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HETEROCYCLE-CONDENSED MORPHINOID DERIVATIVES

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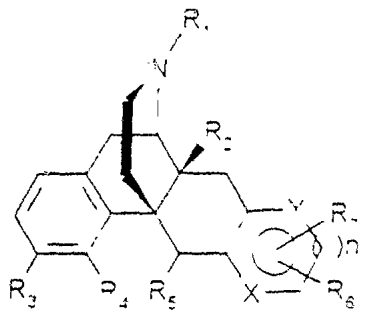
(71) Applicant(s)
SMITHKLINE BEECHAM S.P.A.

(72) Inventor(s)
GIULIO DONDIO; SILVANO RONZONI

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(57) Claim

1 A compound, or salt thereof, of formula (I)



(I)

in which:

R_1 is hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl, or furan-2 or 3-yl alkyl or $(CH_2)_mCOR$ wherein m is 1 to 5 and R represents hydroxy, C_{1-5} alkoxy, OC_{3-6} alkenyl or alkylamino, ~~or R_1 is a group A-B wherein A represents C_{1-10} alkylene and B represents substituted or unsubstituted aryl or heteroaryl.~~

R_2 is hydrogen, hydroxy or C_{1-5} alkoxy, halogen, nitro, NR_8R_9, SR_8, where R_8 and R_9, which may be the same or different, are each hydrogen, C_{1-6} alkyl, or COR_1 where R_1 is defined above.

R_3 is hydrogen, hydroxy, C_{1-5} alkoxy, halogen, SR_8, nitro, NHR_{10}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NHSO_2R_{12}$, where R_{10} and R_{11}, which may be the same or different, are each hydrogen or C_{1-6} alkyl

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R_4 and R_5 which may be the same or different are each independently hydrogen, hydroxy, C_{1-5} alkoxy or together may form an oxy group (-O-),

R_6 is a group



in which R_3 is defined above, there being up to three R_3 groups in the phenyl ring, or R_6 is a group CZR_{12} in which Z is oxygen or sulphur, R_{12} is C_{1-15} alkyl, C_{1-5} alkoxy or $NR_{13}R_{14}$ where R_{13} and R_{14} which may be the same or different are hydrogen, linear or branched C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{4-10} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl, ~~or an optionally substituted heterocyclic ring~~ or may form together a C_{3-6} alkyl ring which may be interrupted by an oxygen or a nitrogen

R_7 is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, or is a group



in which R_3 is defined above, and,

n is 0 or 1,

when n=0, (i) X is NH, oxygen or sulphur and Y is CH or a R_6 or R_7-substituted carbon; or (ii) X is NH and Y is N; and when n=1, then X and Y are both N, or N and CH.

10. A method for the manufacture of a medicament for use as an analgesic, immunosuppressant to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agent, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough and respiratory depression, mental illness, epileptic seizures and other neurologic disorders comprising the step of bringing a compound according to any one of claims 1 to 8 into a form suitable for administration.

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SMITHKLINE BEECHAM S.P.A.
(71) Applicant *(for all designated States except US)*: ~~SMITHKLINE BEECHAM FARMACEUTICI S.P.A.~~ [IT/IT]; Via Zambeletti, I-20021 Baranzate (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DONDIO, Giulio [IT/IT]; SmithKline Beecham Farmaceutici S.p.A., Via Zambeletti, I-20021 Baranzate (IT). RONZONI, Silvano [IT/IT]; SmithKline Beecham Farmaceutici S.p.A., Via Zambeletti, I-20021 Baranzate (I..

(74) Agent: RUSSELL, Brian, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

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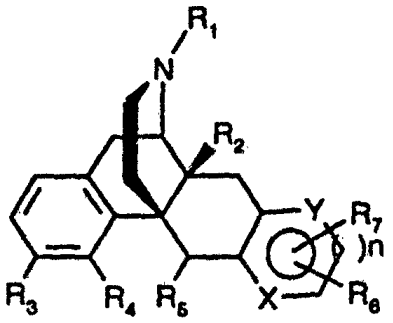
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(54) Title: HETEROCYCLE-CONDENSED MORPHINOID DERIVATIVES

(57) Abstract

Compounds of formula (I), are selective delta opioid agonists and antagonists, and are useful as analgesics and in treating general neurologic disorders.



(I)

HETEROCYCLE-CONDENSED MORPHINOID DERIVATIVES

The present invention is concerned with novel morphinoid compounds, processes for their preparation and their use in medicine.

The presence of at least three populations of opioid receptors (*mu*, *delta* and *kappa*) is now well established and documented and all three appear to be present in the central and peripheral nervous system of many species including man (Lord J.A.H. et al., *Nature* 1977, 267, 495).

