can be carried out using boron tribromide (in a solvent such as dichloromethane or chloroform at about 0 °C), 48 % hydrobromic acid (reflux), or other well known reagents for ether cleavage. The resulting phenols of formula (IX)



wherein

R₁, R₂ and R₃ are as defined above,

are being alkylated using alkyl halides, alkyl sulfates, sulfonic acid esters, aralkyl halides, arylalkenyl halides or acylated using carbonic acid chlorides, or carbonic acid esters to yield compounds of formula (X)



wherein

R₁, R₂ and R₃ are as defined above; and

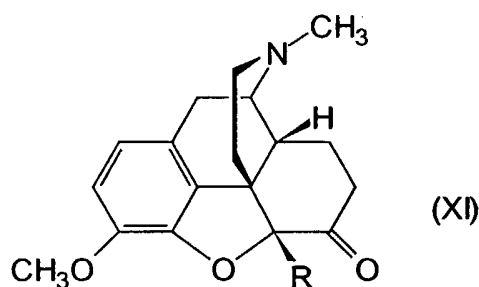
R₄ is hydrogen, C₁-C₆ alkyl, C₇-C₁₆ arylalkyl wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl, C₁-C₆ alkenyl, C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₁-C₆ alkenyl; C₁-C₆ alkanoyl, C₇-C₁₆ arylalkanoyl wherein the aryl is C₆-

C₁₀ aryl and the alkanoyl is C₁-C₆ alkanoyl, C₂-C₁₀ alkyloxyalkyl wherein alkyloxy is C₁-C₄ alkyloxy and alkyl is C₁-C₆ alkyl.

Compounds of the formula (I) wherein R₂ is hydroxy may be obtained from compounds of formula (III) wherein R is defined as above. These compounds may be reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal and solvents such as methanol, ethanol, or glacial acetic acid to give compounds of the formula (V) wherein R₁ is hydrogen and R₂ is defined for R in formula (II).

The following reaction sequence and procedures leading to compounds of formulas (VI), (VII), (VIII), (IX) and (X) wherein the substituent in position 14 is hydroxy and the other substituents are defined as above, is analogous to the reaction sequence and procedures described above. Further conversion to compounds of the formula (I) wherein R₂ is hydroxy is described below.

Compounds of the formula (I) wherein R₂ is hydrogen may be obtained from compounds of the formula (II) wherein R is as defined above or hydrogen. Catalytic hydrogenation followed by acid hydrolysis (s. Boden et al., J. Org. Chem. Vol. 47:1347-1349, 1982) may provide compounds of formula (XI)



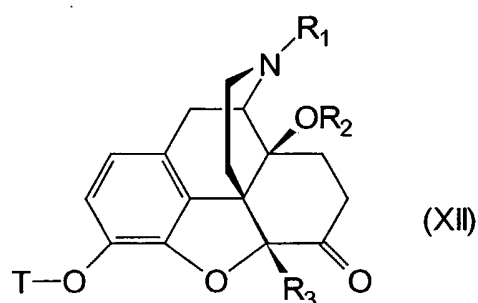
(XIa): R=H (dihydrocodeinone)

wherein R is as defined above in formula (II) or hydrogen.

Compounds of the formula (XI) and (XIa) (Mannich and Löwenheim, Arch.Pharm.Vol. 258:295, 1920) can be converted into compounds of formulas (V), (VI), (VII), (VIII), (IX), and (X) wherein the substituent in position 14 is hydrogen and R₂ and R₃ are as

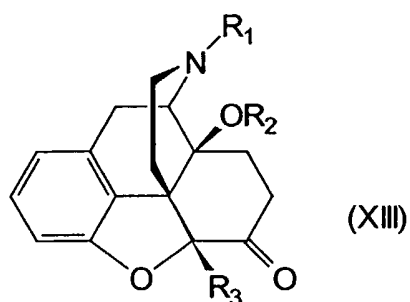
defined above, similarly as outlined above. Further conversion into compounds of the formula (I) wherein R_2 is hydrogen is described below.

Compounds of the formula (I) wherein R_4 is hydrogen may be prepared from compounds of the formula (IX) by alkylation with 5-chloro-1-phenyl- 1H -tetrazole to give the corresponding phenyltetrazolyl ethers of the formula (XII)



wherein R_1 , R_2 and R_3 are as defined above and R_1 also can be CH_3 , and T is phenyltetrazolyl.

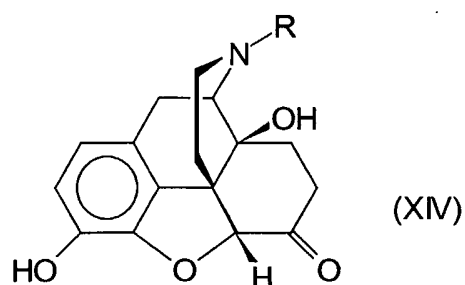
Catalytic hydrogenation may afford (H. Schmidhammer et al., J. Med. Chem. Vol. 27:1575-1579, 1984) compounds of the formula (XIII)



wherein R_1 , R_2 and R_3 are as defined above and R_1 also can be CH_3 ;

In the case R_1 is CH_3 , the N-methyl group has to be removed and the nitrogen alkylated as described above.

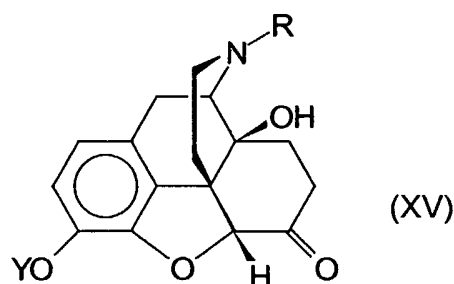
Alternatively, compounds of formula (I) wherein R_1 represents allyl or cyclopropylmethyl and R_3 represents H can be obtained by a shorter route starting either from naloxone (XIVa) or naltrexone (XIVb).



(XIVa): Naloxone - R is allyl

(XIVb): Naltrexone - R is cyclopropylmethyl.

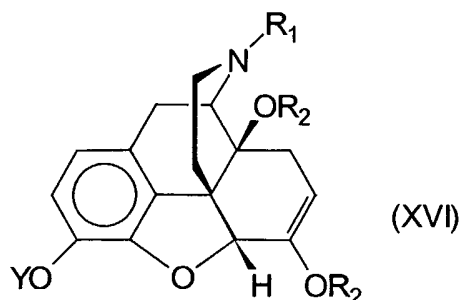
The 3-hydroxy group of compounds of formula (XIV) is being protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxymethyl bromide or trityl chloride (triphenylmethyl chloride) in a solvent such as N,N-dimethyl formamide or dichloromethane in the presence of a base to yield compounds of formula (XV)



wherein

R is allyl or cyclopropylmethyl and Y = CH_2Ph , CH_2OCH_3 , $\text{CH}_2\text{OC}_2\text{H}_5$ or $\text{C}(\text{Ph})_3$.

These compounds are alkylated, alkenylated, cycloalkylalkylated, arylalkylated or arylalkenylated with dialkyl sulfates, alkyl halides, alkenyl halides, arylalkyl halides or arylalkenyl halides in solvents such as N,N-dimethyl formamide or tetrahydrofuran using a strong base such as sodium hydride, potassium hydride or sodium amide. The resulting 6-O,14-O-dialkylated compounds of formula (XVI)

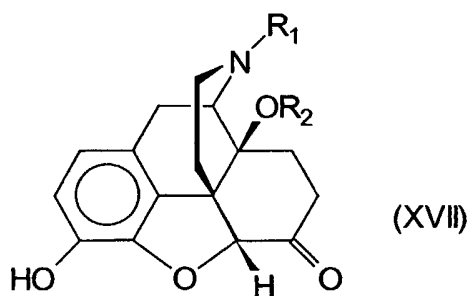


wherein

R_1 is allyl or cyclopropylmethyl; and

R_2 is C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_7 - C_{16} arylalkyl wherein the aryl is C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkoxy, C_7 - C_{16} arylalkenyl wherein the aryl is C_6 - C_{10} aryl and alkenyl is C_1 - C_6 alkenyl; and Y as defined above;

can be hydrolyzed with diluted acids like hydrochloric acid or sulfuric acid to afford compounds of formula (XVII)



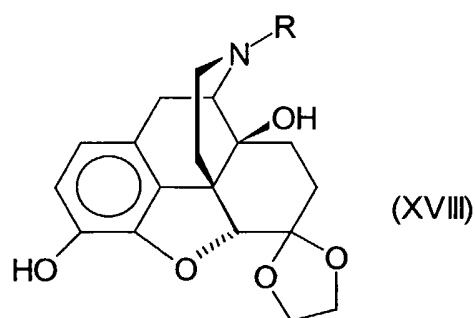
wherein

R_1 is allyl or cyclopropylmethyl; and

R_2 is as defined above (formula XVI).

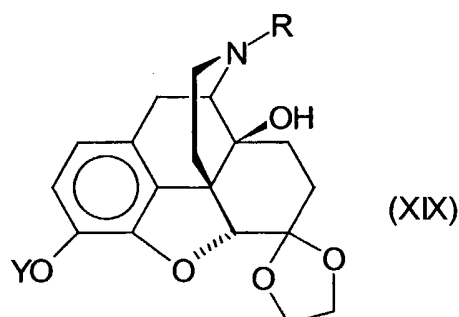
In the case R_2 is alkenyl or arylalkenyl the double bond may be reduced by catalytic hydrogenation to afford the corresponding saturated derivatives. Further conversion into compounds of formula (I) is described below.

Alternatively, compounds of formula (I) wherein R_1 represents allyl or cyclopropylmethyl and R_3 represents H can be prepared also via the following route: The carbonyl group in position 6 of naloxone (XVa) and naltrexone (XVb), respectively, is being protected by reaction with ethylene glycol in the presence of an acid (e.g. methanesulfonic acid) at temperatures between 20 and 200 °C to give ketals of formula (XVIII)



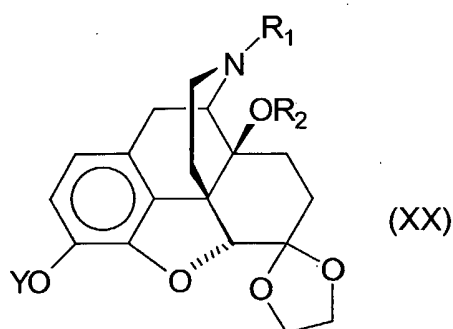
wherein R is allyl or cyclopropylmethyl.

The 3-hydroxy group of these ketals is being protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxymethyl bromide or trityl chloride in a solvent such as N,N-dimethyl formamide or dichloromethane in the presence of a base to yield compounds of formula (XIX)



wherein R is allyl or cyclopropylmethyl and Y is as defined above.

These compounds are alkylated, alkenylated, arylalkylated or arylalkenylated with dialkyl sulfates, alkyl halides, alkenyl halides, arylalkyl halides or arylalkenyl halides in solvents such as N,N-dimethyl formamide or tetrahydrofuran using a strong base such as sodium hydride, potassium hydride or sodium amide. The resulting compounds of formula (XX)



wherein R_1 is allyl or cyclopropylmethyl, R_2 is as defined above (formula (XVI)) and Y is as defined above

can be hydrolyzed in diluted acids like hydrochloric acid or sulfuric acid (a typical mixture for hydrolysis is: concentrated HCl: MeOH: H₂O 3/6/1 v/v/v) to afford compounds of formula (XVII). Compounds of formula (I) wherein R_1 represents allyl or cyclopropyl-ethyl, R_3 represents H, and X represents NH or O can be prepared from compounds of formula (XVII) as described below.

Compounds of the formula (I) wherein R_3 is as defined above and X represents NH are obtained by reaction of compounds of formula (VIII), (X) or (XIII) with phenylhydrazine or substituted phenylhydrazine in solvents such as methanol, ethanol or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr.

Phenylhydrazine substituted at the aromatic ring with hydroxy, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, nitro, cyano, thiocyanato, trifluoromethyl, CO₂H, CO₂ (C₁-C₆) alkyl, CONH₂, CONH (C₁-C₆ alkyl), CON (C₁-C₆ alkyl)₂, SO₂NH₂, SO₂ (C₁-C₆) alkyl or the like may be employed. The reaction may be carried out at a temperature between 20 and 160 °C, preferably between 20 and 80 °C.

Compounds of formula (I) wherein R_3 is as defined above and X represents O are obtained by reaction of compounds of formula (VIII), (IX), (X) or (XIII) with O-phenylhydroxyl amine or substituted (at the aromatic ring) O-phenylhydroxyl-amine in solvents such as methanol ethanol, or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr. O-phenylhydroxylamine substituted at the aromatic ring with hydroxy, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, amino, nitro, cyano, thiocyanato, trifluoromethyl, CO_2H , CO_2 (C_1 - C_6) alkyl, $CONH_2$, $CONH$ (C_1 - C_6 alkyl), CON (C_1 - C_6 alkyl) $_2$, SO_2NH_2 , SO_2 (C_1 - C_6) alkyl or the like may be employed.

The invention will now be described in more detail by the following examples which are not to be construed as limiting the invention.

Examples

Example 1

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 1).

A mixture of 14-O-ethyl-5-methylnaltrexone (H. Schmidhammer et al, *Helv. Chim. Acta*, Vol. 76: 476-480, 1993) (580 mg, 1.51 mmol), phenylhydrazine hydrochloride (394 mg, 2.72 mmol), and 7 ml of glacial acetic acid was refluxed for 23 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x30 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and evaporated. The remaining residue (615 mg brownish foam) was dissolved in little MeOH and Et_2O/HCl was added. Thus, 550 mg (95%) of the compound 1 were isolated. For analysis a small amount was recrystallized from MeOH. m.p. > 260°C (dec.) IR (KBr): 3200 (^+NH , NH, OH) cm^{-1} . CI-MS:m/z 457 ($M^+ + 1$). 1H -NMR ($(d_6)DMSO$): δ 11.34, 9.21. and 8.55 (3 s, ^+NH , NH, OH), 7.32 (m, 2 arom. H), 7.08 (t, J = 8.1 Hz, 1 arom. H), 6.94 (t, J = 8.1 Hz, 1 arom. H), 6.62 (d, J = 8.1 Hz, 1 arom. H); 6.55 (d, J = 8.1 Hz, 1 arom. H), 1.86 (s, $CH_3-C(5)$), 1.01 (t, J = 6.8 Hz, 3H, CH_3CH_2O). Analysis calculated for $C_{29}H_{32}N_2O_3 \cdot HCl \cdot H_2O$ (511.06): C 68.16, H 6.90, N 5.48, Cl 6.94; found: C 67.87, H 6.88, N 5.30, Cl 7.28.

Example 2

Synthesis of 17-Allyl-6,7-dihydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 2).

A mixture of 14-O-ethyl-5-methylnaloxone (H. Schmidhammer et al., *Helv. Chim. Acta* Vol. 76:476-480, 1993) (1.2g, 2.66 mmol), phenylhydrazine hydrochloride (577 mg, 3.99 mmol), and 15 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x80 ml, 1x30 ml). The combined organic layers were washed with H_2O (3x80 ml, 1x30 ml), dried over Na_2SO_4 and evaporated. The residue (1.3 g yellow-brown foam) was purified with column chromatography (alumina basic grade IV, elution with CH_2Cl_2). The corresponding fractions were combined and evaporated to give a colorless oil which was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to yield 200 mg (17%) of the title compound 2. M.p. 168-170°C. IR (KBr): 3200($^+\text{NH}, \text{OH}$) cm^{-1} . CI-MS: M/z 443 ($\text{M}^+ + 1$). $^1\text{H-NMR}$ (CD_3OD):

δ 7.39 (dd, J=7.8, 7.8 HZ, 2 arom. H), 7.14 (t, J=7.8 hz, 1 arom.H), 7.01 (t=7.8 HZ, 1 arom. H), 6.67 (s, 2 arom. H), 6.02 (m, 1 olef. H), 5.72 (m, 2 olef. H), 1.99 (s, $\text{CH}_3\text{-C}(5)$), 1.09 (t, J=6.8 Hz, CH_3). Analysis calculated for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_3 \cdot \text{HCl} \cdot 1.5 \text{H}_2\text{O}$ (506.05): C 66.46, H 6.77 N 5.54, Cl 7.01; found: C 66.55, 6.68, N 5.39, Cl 6.98.

Example 3

Synthesis of 6,7-Dehydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan hydrochloride (compound 5).