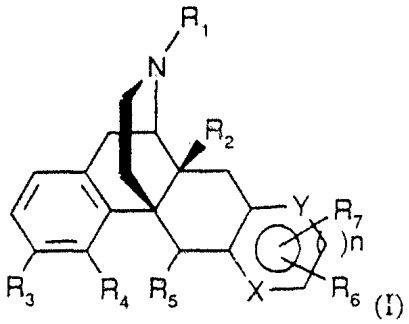
Activation of all three opioid receptor subtypes can lead to antinociception in animal models. In particular, studies with peptidic *delta* agonists have indicated that activation of the *delta* receptor produces antinociception in rodents, primates and can induce clinical analgesia in man (D. E. Moulin *et al. Pain*, 1985, 23, 213). Evidence exists that suggest a lesser propensity of *delta* agonists to cause the usual side-effects associated with *mu* and *kappa* activation (Galligan et al, *J. Pharm. Exp. Ther.*, 1984, 229, 641).

US 5,223,507 and US 5,225,417 (G. D. Searle & Co.) disclose bicycle-condensed morphinoid compounds which are said to be *delta* opioid agonists having therapeutic utility as analgesics agents.

WO 94/07896 (Toray Ind. Inc.) discloses indole-condensed morphinoid compounds useful as immunosuppressants, anti-allergic and anti-inflammatory agents.

We have now discovered a novel class of substituted monoheterocycle-condensed morphinoid derivatives which are potent and selective *delta* opioid agonists and antagonists which may therefore be of potential therapeutic utility as analgesics, immunosuppressants to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agents, brain cell protectant, agents for treating drug and alcohol abuse, gastritis, diarrhoea, cardiovascular and respiratory diseases, cough, mental illness and epilepsy and, in general, for the treatment of those pathological conditions which customarily can be treated with agonists and antagonists of the *delta* opioid receptor.

According to the present invention, there is provided a compound, or a solvate or salt thereof of formula (I):



(I)

in which,

R_1 is hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl or furan-2 or 3-yl alkyl or $(CH_2)_mCOR$ wherein m is 1 to 5 and R represents hydroxy, C_{1-5} alkoxy, OC_{3-6} alkenyl or alkylaryl or ~~R_1 is a group A-B wherein A represents C_{1-10} alkylene and B represents substituted or unsubstituted aryl or heteroaryl;~~

R_2 is hydrogen, hydroxy or C_{1-5} alkoxy, preferably methoxy, halogen, nitro, NR_8R_9, SR_8, where R_8 and R_9, which may be the same or different, are each hydrogen, C_{1-6} alkyl, COR_1 preferably acetyl.

R_3 is hydrogen, hydroxy, C_{1-5} alkoxy, preferably methoxy, halogen, SR_8, preferably hydrogen, nitro, NHR_{10}, $NR_{10}R_{11}$, $NHCOR_{10}$, $NHSO_2R_{10}$, where R_{10} and R_{11}, which may be the same or different, are each hydrogen or C_{1-6} alkyl, preferably methyl;

R_4 and R_5, which may be the same or different, are each independently hydrogen, hydroxy, C_{1-5} alkoxy, preferably methoxy, or together may form an oxy group (-O-).

R_6 is a group



in which R_3 has the same meaning described above, there being up to three R_3 in the phenyl ring, or R_6 is a group $C(Z)R_{12}$, in which Z is oxygen or sulphur, R_{12} is C_{1-18} alkyl, C_{1-18} alkoxy or $NR_{13}R_{14}$, where R_{13} and R_{14} , which may be the same or different, are hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl ~~or an optionally substituted heterocyclic ring~~ or may form together a C_{3-6} alkyl ring which may be interrupted by an oxygen or a nitrogen.

R_7 is hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, or is a group



in which R_3 has the same meaning described above:

n is 0 or 1;

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when n=0, (i) X is NH, oxygen or sulphur and Y is CH or a R_6 or R_7-substituted carbon; or (ii) X is NH and Y is N; and when n=1, then X and Y are both N, or N and CH.

When R_1 is aryl, it is preferably phenyl and when it is aralkyl, it is preferably phenyl-C_{1-6} alkyl.

Examples of R_1 are methyl, ethyl, propyl, allyl and cyclopropylmethyl.

Examples of R_2 are hydrogen and hydroxy.

Examples of R_3 are hydrogen, hydroxy and methoxy.

Examples of R_4 and R_5 are hydrogen, hydroxy, methoxy or together as an oxy group.

Examples of R_6 are COO-iPr, $CONEt_2$, CONH-i-Pr, $CON(i\text{-}Pr)_2$, $CONHCH_2Ph$, $CON(\text{-}CH_2\text{-})_4$, $CON(\text{-}C_2H_4OC_2H_4\text{-})$, $CON(i\text{-}Bu)_2$ and $CONH(CH_2)_3NEt_2$.

An example of R_7 is methyl.

A group of preferred compounds of formula (I) is that in which n = 0, X is NH and Y is CH or a R_6- or R_7-substituted carbon atom, where R_6 is a group -C(Z)-R_{12} where R_{12} is C_{1-6} alkyl, C_{1-4} alkoxy or $NR_{13}R_{14}$ where R_{13} and R_{14} are as defined above and Z is oxygen; and R_7 is methyl.