A mixture of 4,5 α -epoxy-14-ethoxy-3-methoxy-5-methylmorphinan-6-one hydrochloride (H. Schmidhammer et al., *Helv. Chim. Acta* Vol. 76, 476-480, 1993) (3.0 g, 7.88 mmol), potassium carbonate (3.9 g, 28.2 mmol), 2-phenylethyl bromide (1.41 ml, 10.4 mmol), and of 20 ml anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 2h. After cooling and addition of 130 ml of H₂O, the mixture was extracted with diethyl ether (3x60 ml). The combined organic layers were washed with H₂O (3x70 ml), dried over Na₂SO₄ and evaporated. The residue (3.6 yellow oil) was crystallized from MeOH to afford 2.1 g (70%) of 4,5 α -epoxy-14-ethoxy-3-methoxy-5-methyl-17-(2-phenyl)ethylmorphinan-6-one (compound 3). M.p. 86-89°C. IR (KBr): 1725 (CO) cm⁻¹. CI-MS: m/z 448 (M⁺+1). ¹H-NMR (CDCl₃): δ 7.21 (m, 5 arom. H), 6.64 (d, J=8.2 Hz, 1 arom. H), 6.54 (d, J=8.2 Hz, 1 arom. H.), 3.85 (s, OCH₃), 1.60 (s, CH₃-C(5)), 1.12 (t, J=6.8 Hz, CH₃). Analysis calculated for C₂₈H₃₃NO₄ (447.55): C 75.14, H 7.43, N 3.13; found: C 75.04, H 7.69, N 3.26.

A solution of the compound 3 (1.5 g, 3.35 mmol) in 5 ml of 48% HBr was refluxed for 30 min and then evaporated. The residue was dissolved in MeOH and again evaporated (this procedure was repeated twice) to give a grey crystalline residue (1.7 g) which was treated with hot MeOH to yield 950 mg (63%) of the compound 4. M.p. >270°C. IR (KBr): 1720 (CO) cm⁻¹. CI-MS: m/z 434 (M⁺+1). ¹H-NMR (DMSO-d₆): δ 9.38 and 8.48 (2 s, ^{*}NH, OH), 7.33 (m, 5 arom. H), 6.68 (d, J=8.2 Hz, 1 arom. H), 6.64 (d, J=8.2 Hz, 1 arom. H), 1.51 (s, CH₃-C(5)), 1.34 (t, J=6.8 Hz, CH₃). Analysis calculated for C₂₇H₃₁NO₄. HBr (514.45): C 63.04, H 6.27, N 2.72, Br 15.53; found: C 63.15, H 6.48, N 2.61, Br 15.37.

A mixture of the compound 4 (700 mg, 1.61 mmol), phenylhydrazine hydrochloride (513 mg), 3.54 mmol), and 15 ml of glacial acetic acid was refluxed for 6 h. The reaction mixture was poured on ice, alkalized with conc. NH₄OH and extracted with CH₂Cl₂ (3x80 ml, 1x30 ml). The combined organic layers were washed with H₂O (3x80 ml), dried over Na₂SO₄ and evaporated. The residue (600 mg slightly brown foam)

was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to yield 360 mg (51%) of the title compound 5 as slightly pink crystals. M.p. >225°C. IR (KBr): 3400 and 3200 (ν NH, NH, OH). CI-MS: m/z 507 ($M^+ + 1$). $^1\text{H-NMR}$ (DMSO- d_6): δ 11.34, 9.19 and 8.97 (ν NH, NH, OH), 7.34 (m, 7 arom. H), 7.08 (t, J=7.9 Hz, 1 arom.), 6.94 (t, J=7.9 Hz, 1 arom. H), 6.62 (d, J=8.4 Hz, 1 arom. H), 6.57 (d, J=8.4 Hz, 1 arom. H), 1.87 (s, CH₃-C(5)), 0.96 (t, J=6.9 Hz, CH₃). Analysis calculated for C₃₃H₃₄N₂O₃ · HCl · 2 H₂O (579.14): C 68.44, H 6.79, N 4.84, Cl 6.12; found: C 68.81, H 6.55, N 4.72, Cl 6.40.

Example 4

Synthesis of 17-Allyl-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 6).

A mixture of 14-O-methyl-5-methylnaloxone (H. Schmidhammer et al., *Helv. Chim. Acta* Vol. 77:1585-1589, 1994) (1.0 g, 2.8 mmol), phenylhydrazine hydrochloride (728 mg, 5.04 mmol), and 15 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH₄OH and extracted with CH₂Cl₂ (3x80 ml, 1x30 ml). The combined organic layers were washed with H₂O (3x80 ml), dried over Na₂SO₄ and evaporated. The residue (1.1 g brownish foam) was converted in the usual way into the hydrochloride salt and crystallized from acetone to yield 190 mg (19%) of the title compound 6 as slightly brown crystals. M.p. >280°C. IR (KBr): 3200 (ν NH, NH, OH), $^1\text{H-NMR}$: δ 7.32 (dd, J=7.9, 7.9 Hz, 2 arom. H), 7.06 (t, J=7.9 Hz, 1 arom. H), 6.93 (t, J=7.9 Hz, 1 arom. H), 6.63 (d, J=8.2 Hz, 1 arom. H), 6.55 (d, J=8.2 Hz, 1 arom. H), 6.02 (m, 1olef.H), 5.63 (m, 1 olef. H), 3.15 (s, OCH₃), 2.07 (s, CH₃-C(5)). Analysis calculated for C₂₇H₂₈N₂O₃ · HCl · 1.7 H₂O · 0.9 MeOH (524.44): C 64.41, H 7.09, N 5.22; found: C 64.44, H 6.87, N 4.94.

Example 5

Synthesis of 6,7-Dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan Hydrochloride (compound 9).

A mixture of 4,5 α -epoxy-3,14-dimethoxy-5-methylmorphinan-6-one hydrochloride (H. Schmidhammer et al., *Helv. Chim. Acta* Vol. 77:1585-1589, 1994) (2.24 g, 6.12 mmol), potassium carbonate (3.0 g, 21.9 mmol), 2-phenylethyl bromide (1.05 ml, 7.74 mmol), and 15 ml of anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 2 h. After cooling and addition of 110 ml of H₂O, the mixture was extracted with diethyl ether (3x60 ml). The combined organic layers were washed with H₂O (3x70 ml), dried over Na₂SO₄ and evaporated. The residue (2.9 yellow oil) was converted into the hydrobromide salt in the usual way and crystallized from MeOH to give 1.4 g (63%) of 4,5 α -epoxy-3,14-dimethoxy-5-methyl-17-(2-phenyl)ethylmorphinan-6-one hydrobromide (compound 7) as colorless crystals. A small portion of this material was recrystallized from MeOH for analyses. M.p. 94-96°C. IR (KBr): 3400 (ν NH), 1720 (CO) cm⁻¹. CI-MS: m/z 434 (M⁺+1). ¹H-NMR (DMSO-d₆) δ 10.15 (s, ν NH), 7.30 (m, 5 arom. H), 6.74 (d, J=8.2 Hz, 1 arom. H), 6.68 (d, J=8.2 Hz, 1 arom.), 3.87 (s, OCH₃-C(3)), 3.58 (s, OCH₃-C(14)), 1.60 (s, CH₃-C(5)). Analysis calculated for C₂₇H₃₁NO₄. HBr (514.44): C 63.04, H 6.27, N 2.72; found: C 63.18, H 6.60, N 2.39.

A solution of the compound 7 (1.4 g, 3.32 mmol) in 5 ml of 48% HBr was refluxed for 30 min and then evaporated. The residue was dissolved in MeOH and again evaporated (this operation was repeated once) to afford a brownish crystalline residue (1.8 g) which was treated with hot MeOH to yield 590 mg (42%) of the compound 8.HBr. A small portion was recrystallized for analyses. M.p.>316°C. IR (KBr):3400 (ν NH, OH), 1722 (CO)cm⁻¹. CI-MS: m/z 420 (M⁺+1). ¹H-NMR (DMSO-d₆) δ 8.95 and 8.45 (2s, ν NH,OH), 6.90 (m, 5 arom. H), 6.23 (dd, J=8.2, 8.2 Hz, 2 arom. H), 2.97 s, OCH3), 1.08 (s, CH₃-C(5)). Analysis calculated for C₂₆H₂₉NO₄. HBr. 0.2 MeoH (506.85): C 62.09, H 6.13, N 2.76, Br 16.77; found: C 61.79, H 6.18, N 2.63, Br 16.12.