Particularly preferred compounds of formula (I) are those in which R_6 are $CONEt_2$ and $CON(i\text{-}Pr)_2$.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salts of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

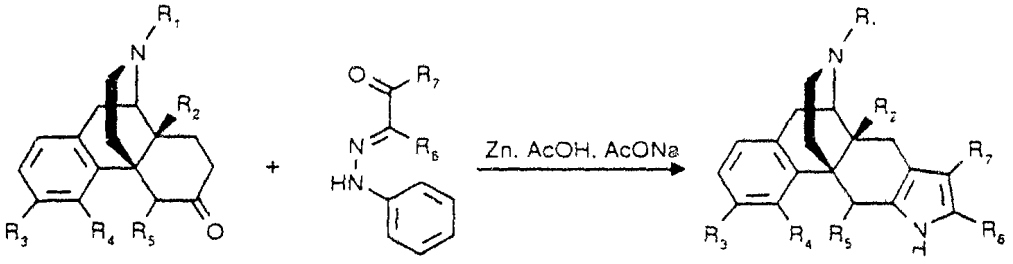
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The compounds of formula (I) may exists in more than one stereoisomeric form, and the invention extends to all such forms as well as to their mixtures thereof, including racemates.

The compounds of formula (I), or salts or solvates thereof, may be prepared by the methods illustrated in the following general reaction schemes, or by modification thereof, using readily available starting materials, reagents and conventional synthetic procedures. If a particular enantiomer of a compound of the present invention is desired, it may be synthesised starting from the desired enantiomer of the starting material and performing reactions not involving racemization processes or it may be prepared by chiral synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxy, diastereomeric salts are formed with an appropriate optically active acid or base, followed by resolution of diastereomeric salts by fractional crystallization and subsequent recovery of the pure enantiomers.

Compounds (I) in which n = 0, X = NH and Y is a R_7-substituted carbon atom, may be obtained starting from ketones of formula (II) and hydrazones of formula (III), in the presence of Zn and CH_3COONa in CH_3COOH as solvent (Khimiya Geterot. Soed., 1972, 342) as described in scheme 1:

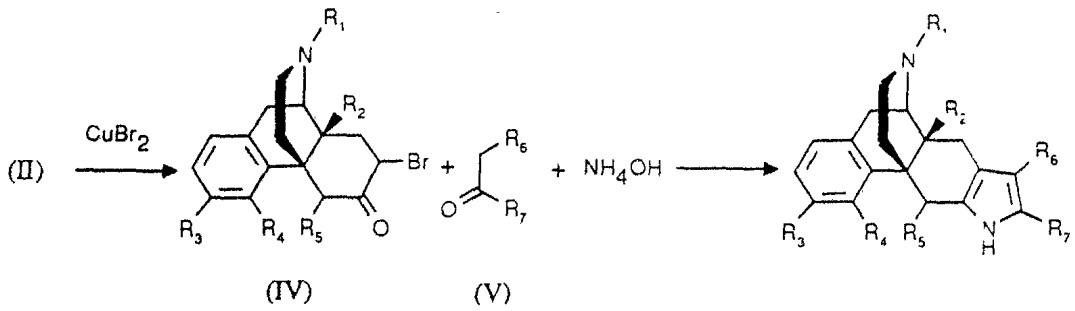
Scheme 1



(II) (III)

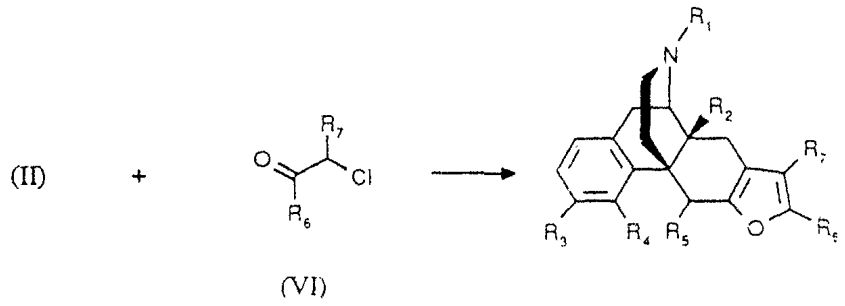
Compounds (I) in which n = 0, X = NH and Y is a R_6-substituted carbon atom, may be obtained by cyclization of halogeno ketones of formula (IV), with ketones of formula (V) in the presence of NH_4OH (Can. J. Chem., 1970, 48, 1689) as described in scheme 2:

Scheme 2



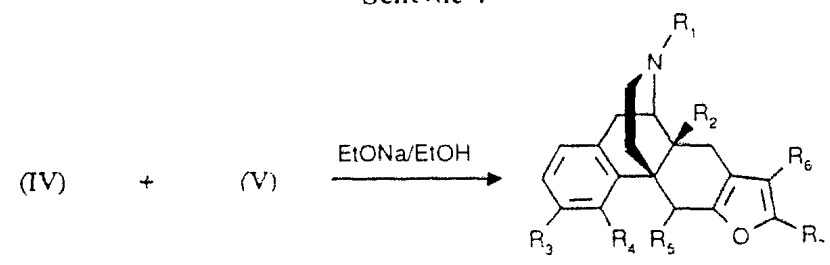
Compounds (I) in which n = 0, X = O and Y is a R7-substituted carbon atom, may be obtained by cyclising ketones of formula (II) with α-halogenoketones (preferably α-chloroketones) of formula (VI), in the presence of a base (J. Org. Chem., 1984, 49, 2317) as described in scheme 3:

Scheme 3



Compounds (I) in which n = 0, X = O and Y is a R_6-substituted carbon atom, may be obtained by cyclization of the bromoketones (IV) with ketones (V) in ethanol in the presence of a base (preferably EtONa) (J. Chem. Soc. Perkin I, 1972, 2372) as described in scheme 4:

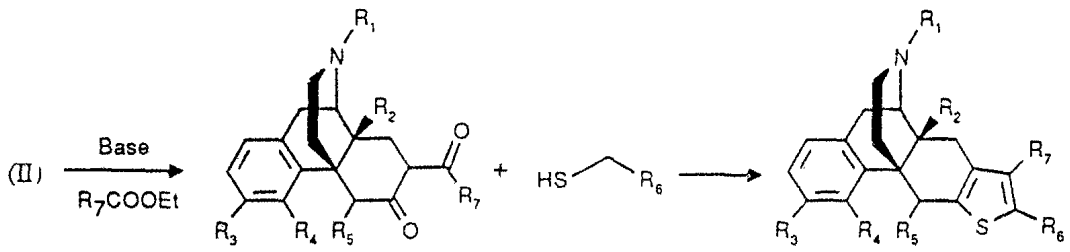
Scheme 4



Compounds (I) in which n = 0, X = S and Y is a R7-substituted carbon atom, may be prepared from β-diketones of general formula (VII) (synthesised by Claisen reaction, starting from ketones (II) and esters of formula R7-COOEt; J. Am. Chem. Soc., 1945,

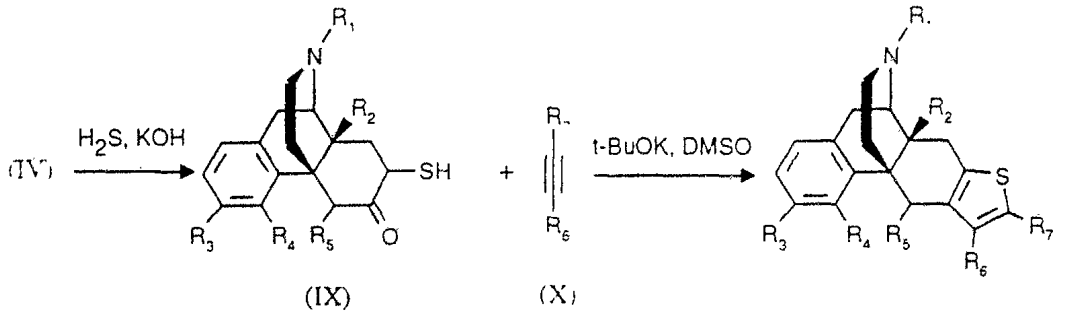
67, 1510) and mercapto derivatives of formula (VIII) in the presence of HCl (DE 1.088.507; C.A., 1962, 56, 456) as described in scheme 5:

Scheme 5



Compounds (I) in which n = 0, Y = S and X is a R_6-substituted carbon atom, may be obtained by reacting α-mercaptoketones (IX) (which may be prepared starting from the bromoketones (IV) and H_2S/KOH, J. Am. Chem. Soc., 1985, 107, 4175) with an alkyne derivative of formula (X), in a solvent such as DMSO, in the presence of a base such as t-BuOK (Chem Ber., 1964, 97, 2109) as described in scheme 6:

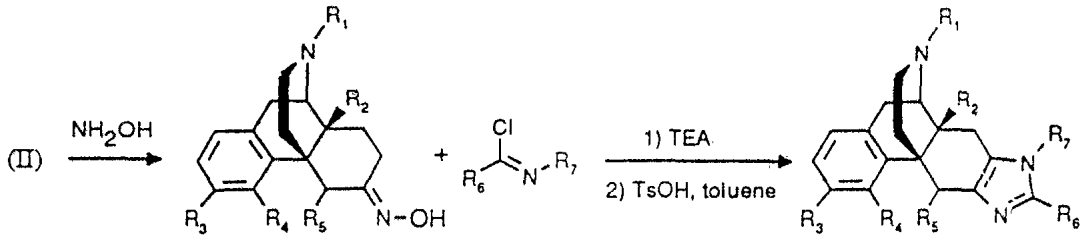
Scheme 6



Compounds (I) in which n = 0, X and Y are both N, may be obtained from hydroxyimino derivatives (XV) and R_6- R_7-substituted imidoyl chlorides of formula (XVI) in basic media, and subsequent treatment of the intermediates with H^+ in refluxing toluene (J. Org. Chem., 1993, 58, 7092) as described in the scheme 7:

Scheme 7

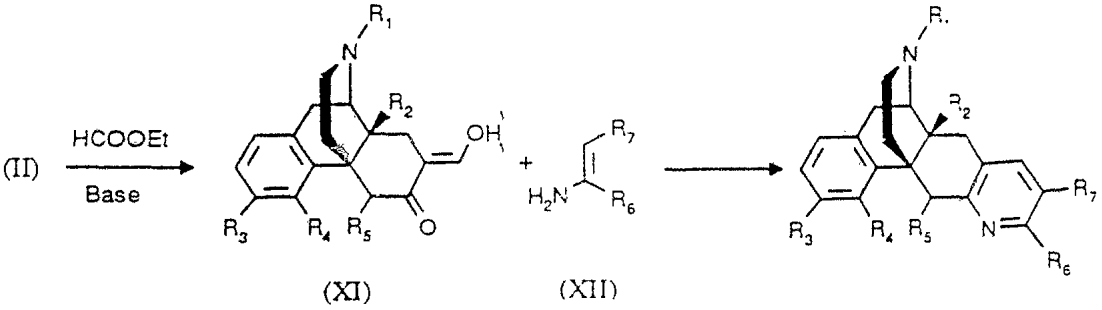
SUBSTITUTE SHEET (RULE 26)



(XV) (XVI)

Compounds (I) in which n = 1, X = N and Y = CH may be obtained by reacting α-hydroxymethylenketones (XI) (which may be prepared from ketones (II) by condensation with HCOOEt in the presence of a base; Org. Synth. Coll., 1963, 4, 536) with enamines (XII) (J. Ind. Chem. Soc., 1935, 12, 289) as described in scheme 8:

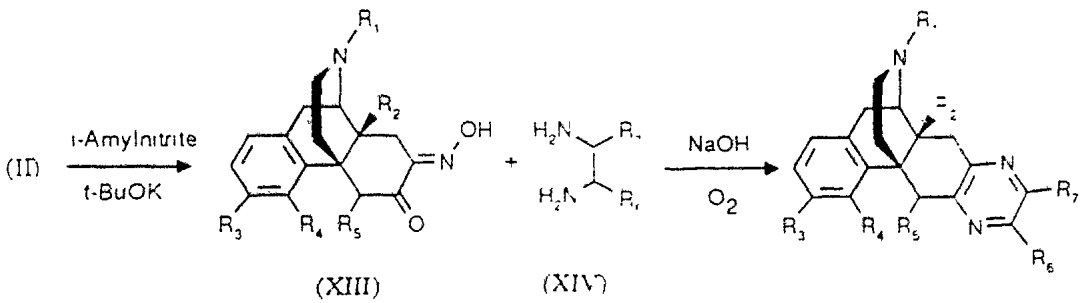
Scheme 8



(XI) (XII)

Compound (I) in which n = 1, and X = Y = N may be obtained starting from α-hydroxyiminoketones (XIII) (which may be prepared from ketones II) and i-amylnitrite/t-BuOK as described in J. Med. Chem., 1991, 34, 1715) with ethanediamines (XIV) and subsequent aromatization of the intermediate in basic media (Chem. Ber., 1967, 100, 555) as described in scheme 9:

Scheme 9



(XIII) (XIV)

The compounds of formula (I) may be converted into their pharmaceutically acceptable salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example, hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

In general compounds of formula (I) acting as selective *delta* receptor ligands may be useful as analgesics, immunosuppressants to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agents, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough and respiratory depression, mental illness, epileptic seizures and other neurologic disorders (herein after referred to as 'Conditions'). In particular, the activity of the compounds of formula (I) as *delta* agonists in standard tests indicates that they are of potential therapeutic utility as analgesic agents for the amelioration or elimination of pain.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Conditions.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the Conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the Conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl

alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention as selective *delta* ligands is determined in radioligand binding assays as described below.

Mouse brain membranes were prepared as described by Kosterlitz (*Br. J. Pharmacol.*, 1981, 73, 939.). The binding of the preferential *delta* ligand [^{3}H]-[D-Ala^2,D-Leu^5]-enkephalin (DADLE) was evaluated at its K_D concentration (1.3 nM) in presence of 40 nM of the unlabelled *mu* ligand [D-Ala^2, MePhe^4, Gly-ol^5]-enkephalin (DAMGO). The binding of the *mu* ligand [^{3}H]-DAMGO (*Eur. J. Pharmacol.*, 1989, 166, 213) and of the *kappa* ligand [^{3}H]-U69593 (*Excerpta Medica*, 1990, 211) were carried out at 0.5 nM. The non-specific binding was determined in presence of naloxone (10 μM) for all tritiated ligands. Binding data were expressed as percentage of inhibition and fitted the following equation: $f(x) = 100 \cdot X/(IC_{50} + X)$ where X are cold drug concentration values. The IC_{50} obtained were used to calculate the inhibitory constants (K_i) accordingly to the Cheng and Prusoff relation (*Biochem. Pharmacol.*, 1973, 22, 3099).

The *delta* agonist/antagonist activity of the compounds of the present invention is determined in the mouse vas deferens (MVD) bioassay as described below.