A mixture of the compound 8. HBr (468 mg, 0.93 mmol), phenylhydrazine hydrochloride (343 mg, 2.36 mmol), and 15 ml of glacial acetic was refluxed for 7 h. After cooling, the reaction mixture was poured on ice, alkalized with con. NH₄OH and extracted with CH₂Cl₂ (3x70 ml, 1x30 ml). The combined organic layers were washed with H₂O (3x80 ml), dried over Na₂SO₄ and evaporated. The residue (410 mg slightly brown foam) was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to give 390 mg (83%) of the title compound 9 as slightly pink crystals. An analytic sample was obtained by recrystallization of a small

portion of this material from MeOH/diethyl ether. M.p. 257-260°C (dec.). IR (KBr): 3460 (ν NH, NH, OH) cm^{-1} . CI-MS: m/z 493 ($M^+ + 1$). $^1\text{H-NMR}$ (DMSO- d_6) δ 11.30, 9.20 and 9.05 (3 s, ν NH, NH, OH), 7.25 (m, 7 arom. H), 7.10 (t, $J=8.2$ Hz, 1 arom. H), 6.96 (t, $J=8.2$ Hz, 1 arom. H), 6.59 (dd, $J=8.2, 8.2$ Hz, 2 arom. H), 3.32 (s, OCH₃), 1.87 (s, CH₃-C(5)). Analysis calculated for C₃₂H₃₂N₂O₃·HCl·3.7 MeOH (647.63): C 66.21, H 7.44, N 4.33; found: C 66.04, H 7.13, N 4.60.

Example 6

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan Hydrochloride (compound 10).

A mixture of 14-O-methyl-5-methylnaltrexone (H.Schmidhammer et al., *Helv. Chim. Acta* Vol. 77: 1585-1589, 1994) (620 mg, 1.68 mmol), phenylhydrazine hydrochloride (365 mg, 2.52 mmol), and 7 ml of glacial acetic acid was refluxed for 17.5 h. After cooling, the reaction mixture was poured on ice, alkalized with NH₄OH and extracted with CH₂Cl₂ (3x70 ml, 1x20 ml). The combined organic layers were washed with H₂O (3x80 ml), dried over Na₂SO₄ and evaporated. The residue (1.11 g brown foam) was purified by column chromatography (silica gel 230-400 mesh, mobile phase CH₂Cl₂/MeOH 90:9). The corresponding fractions were combined and evaporated to afford a slightly yellow foam which was dissolved in MeOH and treated with ethereal HCl to yield 520 mg (65%) of the compound 10 as colorless crystals. For analyses a small sample was recrystallized from MeOH. M.p. >250°C (dec.). IR (KBr): 3515 and 3220 (ν NH, NH, OH) cm^{-1} . CI-MS: m/z 443 ($M^+ + 1$). $^1\text{H-NMR}$ (DMSO- d_6): δ 11.30, 9.12, 8.93 (3 s, ν NH, NH, OH), 7.34 (m, 2 arom. H), 7.09 (t, $J=8.3$ Hz, 1 arom. H), 6.95 (t, $J=8.3$ Hz, 1 arom. H), 6.63 (d, $J=8.1$ Hz, 1 arom. H), 6.56 (d, $J=8.1$ Hz, 1 arom. H), 3.24 (s, OCH₃), 1.87 (s, CH₃-C(5)). Analysis calculated for C₂₈H₃₀N₂O₃·HCl·0.7 H₂O (491.67): C 68.41, H 6.64, N 5.70, Cl 7.21; found: C 68.52, H 6.86, N 5.65, Cl 7.48.

Example 7

Synthesis of 17-Allyl-6,7-dehydro-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2',3'-indolomorphinan. CH₃SO₃H (compound 15).

A mixture of 7,8-dihydro-5-methyl-14-n-propyloxycodeinone (9; 2.67 g, 7.19 mmol), KHCO₃ (3.6 g, 35.93 mmol), 1-chloroethyl chloroformate (4.73 ml, 43.12 mmol), and 35 ml of 1,2-dichloroethane was stirred under reflux for 3.5 h. After cooling, the inorganic material was filtered off and the filtrate evaporated. The residue (4.67 g of a yellowish oil of 17-(1-chloroethoxy)- carbonyl-4,5 α -epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 11); pure by TLC) was not further purified and characterized. A solution of the compound 11 in MeOH was refluxed for 1 h and then evaporated. The residue (3.54 g slightly brown foam) was crystallized from 2.5 ml MeOH/2 ml diethyl ether to give 1.68 g (66%) of 4,5 α -epoxy-3-methoxy-5-methyl-14-n-propyloxy-morphinan-6-one hydrochloride (compound 12). M.p. 186-188°C. IR (KBr): 3425 (⁺NH₂), 1725 (CO)cm⁻¹. EI-MS: m/z 357 (M⁺). ¹H-NMR (DMSO-d₆): σ 10.11 and 8.15 (2 broad s, ⁺NH₂), 6.83 (d, J=8.2 Hz, 1 arom. H), 6.74 (d, J=8.2 Hz, 1 arom. H), 3.78 (s, CH₃O), 1.48 (s, CH₃-C(5)), 0.95 (t, J=7.4 Hz, CH₃). Analysis calculated for C₂₁H₂₇NO₄. HCl. 0.6 MeOH (413.14): C 62.80, H 7.42, N 3.39, Cl 8.58; found: C 62.66, H 7.34, N 3.40, Cl 8.98. A mixture of the compound 12 (1.45 g, 3.68 mmol), allyl bromide (0.36 ml, 4.06 mmol), potassium carbonate (2.9 g, 20.8 mmol), and 10 ml of anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 1.5 h. The inorganic solid was filtered off and the filtrate evaporated to give 1.7 g of a yellowish oily residue. This residue was partitioned between CH₂Cl₂ and H₂O. The organic layer was washed with H₂O and brine, dried over Na₂SO₄ and evaporated. The residue (1.375 g of a slightly yellow oil) was crystallized from ethanol to yield 1.28 g (88%) of 17-allyl-4,5 α -epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 13) as slightly yellow crystals. M.p. 122-124°C. IR(KBr): 1720 (CO)cm⁻¹. EI-MS: m/z 397 (M⁺). ¹H-NMR (CDCl₃): δ 6.63 (d, J=8.3 Hz, 1 arom. H), 6.55 (d, J=8.3 Hz, 1 arom. H), 5.79 (m, 1 olef. H), 5.13 (m, 2 olef. H), 3.84 (s, OCH₃), 1.60 (s, CH₃-C(5)), 1.00 (t, J=7.4 Hz, CH₃). Analysis calculated for C₂₄H₃₁NO₄ (397.51): C 72.52, H 7.86, N 3.52; found: C 72.14, H 7.76, N 3.44. A 1 M solution of boron tribromide in CH₂Cl₂ (10.8 ml) was added to an ice-cooled solution of the compound 13 (577 mg, 1.45 mmol) in 75 ml of CH₂Cl₂ at once. After stirring at 0-5°C for 2 h, a mixture of 20 g

ice and 4 ml of conc. NH_4OH was added. The resulting mixture was stirred at room temperature for 30 min and the extracted with CH_2Cl_2 (3x50 ml). The combined organic layers were washed with brine (70 ml), dried over Na_2SO_4 and evaporated. The residue (600 mg brownish foam) was converted into the hydrobromide salt in the usual way and crystallized from MeOH to afford 314 mg (47%) of 17-allyl-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxymorphinan-6-one hydrobromide (compound 14). M.p. 244-247°C (dec.). IR (KBr): 3441 and 3332 (^+NH , OH), 6.68 (d, $J=8.2$ Hz, 1 arom. H), 6.62 (d, $J=8.2$ Hz, 1 arom. H), 5.92 (m, 1 olef. H), 5.67 (m, 2 olef. H), 1.49 (s, $\text{CH}_3\text{-C}(5)$), 0.96 (t, $J=7.2$ Hz, CH_3).