Vasa deferentia were obtained from CD-1 mice and were suspended in a Mg^{2+}-free Krebs buffer at 37 °C. The tissues were electrically stimulated with pulse trains having the following parameters: train duration 50 ms, stimulus duration 2 ms, frequency of stimuli 50 Hz, maximal voltage 60-70 V, train frequency 0.1 Hz. Concentration response curves for each compounds were constructed cumulatively. Linear regression analysis and IC_{50} concentrations were evaluated according to Tallarida and Murray (*Manual of Pharmacological Calculations*, Springer Verlag NY, 1981).

The most potent compounds described in the present invention showed affinities for the *delta* receptor ranging from 0.5 to 200 nM with *delta* selectivity ranging from 20 to 1500 times in respect to the other opioid receptor types. These compounds displayed also potent *delta* agonist or antagonist properties in the MVD preparation. Selective *delta* agonists (antagonised by the selective *delta* antagonist naltrindole) displayed IC_{50}s ranging from 1 to 500 nM. For example, the compound

of Example 7 shows a Ki *delta* = 1.59 nM, Ki *mu*/Ki *delta* = 218 and Ki *kappa*/Ki *delta* = 2259. In the MVD this compound shows an IC_{50} = 25 nM selectively antagonised by 30 nM of NTI (10-fold shift of the dose-response curve).

Mouse abdominal constriction (MAC) (*Proc. Soc. Exp. Biol. Med.*, 1957, 95, 729), mouse tail-flick (MTF) (*J. Pharm. Exp. Ther.*, 1941, 72, 74) and mouse tail-flick warm water (MTF-WW) (*Life Sci.*, 1986, 39, 1795) were adopted to evaluate the antinociceptive efficacy of the compounds of the present invention.

The following Examples 1 to 4 illustrate the preparation of compounds of general formula (I) of the present invention. Examples 1 to 19 are summarised in the Chemical Table, Examples 5 to 19 being obtained according to the same general procedure as described in Examples 1 to 3, starting from the corresponding known ketones of general formula (II) and the corresponding known hydrazones of general formula (III).

EXAMPLE 1

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a-(9H)-diol hydrochloride

0.9 g (2.7 mmols) of oxymorphone hydrochloride, 2.09 g (8.1 mmols) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, were dissolved in a mixture of 15 ml of glacial acetic acid and 0.64 g (8.1 mmols) of CH_3COONa. The solution was heated to 60 °C then, under nitrogen atmosphere, 1.06 g (16.2 mmol) of zinc dust were added portionwise. The resulting mixture was refluxed for 2 h and cooled to room temperature. The reaction mixture was poured in ice and the pH was adjusted to 8 with 25% NH_4OH and then extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:0.5), dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and recrystallized twice from EtOH to yield 0.38 g of the title compound.

EXAMPLE 2

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-10-methyl-7-(2-propenyl)-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a-(9H)-diol hydrochloride

1.0 g (2.75 mmoles) of naloxone hydrochloride, 2.15 g (8.25 mmoles) di N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.68 g (8.25 mmoles) of CH_3COONa, 1.06 g (16.2 mmoles) of zinc dust and 15 ml of glacial acetic acid were treated as described in the Example 1. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:0.5), dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and recrystallized twice from EtOH to yield 0.95 g of the title compound.

EXAMPLE 3

[8R-(4bS*,8α,8aβ,12bβ)]-7-Cyclopropylmethyl-11-diethylaminocarbonyl-10-methyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a-(9H)-diol hydrochloride

0.5 g (1.33 mmoles) of naltrexone hydrochloride, 1.04 g (4 mmoles) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.33 g (4 mmoles) of CH_3COONa, 0.783 g (12 mmoles) di zinc dust and 10 ml of glacial acetic acid were treated as described in the Example 1. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:0.5), dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and recrystallized from MeOH to yield 0.15 g of the title compound.

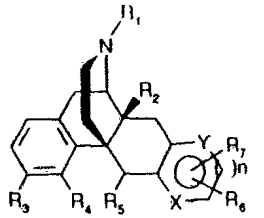
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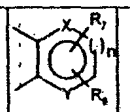
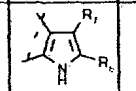
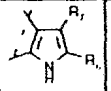
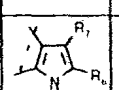
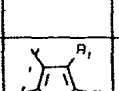
[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-10-methyl-7-propyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a-(9H)-diol hydrochloride

0.57 g (1.2 mmoles) of [8R-(4bS*,8α,8aβ,12bβ)]-11-diethylaminocarbonyl-10-methyl-7-(2-propenyl)-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a-(9H)-diol hydrochloride were dissolved in 120 ml of abs. EtOH and hydrogenated over Pd/C 10% at 30 p.s.i. for 2 h at room temperature. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in a mixture of MeOH/EtOH 1:1 and the solution brought to

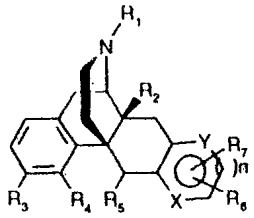
acidic pH with HCl/Et_2O. The precipitate was filtered and recrystallized from EtOH to yield 0.28 g of the title compound.