A mixture of the compound 14 (300 mg, 0.65 mmol), phenylhydrazine hydrochloride (187 mg, 1.29 mmol), and 30 ml of glacial acetic acid was refluxed for 7.5 h. After cooling, the reaction mixture was poured on ice, alkalinized with conc. NH_4OH and extracted with CH_2Cl_2 (3x60 ml). The combined organic layers were washed with H_2O (3x80 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated. The residue (325 mg brownish foam) was converted into the methane sulfonate in the usual way and recrystallized from MeOH/diethyl ether to yield 264 mg (74%) of the title compound 15. Recrystallization of a small portion of this material from ethanol afforded an analytical sample. M.p. >256°C. FAB-MS: m/z 457 (M^++1), $^1\text{H-NMR}$ (DMSO-d_6): δ 11.29, 9.17 and 8.45 (3 s, ^+NH , NH, OH), 7.32 (d, $J=8.2$ Hz, 2 arom. H), 7.10 (t, $J=8.2$ Hz, 1 arom. H), 6.94 (t, $J=8.2$ Hz, 1 arom. H), 6.59 (s, 2 arom. H), 5.90 (m, 1 olef. H), 5.68 (m, 2 olef. H), 1.88 (s, $\text{CH}_3\text{-C}(5)$), 0.55 (t, $J=7.3$ Hz, CH_3). Analysis calculated for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_3\text{H} \cdot 0.5 \text{H}_2\text{O}$ (561.70): C 64.15, H 66.4, N 4.99, S 5.72; found: C 64.08, H 6.87, N 5.09, S 5.87.

Example 8

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2,3'-indolomorphinan. $\text{CH}_3\text{SO}_3\text{H}$ (compound 18).

A mixture of 4,5 α -epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one hydrochloride (compound 12 of Example 7) (1.46 g, 3.71 mmol), potassium carbonate (2.24 g, 16.24 mmol), cyclopropylmethyl chloride (0.43 ml, 4.44 mmol), and 15 ml of anhydrous N,N-dimethyl formamide was stirred at 85°C (bath temperature) for 36 h.

The inorganic solid was filtered off and the filtrate evaporated. A solution of the residue in 30 ml of CH_2Cl_2 was washed with H_2O (3x30 ml), dried over Na_2SO_4 and evaporated. The residue (1.69 g orange-yellow oil) was dissolved in diethyl ether and treated with ethereal HCl to give 920 mg (55%) of 17-(cyclopropylmethyl)-4,5 α -epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one hydrochloride (compound 16) as colorless powder. M.p. 156-158°C. IR (KBr): 3400 ($^*\text{NH}$), 1723 (CO) cm^{-1} . CI-MS: m/z 412 (M^++1). $^1\text{H-NMR}$ (DMSO-d_6): δ 8.57 (s, $^*\text{NH}$), 6.85 (d, $J=8.2$ Hz, 1 arom. H), 6.75 (d, $J=8.2$ Hz, 1 arom. H), 3.79 (s, OCH_3), 1.51 (s, $\text{CH}_3\text{-C}(5)$), 0.97 (t, $J=7.4$ Hz, CH_3). Analysis calculated for $\text{C}_{25}\text{H}_{33}\text{NO}_4 \cdot \text{HCl} \cdot 0.6 \text{H}_2\text{O}$ (458.81): C 65.45, H 7.73, N 3.05, Cl 7.73; found: C 65.45, H 7.85, N 3.08, Cl 7.84.

A 1 M solution of boron tribromide in CH_2Cl_2 (7.3 ml) was added at once to an ice-cooled solution of the compound 16 (480 mg, 0.97 mmol) in 50 ml of CH_2Cl_2 . After 50 min stirring at 0-5°C, a mixture of 13 g ice and 3 ml conc. NH_4OH was added. The resulting mixture was stirred at room temperature for 30 min and the extracted with CH_2Cl_2 (3x30 ml). The combined organic layers were washed with brine (45 ml), dried over Na_2SO_4 and evaporated. The residue (204 mg slightly brown foam) was treated with 0.5 ml hot MeOH to afford 302 mg (55%) of 17-(cyclopropylmethyl)-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 17). M.p. 184-186°C. IR (KBr): 3390 (OH), 1720 (CO) cm^{-1} . CI-MS: m/z 397 (M^++1). $^1\text{H-NMR}$ (CDCl_3): δ 10.24 (broad s, OH), 6.73 (d, $J=8.2$ Hz, 1 arom. H), 6.65 (d, $J=8.2$ Hz, 1 arom. H), 1.62 (s, $\text{CH}_3\text{-C}(5)$), 1.00 (t, $J=7.3$ Hz, CH_3). Analysis calculated for $\text{C}_{24}\text{H}_{31}\text{NO}_4 \cdot 0.6 \text{MeOH}$ (416.74): C 70.90, H 8.08, N 3.36; found: C 70.76, H 7.73, N 3.52.

A mixture of compound 17 (230 mg, 0.58 mmol), phenylhydrazine hydrochloride (142 mg, 0.98 mmol), and 23 ml of glacial acetic acid was refluxed for 3.5 h. After cooling, the reaction mixture was poured on ice, alkalized with con. NH_4OH and extracted with CH_2Cl_2 (3x40 ml). The combined organic layers were washed with H_2O 2x50 ml and brine (50 ml), dried and evaporated. The residue (262 mg yellow-brown foam) was converted in the usual way into the methane sulfonate and crystallized from MeOH /diethyl ether to yield 204 mg (62%) of the compound 18. M.p. 295-298°C (dec.) FAB-MS: m/z 471 (M^++1). $^1\text{H-NMR}$ (DMSO-d_6) δ 11.27, 9.12 and 8.46 (3s, $^*\text{NH}$, NH, OH), 7.14 (m, 4 arom. H), 6.59 (s, 2 arom. H), 1.90 (s, $\text{CH}_3\text{-C}(5)$), 0.67 (t, $J=7.3$ Hz,

CH₃) Analysis calculated for C₃₀H₃₄N₂O₃ · CH₃SO₃H · 1.5 H₂O (584.74): C 62.71, H 6.96, N 4.72, S 5.40; found: C 62.67, H 6.96, N 4.79, S 5.40.

Examples 9-24, and 28-30 illustrate further compounds, which can be prepared according to one of the methods described above.

Example 9

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 19).

M.p. 129-130°C. ¹H-NMR (CDCl₃): δ 7.45 (d, J = 8.3 Hz, 1 arom. H), 7.37 (d, J = 8.3 Hz, 1 arom. H), 7.25 (m, 1 arom. H), 7.16 (m, 1 arom.), 6.86 (d, J = 8.3 Hz, 1 arom. H), 6.60 (d, J = 8.3 Hz, 1 arom. H), 5.63 (s, H-C(5)), 5.17 and 5.06 (2 d, J = 6.6, 6.6 Hz, OCH₂O), 3.42 (s, CH₃O).

Example 10

17-Cyclopropylmethyl-6,7-dehydro-4,5 α -epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2',3'-(N-methoxymethylindolo)morphinan (compound 20).

¹H NMR (CDCl₃): δ 7.44 (m, 2 arom. H), 7.20 (m, 1 arom. H), 7.07 (m, 1 arom. H), 6.82 (d, J = 8 Hz, 1 arom. H), 6.58 (J = 8 Hz), 5.81 (s, H-C(5)), 5.79 and 5.50 (2 d, J = 10.8, 10.8 Hz, NCH₂O), 5.12 and 5.50 (2 d, J = 6.4, 6.4 Hz, OCH₂O), 3.41 and 3.33 (2 s, 2 CH₃O).

Example 11

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzoyloxy)-4,5 α -epoxy-14-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 21).

M.p. 180-182 °C. ¹H NMR (CDCl₃): δ 7.41 (d, J = 8.3 Hz, 1 arom. H), 7.33 (d, J = 8.3 Hz, 1 arom. H), 7.23 (m, 1 arom. H) 7.14 (m, 2 arom. H), 7.03 and 7.01 (2 d, J = 7.3, 7.3 Hz), 6.84 (d, J, 8.3 Hz, 1 arom. H) 6.59 (d, J = 8.3 Hz, 1 arom. H), 5.56 (s, H-C(5)), 5.32 and 4.68 (2 d, J = 8.7, 8.7 Hz, OCH₂Ar), 5.16 and 5.05 (2 d, J = 6.6, 6.6 Hz, OCH₂O), 3.41 (s, CH₃O).

Example 12

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzoyloxy)-4,5 α -epoxy-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan (compound 22).

M.p. 193-195 °C (dec). ¹H NMR (CDCl₃): δ 7.42 (d, J = 8.3 Hz, 1 arom. H), 7.33 (d, J = 8 Hz, 1 arom. H), 7.24 (m, 1 arom. H) 7.14 (m, 2 arom. H), 7.03 and 7.01 (2 d, J = 7.3 Hz, 1 arom. H), 6.64 (d, J, 8.1 Hz, 1 arom. H) 6.56 (d, J = 8.1 Hz, 1 arom. H), 5.58 (s, H-C(5)), 5.32 and 4.68 (2 d, J = 8.6 Hz, OCH₂ Ar).

Example 13

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-14-(3'-nitrobenzoyloxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 23).

¹H NMR (CDCl₃): δ 8.25 (s, 1 arom. H), 7.28 (m, 4 arom. H), 7.15 (m, 1 arom. H) 6.87 (d, J = 8.3 Hz, 1 arom. H), 6.62 (d, J = 8.3 Hz, 1 arom. H), 5.66 (s, H-C(5)), 5.17 and 5.07 (2 d, J = 6.6 Hz, OCH₂O) 4.92 and 4.44 (2 d, J = 11.5 Hz, OCH₂Ar), 3.42 (s, CH₃O).

Example 14

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride (compound 24).

M.p. > 230 °C (dec). ¹H NMR (DMCO-d₆): δ 9.40 (s, OH), 9.15 (broad s, ⁺NH), 7.84 (s, 1 arom. H) 7.60 (d, J = 8.8 Hz, 1 arom. H), 7.53 (d, J = 7.6 Hz, 1 arom. H), 7.45 (d, J = 8 Hz, 1 arom. H) 7.23 (d, J = 7.6 Hz, 1 arom. H), 7.19 (d, J = 7.6 Hz, 1 arom. H), 6.98 (m, 1 arom. H) 6.88 (d, J = 7.6 Hz, 1 arom. H) 6.69 (d, J = 8.3 Hz, 1 arom. H), 6.66 (d, J = 8.3 Hz, 1 arom. H), 6.03 (s, H-C(5)), 4.98 and 4.87 (2 d, J = 14, 14 Hz, OCH₂Ph).

Example 15

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-14-(2-naphtylmethoxy)-6,7-2'-3'-benzo[b]furanmorphinan (compound 25).

M.p. 198-201 °C. ¹H NMR (CDCl₃): δ 7.72-7.08 (m, 11 arom. H), 6.86 (d, J = 8.3 Hz, 1 arom. H), 6.62 (d, J = 8.3 Hz, 1 arom. H), 5.68 (s, H-C(5)), 5.17 and 5.07 (2 d, J = 6.6, 6.6 Hz, OCH₂O), 5.01 and 4.57 (2 d, J = 11.2, 11.2 Hz, OCH₂Ar), 3.42 (s, CH₃O).

Example 16

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(2'-naphthylmethoxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride (compound 26).

M.p. > 215 °C. ¹H NMR (DMSO-d₆): δ 9.42 (s, OH), 9.00 (broad s, ⁺NH), 7.68-6.85 (m, 11 arom. H), 6.71 (d, J = 8 Hz, 1 arom. H), 6.67 (d, J = 8 Hz, 1 arom. H), 6.04 (s, H-C(5)), 4.92 (s, OCH₂Ar).

Example 17

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-(2'-fluorobenzyloxy)-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanmorphinan (compound 27).

¹H NMR (DMSO-d₆): δ 7.56 (d, J = 8 Hz, 1 arom. H), 7.49 (d, J = 8 Hz, 1 arom. H), 7.31 (m, 1 arom. H), 7.21 (m, 1 arom. H), 6.81 (d, J = 8.4 Hz, 1 arom. H), 6.67 (d, J = 8.4 Hz), 5.72 (s, H-C(5)), 5.06 and 5.01 (2 d, J = 6.4, 6.4 Hz, OCH₂O), 4.89 and 4.57 (2 d, J = 11.6, 11.6 Hz, OCH₂Ar), 3.33 (s, CH₃O).

Example 18

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-(2'-fluoro-benzyloxy)-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan Hydrochloride (compound 28).

M.p. > 215 °C. ¹H NMR (CDCl₃): δ 9.45 (s, OH), 9.04 (broad s, ⁺NH), 7.54 (d, J = 8.4 Hz, 1 arom. H) 7.31-6.73 (m, 7 arom. H), 6.71 (d, J = 8.2 Hz, 1 arom. H), 6.66 (d, J = 8.2 Hz, 1 arom. H), 5.98 (s, H-C(5)), 4.81 and 4.84 (2 d, J = 12 Hz, OCH₂Ar).

Example 19

14-Cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan (compound 29).

M.p. 156-159 °C. ¹H NMR (CDCl₃): δ 7.47 (d, J = 8 Hz, 1 arom. H), 7.33 (d, J = 8 Hz, 1 arom. H), 7.28-7.07 (m, 7 arom. H), 6.84 (d, J = 8.4 Hz, 1 arom. H), 6.59 (d, J = 8.4 Hz, 1 arom. H), 6.38 (d, J = 16 Hz, 1 olef. H), 6.13 (m, 1 olef. H), 5.68 (s, H-C(5)), 5.16 and 5.06 (2 d, J = 6.4, 6.4 Hz, OCH₂O), 4.46 and 4.11 (2 m, OCH₂Ar), 3.42 (s, CH₃O).

Example 20

14-Cinnamyloxy-17-cyclopropylmethyl-6,7-dehydro-4,5 α -epoxy-3-hydroxy-6,7-2'-3'-benzo[b]furanomorphinan Salicylate (compound 30).

¹H NMR (CDCl₃): δ 7.94 (d, J = 8 Hz, 1 arom. H), 7.35 (d, J = 8 Hz, 1 arom. H), 7.30-6.73 (m, 12 arom. H), 6.56 (d, J = 8 Hz, 1 arom. H), 5.96 (s, 2 olef. H), 5.55 (s, H-C(5)), 4.33-4.02 (m, OCH₂Ar).

Example 21

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-methoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan (compound 31).

¹H NMR (DMSO-d₆): δ 7.7.56 (d, J = 8 Hz, 1 arom. H), 7.52 (d, J = 8 Hz, 1 arom. H), 7.32 (dd, J = 8, 8 Hz, 1 arom. H), 5.64 (s, H-C(5)), 5.05 and 5.00 (2 d, J = 6.4, 6.4 Hz, OCH₂O), 3.32 (CH₃O).

Example 22

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-6,7-2'-3'-benzo[b]furanomorphinan hydrochloride (compound 32).

M.p. > 240 °C. ^1H NMR (DMSO-d₆): δ 9.47 (s, OH), 9.17 (broad s, *NH), 7.61 (d, J = 8 Hz, 1 arom. H), 7.53 (d, J = 8 Hz, 1 arom. H), 7.36 (dd, J = 8, 8 Hz, 1 arom. H), 7.27 (dd, J = 8, 8 Hz, 1 arom. H), 6.72 (d, J = 8.4 Hz, 1 arom. H), 6.65 (d, J = 8.4 Hz, 1 arom. H), 5.90 (s, H-C(5)), 3.35 (s, CH₃O).

Example 23

17-(Cyclopropylmethyl)-14-(2'-chlorobenzyloxy)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-6,7-2'-3'-(N-methoxymethylindolo)morphinan (compound 33).

^1H NMR (CDCl₃): δ 7.56 (m, 1 arom. H), 7.44 (m, 1 arom. H), 7.37-7.17 (m, 3 arom. H), 7.01 (m, 1 arom. H), 6.91 (m, 1 arom. H), 6.83 (d, J = 8.2 Hz, 1 arom. H), 6.59 (dd, J = 8.2, 8.2 Hz, 1 arom. H), 5.90 (s, H-C(5)), 5.82 and 5.55 (2 d, J = 11.2, 11.2 Hz, NCH₂O), 5.13 and 5.03 (2 d, J = 6.4, 6.4 Hz, OCH₂O), 4.98 and 4.56 (2 d, J = 13, 13 Hz, OCH₂Ar), 3.40 and 3.26 (2 s, 2 CH₃O).

Example 24

17-(Cyclopropylmethyl)-14-(2'-chlorobenzoyloxy)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride (compound 34).

M.p. > 250 °C (dec). ¹H NMR (DMSO-d₆): δ 11.38 (s, NH), 9.38 (s, OH), 8.76 (broad s, ⁺NH), 7.34-6.85 (m, 8 arom. H), 6.72 (d, J = 8 Hz, 1 arom. H), 6.64 (d, J = 8 Hz, 1 arom. H), 5.93 (s, H-C(5)), 4.80 and 4.67 (2 d, J = 13, 13 Hz, OCH₂ Ar).

Example 25

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-3,14-dimethoxy-4,5 α -epoxy-6,7-2'-3'-benzo[b]furanomorphinan (compound 35).