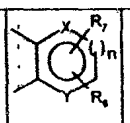
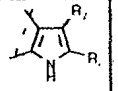
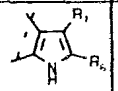
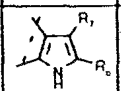
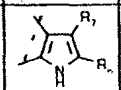
CHEMICAL TABLE



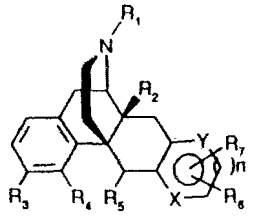
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1	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H) diol hydrochloride	Me	OH	OH	-O-			$CONEt_2$	Me	-333.8	303 dec.	437 (M+); EI	(DMSO): 11.20(s,1H); 9.16(s,1H); 9.15(s br,1H); 6.60(ABq,2H); 6.12(s br,1H); 5.40(s,1H); 3.69(d br,1H); 3.47-3.30(m,5H); 3.18-3.02(m,2H); 2.86(s br,3H); 2.75-2.65(m,1H); 2.55-2.45(m,1H); 2.45(d,1H), 2.23(d,1H); 1.82(s,3H); 1.70(d,br); 1.02(t,6H).
2	[8R (4bS*,8α,8aβ,12bβ)]-11 Diethylaminocarbonyl 10 methyl-7 (2 propenyl) 5,6,7,8,12,12b hexahydro-4,8-methanobenzofuro[3,2 e]pyrrolo[2,3-g] isoquinoline 1,8a(9H) diol hydrochloride	Allyl	OH	OH	-O-			$CONEt_2$	Me	-311.7	281 dec.	464 (M+); FAB	((CDCl3): 9.15(s br,1H); 6.67(d,1H); 6.53(d,1H); 5.90-5.76(m,1H); 5.51(s,1H); 5.26-5.15(m,2H); 3.62-3.51(m,2H); 3.45-3.33(m,2H); 3.16(d,1H); 3.14(d,1H); 3.07(m,1H), 2.73(dd,1H); 2.59(d br,1H); 2.44(d,1H); 2.31(d,1H); 2.28(m,1H); 1.90(s,3H); 1.72(m,1H); 1.11(t,6H).
3	[8R (4bS*,8α,8aβ,12bβ)]-7-Cyclopropylmethyl-11-diethylaminocarbonyl-10-methyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride	CPM	OH	OH	-O-			$CONEt_2$	Me	-358.1	298 dec.	478 (MH+) FAB	(DMSO): 11.15(s,1H); 9.12(s br,1H); 8.90(s,1H); 6.61(d,1H); 6.53(d,1H); 6.23(s br,1H); 5.40(s,1H); 4.03(d,1H); 3.50-3.30(m,5H); 3.18(dd,1H); 3.08(d br,1H); 2.93(m,1H); 2.75-2.57(m,1H); 2.58(d,1H); 2.57(m,2H); 2.22(d,1H); 1.80(s,3H); 1:62(d br,1H); 1.07(d br,1H); 1.06(m,1H); 0.78-0.35(m,4H).
4	[8R (4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-10 methyl-7-propyl 5,6,7,8,12,12b hexahydro 4,8 methanobenzofuro[3,2 e]pyrrolo[2,3 g] isoquinoline-1,8a(9H)-diol hydrochloride	n-Pr	OH	OH	-O-			$CONEt_2$	Me	-365.1	306-307	466 (M+) FAB	((CDCl3): 9.28(s br,1H); 6.75(d,1H); 6.61(d,1H); 5.60(s,1H); 3.74-3.62(m,2H); 3.54-3.44(m,2H); 3.24(d,1H); 3.13(d,1H); 2.85(dd,1H); 2.67(m,1H); 2.56(m,2H); 2.55(d,1H); 2.41(d,1H), 2.40(m,2H), 1.99(s,3H), 1.82(m,1H); 1.69-1.57(m,2H); 1.20(t,6H); 1.04(t,3H).