Sodium hydride (144 mg, 6 mmol; obtained from 240 mg of 60% sodium hydride dispersion in oil by washings with n-hexane) was added to a solution of naltriben methanesulfonate (P.S. Portuguese et al., J. Med. Chem., Vol. 34: 1715-1720, 1991) 500 mg, 0.97 mmol) in 10 ml of anhydrous N,N-dimethyl-formamide at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and then at room temperature for another 30 min. After cooling to 0 °C, dimethyl sulfate (380 μ l, 4 mmol) was added and stirring was continued at first at 0 °C for 30 min and then at room temperature for 3 h. Excess sodium hydride was destroyed by addition of MeOH and H₂O. The resulting mixture was extracted with ethyl acetate (3 x 40 ml), the combined organic layers were washed with H₂O (2 x 30 ml) and brine (2 x 30 ml), dried over Na₂SO₄ and evaporated to give a crystalline residue which was recrystallized from MeOH to afford 320 mg (74 %) of compound 35. M.p. 221-224 °C (dec.). ¹H NMR (CDCl₃): δ 7.47-7.14 (m, 4 arom. H), 6.64 (d, J = 8.4 Hz, 1 arom. H), 6.59 (d, J = 8.4 Hz, 1 arom. H), 5.62 (s, H-C(5)), 3.78 (s, CH₃O-C(3)), 3.31 (s, CH₃O-C(14)).

Example 26

Synthesis of 17-Cyclopropylmethyl-6,7-dehydro-4,5 α -epoxy-14-hydroxy-6,7-2',3'-benzo[b]furanomorphinan (compound 36).

A mixture of 3-deoxyonaltrexone (R. Krassnig and H. Schmidhammer, Heterocycles, Vol. 38: 877-881, 1994) (1,3 g, 3.99 mmol), O-phenylhydroxylamine hydrochloride (750 mg, 5.15 mmol), methanesulfonic acid (0.75 ml, 11.55 mmol), and ethanol (30 ml) was refluxed for 20 h. After cooling, the mixture was diluted with H₂O, alkalinized with conc. NH₄OH and extracted with CH₂Cl₂ (4 x 40 ml). The combined organic layers were washed with H₂O (2 x 30 ml) and brine (30 ml), dried over Na₂SO₄ and evaporated to give a brownish oil which was crystallized from MeOH to yield 1.1 mg (69 %) of compound 36. M.p. > 260 °C. ¹H NMR (CDCl₃): δ 7.45 (d, J = 8 Hz, 1 arom. H), 7.37 (d, J = 8 Hz, 1 arom. H), 7.26-7.13 (m, 2 arom. H), 7.01 (dd, J = 7.8, 7.8 Hz, 1 arom. H), 6.67 (d, J = 7.8 Hz, 1 arom. H), 6.59 (d, J = 7.8 Hz, 1 arom. H), 5.59 (s, H-C(5)), 5.00 (broad s, OH).

Example 27

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride (compound 37).

A mixture of 3-deoxyonaltrexone (R. Krassnig and H. Schmidhammer, Heterocycles, Vol. 38: 877-881, 1994) (1,5 g, 4.6 mmol), phenylhydrazine hydrochloride (1.0 mg, 6.9 mmol), 1M HCl in ether (5 ml), and methanol (20 ml) was stirred at room temperature for 3 days. After concentration to ca. half of the original volume in vacuo, the solution was refrigerated overnight. The colorless crystals formed were collected to yield 1.54 g (77 %) of compound 37. M.p. > 240 °C (dec.). ¹H NMR (DMSO-d₆): δ 11.37 (s, NH), 9.01 (broad s, +NH), 7.36-6.94 (m, 5 arom. H), 6.78 (d, J = 7.8 Hz, 1 arom. H), 6.59 (d, J = 7.8 Hz, 1 arom. H), 6.55 (s, OH).

Example 28

17(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(3'-chlorobenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan, hydrochloride (compound 39).

¹H NMR (DMSO-d₆): δ 9.40 (s, OH), 8.59 (broad s, +NH), 7.53-6.90 (m, 8 arom. H), 6.65 (s, 2 arom. H), 6.03 (s, H-C(5)), 4.74 and 4.62 (2 d, J=13.6, 13.6 Hz, OCH₂(3'-

ClPh)). Analysis calculated for $C_{33}H_{30}ClNO_4 \cdot HCl \cdot 1.5 H_2O$: C 65.67, H 5.68, N 2.32; found: C 65.31, H 5.37, N 2.33.

Example 29

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(2'-chlorobenzoyloxy)-6,7,2',3'-benzo[b]furanomorphinan Hydrochloride (compound 41).

M.p. > 220°C. 1H NMR (DMSO- d_6): δ 9.40 (s, OH), 8.59 (broad s, +NH), 7.56-6.90 (m, 8 arom. H), 6.66 (m, 2 arom. H), 6.03 (s, H-C(5)), 4.74 (s, OCH₂(2-ClPh)).

Analysis calculated for $C_{33}H_{30}ClNO_4 \cdot HCl \cdot 1.5 H_2O$: C 65.67, H 5.68, N, 2.32. Found: C 65.72, H 5.48, N 2.25.

Example 30

14-Allyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-1'-allyl-6,7-2',3'-indolomorphinan hydrochloride (compound 42).

NMR of the free base (colorless oil)

¹H NMR (CDCl₃): δ 7.40 (d, J = 8.4 Hz, 1 arom. H), 7.24 (m, 1 arom. H), 7.15 (m, 1 arom. H), 7.03 (m, 1 arom. H), 6.57 (d, J = 8.4 Hz, 1 arom. H), 6.50 (d, J = 8.4 Hz, 1 arom. H), 6.08 (m, 1 olef. H), 5.76 (m, 1 olef. H), 5.72 (s, H-C(5)), 5.15-4.75 (m, 6 H, CH₂N, 2 CH₂ = C), 4.24 and 3.92 (2 dd, J = 12.4, 4.8 Hz, CH₂O).

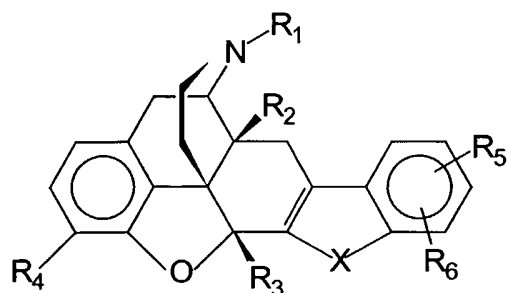
This free base was dissolved in ethyl ether and treated with HCl/ether solution HCl at 0°C. Isolation of the precipitate provided the title compound 42 as a solid.

Pharmaceutical preparations

For the preparation of a pharmaceutical formulation, the active ingredient may be formulated to an injection, capsule, tablet, suppository, solution, ointment, cream, paste, plaster, patch or the like. The pharmaceutical formulation may comprise the compound of formula (I) alone or may also comprise expedients such as stabilizers, buffering agents, diluents, isotonic agents, antiseptics and the like. The pharmaceutical formulation may contain the above described active ingredient in the amount of 0.01-95 % by weight. The dose of the active ingredient may be appropriately selected depending on the objects of administration, administration route and conditions of the patients.

CLAIMS

1. Use of a compound according to the formula (I)



(I)

wherein

R_1 represents C_1 - C_{10} alkenyl; C_4 - C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3 - C_6 cycloalkyl and the alkyl is C_1 - C_4 alkyl; C_4 - C_{10} cykloalkenylalkyl wherein the cycloalkenyl is C_3 - C_6 cykloalkenyl and the alkyl is C_1 - C_4 alkyl; C_7 - C_{16} arylalkyl wherein the aryl is C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkyl; C_8 - C_{16} arylalkenyl wherein the aryl is C_6 - C_{10} aryl and the alkenyl is C_2 - C_6 alkenyl;

R_2 represents hydrogen, hydroxy, C_1 - C_6 alkoxy; C_1 - C_6 alkenyloxy; C_7 - C_{16} arylalkyloxy wherein the aryl is C_6 - C_{10} aryl and the alkyloxy is C_1 - C_6 alkyloxy; C_7 - C_{16} arylalkenyloxy wherein the aryl is C_6 - C_{10} aryl and the alkenyloxy is C_1 - C_6 alkenyloxy; C_1 - C_6 alkanoyloxy; C_7 - C_{16} arylalkanoyloxy wherein the aryl is C_6 - C_{10} aryl and the alkanoyloxy is C_1 - C_6 alkanoyloxy;

R_3 represents hydrogen, C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_7 - C_{16} arylalkyl wherein the aryl is C_6 - C_{10} aryl and the alkyl is C_1 - C_6 alkyl; C_7 - C_{16} arylalkenyl wherein the aryl is C_6 - C_{10} aryl and the alkenyl is C_1 - C_6 alkenyl; hydroxy(C_1 - C_6)alkyl; alkoxyalkyl wherein the alkoxy is C_1 - C_6 alkoxy and the alkyl is C_1 - C_6 alkyl; CO_2H ; $CO_2(C_1-C_6$ alkyl);

R_4 is hydrogen, hydroxy; C_1 - C_6 alkoxy; C_7 - C_{16} arylalkyloxy wherein the aryl is C_6 - C_{10} aryl and the alkyloxy is C_1 - C_6 alkyloxy; C_1 - C_6 alkenyloxy; C_1 - C_6 alkanoyloxy; C_7 - C_{16} arylalkanoyloxy wherein the aryl is C_6 - C_{10} aryl and the alkanoyloxy is C_1 - C_6 alkanoyloxy; C_2 - C_{10} alkyloxyalkoxy wherein alkyloxy is C_1 - C_4 alkyloxy and alkoxy is C_1 - C_6 alkoxy;

R₅ and R₆ each independently represent hydrogen; OH; C₁-C₆ alkoxy; C₁-C₆ alkyl; hydroxyalkyl wherein the alkyl is C₁-C₆ alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO₂H; CO₂(C₁-C₆ alkyl); CONH₂; CONH(C₁-C₆ alkyl); CON(C₁-C₆ alkyl)₂; amino; C₁-C₆ monoalkyl amino; C₁-C₆ dialkyl amino; C₅-C₆ cyhloalkyl amino; SH; SO₃H; SO₃(C₁-C₆ alkyl); SO₂(C₁-C₆ alkyl); SO₂NH₂; SO₂NH(C₁-C₆alkyl); SO₂NH(C₇-C₂₀ arylalkyl); SO(C₁-C₆ alkyl); or R₅ and R₆ together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C₁-C₆ alkyl; trifluoromethyl; C₁-C₆ alkoxy, CO₂H, CO(C₁-C₆ alkyl), amino, C₁-C₆ monoalkylamino, C₁-C₆ dialkylamino, SH; SO₃H; H; SO₃(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), SO(C₁-C₆ alkyl), and

X represents oxygen; sulfur; CH = CH or NR₉ wherein R₉ is H, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₇-C₁₆ arylalkyl

wherein the aryl is C₆-C₁₀ aryl and the alkyl is C₁-C₆ alkyl, C₇-C₁₆ arylalkenyl wherein the aryl is C₆-C₁₀ aryl and the alkenyl is C₁-C₆ alkenyl; C₁-C₆ alkanoyl, and whereinaryl is unsubstituted or mono- or di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C₁-C₃ alkyl, C₁-C₃ alkoxy, CO₂H, CO₂ (C₁-C₃)alkyl, CONH₂, CONH(C₁-C₃ alkyl), CON(C₁-C₃ alkyl), CO(C₁-C₃ alkyl), amino, (C₁-C₃ monoalkyl)amino, (C₁-C₃ dialkyl)amino, C₅-C₆ cyhloalkylamino (C₁-C₃ alkanoyl)amino, SH, SO₃H, SO₃ (C₁-C₃ alkyl), SO₂ (C₁-C₃ alkyl), SO(C₁-C₃ alkyl), C₁-C₃ alkylthio or C₁-C₃ alkanoylthio; and

with the proviso that when R₂ is hydroxy, R₃ cannot be hydrogen, except when R₄ is hydrogen, OCH₂OCH₃, OCH₂OC₂H₅ or OC(Ph)₃ and pharmacologically acceptable salts thereof, for the preparation of a medicament for the treatment and/or prevention of disorders susceptible to the inhibition of the target cacineurin.

2. Use according to claim 1, wherein

R₁ is selected from allyl, cinnamyl, cyclopropylmethyl or cyclobutylmethyl;

R₂ is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO₂, CN, CF₃, CH₃ or OCH₃;

Allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R₃ is selected from hydrogen, methyl, ethyl, benzyl or allyl;

R₄ is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R₅ and R₆ are each and independently selected from hydrogen; nitro; cyano; chloro, fluoro, bromo trifluoromethyl; CO₂H; CO₂ CH₃; CONH₂; CONH CH₃; SH; SO₂NH₂; N(CH₃)₂; SO₂CH₃; X is selected from oxygen; NH or N CH₃, N-benzyl, N-allyl.

3. Use according to claim 1, wherein the compound of formula (I) is in the form of a pharmaceutically acceptable salt.
4. Use according to claim 1, wherein the salt is an inorganic salt.
5. Use according to claim 1, wherein the salt is an organic salt.
6. Use according to claim 1, wherein compound of formula (I) is

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan x HCl;

17-Allyl-6,7-dehydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan x HCl;

6,7-Dehydro-4,5 α -epoxy-14-ethoxy-3-hydroxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan x HCl;

17-Allyl-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan x HCl;

6,7-Dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan x HCl;

17-Allyl-6,7-dehydro-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2',3'-indolomorphinan x HCl

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2',3'-indolomorphinan x CH₃SO₃H;

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzyloxy)-4,5 α -epoxy-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan;

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzyloxy)-4,5 α -epoxy-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-14-(2'-naphthylmethoxy)-6,7-2',3'-benzo[b]furanomorphinan;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(2'-naphthylmethoxy)-6,7-2',3'-benzo[b]furanomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-(2'-fluorbenzyloxy)-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-(2'-fluorbenzyloxy)-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan x HCl;

14-Cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan;

14-Cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-6,7-2'-3'-benzo[b]furanomorphinan Salicylate;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-14-methoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan;

17-(Cyclopropylmethyl)-14-(2'-chlorbenzyloxy)-6,7-dehydro-4,5 α -epoxy-3-(methoxymethoxy)-6,7-2',3'-(N-methoxymethylindolo)morphinan;

17-(Cyclopropylmethyl)-14-(2'-chlorbenzyloxy)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-6,7-2',3'-indolomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(3'-chlorbenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan x HCl;

17-(Cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-14-(2'-chlorbenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan x HCl;

14-Allyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5 α -epoxy-3-hydroxy-1'-allyl-6,7-2',3'-indolomorphinan x HCl;

17-(Cyclobutylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -ethoxy-5 β -methylindolo[2',3':6,7]morphinan-3-ol Hydrochloride;

14 β -(Benzyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol;

14 β -[(4-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride;

17-(Cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -[(2-phenylbenzyl)oxy]indolo[2',3':6,7]morphinan-3-ol Hydrochloride;

14 β -[(4-tert.-Butylbenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride;

17-(Cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-14 β -[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol.

7. Use according to any of claims 1 to 6 wherein the disorder is selected among inflammatory disorders, in particular inflammatory intestinal diseases, skin disorders, in particular neurodermatitis and psoriasis, neurodegenerative disorders, Central Nervous System disorders, ischemic disorders, allergic diseases, nerve injuries, cancer, disorders of the intestine tract, pruritus, heart disorders, cardiovascular disorders, stroke, diabetes mellitus, glaucoma, psychic disorders, addiction and drug abuse, overweight and obesity, ileus and side-effects associated with the treatment with opioid analgesics.
8. Use according to claim 7, wherein the disorder is neurodermatitis.
9. Use according to claim 7, wherein the disorder is psoriasis.
10. Use according to any of claims 1 to 6, wherein the disorder is susceptible towards a modulation of the activity of cells in the immune system.
11. Use according to claim 7, wherein the disorder is an inflammatory intestinal (bowel) disease.
12. Use according to claim 7, wherein the disorder is an inflammatory disorder, in particular inflammatory intestinal diseases, intestinal diseases, colon irritabile, Crohn's disease, colitis ulcerosa, bronchial asthma, uveitis, blepharitis, inflammatory myopathies, rosacea, erythema, lichen, inflammatory disorders, atopic dermatitis, allergic contact dermatitis. ischemic disorders, stroke,

cardiac infarction, multiple sclerosis, phlebitis, ascites, glaucoma, scleroderma, systemic sclerosis.

13. Use according to claim 7, wherein the disorder are side effects associated with the treatment with opioid analgesics, such as morphine, fentanyl or oxycodone, in particular pruritus, ileus, vomiting, nausea, sedation, dizziness, confusion, addiction, constipation, respiratory depression.