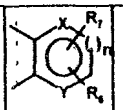
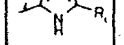
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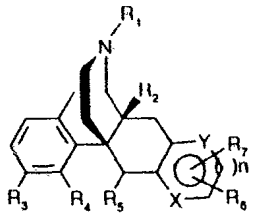
Ex.	name	R_1	R_2	R_3	R_4	R_5		R_6	R_7	$[\alpha]_D^{20}$ C=0.1, MeOH	MP (° C)	m/z	NMR
5	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisopropylaminocarbonyl-7,10-dimethyl 5,6,7,8,12,12b hexahydro 4,8 methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride	Me	OH	OH	-O-			$CON(i\text{-}Pr)_2$	Me	-354.3	294 dec.	466 (MH)+ TSP	(DMSO): 11.08(s,1H); 9.16(s,1H); 9.15(s br,1H); 6.66(d,1H); 6.58(d,1H); 6.07(s br,1H); 5.41(s,1H); 3.78-3.62(m,3H); 3.39(d,1H); 3.11(dd,1H); 3.06(m,1H); 2.84(s br,3H); 2.74-2.62(m,1H); 2.50(m,1H); 2.47(d,1H); 2.22(d,1H); 1.79(s,3H); 1.70(dd,1H); 1.25(d,12H).
6	[8R-(4bS*,8α,8aβ,12bβ)]-11-Benzylaminocarbonyl-7,10-dimethyl 5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline 1,8a(9H)-diol hydrochloride	Me	OH	OH	-O-			$CONHCH_2Ph$	Me	-466.3	>300	472 (MH)+ FAB	(DMSO): 11.50(s,1H); 9.21(s,1H); 9.20(s br,1H); 8.21(ABX,1H); 7.36-7.20(m,5H); 6.67(d,1H); 6.59(d,1H); 6.20(s br,1H); 5.42(s,1H); 4.42(ABX,2H); 3.73(d,1H); 3.40(d,1H); 3.14(dd,1H); 3.08(m,1H); 2.85(s br,3H); 2.78-2.62(m,1H); 2.53(d,1H); 2.49(m,1H); 2.21(d,1H); 2.09(s,3H); 1.73(dd,1H).
7	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-1 methoxy-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride	Me	H	OMe	-O-			$CONEt_2$	Me	-422.7	289-290 dec.	436 (MH+); FAB	(DMSO): 11.50(s br,1H); 11.20(s,1H); 6.80(d,1H); 6.70(d,1H); 5.54(s,1H); 3.95(s br,1H); 3.72(s,3H); 3.40-3.25(m,4H); 3.25(d,1H); 3.25-3.10(m,1H); 3.06-2.88(m,2H); 2.81(s br,3H); 2.80-2.62(m,1H); 2.42-2.22(m,2H); 1.92(dd,1H); 1.89(s,3H); 1.66(dd,H).
8	[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-11-pyrrolidinocarbonyl-5,6,7,8,12,12b hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline 1,8a(9H) diol hydrochloride	Me	OH	OH	-O-			$CON(CH_2)_4$	Me	-463.2	290 dec.	436 (M+) FAB	(DMSO): 11.10(s,1H); 9.11(s,2H); 6.65(d,1H); 6.55(d,1H); 5.40(s,1H); 3.62(m,1H); 3.42(m,4H); 3.30(m,1H); 3.15-3.00(m,2H); 2.80(s br,3H); 2.50(m,2H); 2.45(d,1H); 2.22(d,1H); 1.88(s,3H); 1.81(m,4H); 1.68(d br,1H).

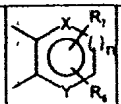
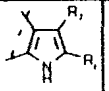
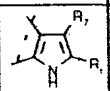
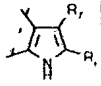
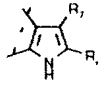
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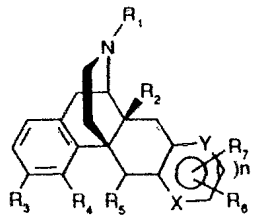
Ex.	name	R_1	R_2	R_3	R_4	R 5		R_6	R_7	$[\alpha]_D^{20}$ C=0.1, MeOH	MP (° C)	m/z	NMR
9	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl 7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1(9H)-ol hydrochloride	Me	H	OH	-O-			$CONEt_2$	Me	-385 9	273 dec.	422 (MH+) FAB	(DMSO, base): 11.00(s,1H); 8.82(s,1H); 6.53(d.1H); 6.44(d,1H); 5.38(s,1H); 3.40(m,4H); 3.20(d,1H); 2.98(d,1H); 2.50-2.22(m,4H); 2.29(s,3H); 2.19(dd,1H); 1.90(ddd,1H); 1.79(s,3H); 1.68(m,2H).
10	[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl 11-morpholinocarbonyl-5,6,7,8,12,12b hexahydro-4,8-methanobenzofuro[3,2 e]pyrrolo[2,3 g] isoquinoline-1,8a(9H)-diol hydrochloride	Me	OH	OH	-O-			$CO[N(CH_2)_4O]$	Me	-325.2	270-280 dec.	451 (M+);EI	(DMSO): 11.30(s,1H); 9.20(s,1H); 9.16(s br,1H); 6.62(d,1H); 6.58(d,1H); 6.19(s,1H); 5.40(s,1H); 3.70(d,1H); 3.58(m,4H); 3.48(m,4H); 3.40(d,1H); 3.12(dd,1H); 3.08(m,1H); 2.85(d,3H); 2.75-2.62(m,1H); 2.50(m,1H); 2.48(d,1H); 2.23(d,1H); 1.86(s,3H); 1.71(dd,1H).
11	[10R,4bS-(4bβ,9aβ)] 7-Diisopropylaminocarbonyl-8,14-dimethyl-4-hydroxy-3-methoxy-4b,5,9,9a,10,11-hexahydro-(6H)-[2,3-h]pyrrolo[10,4b]imino ethanophenanthrene (*)	Me	H	OMe	OH	H		$CON(i\text{-}Pr)_2$	Me	-121.1	214-216	465 (M+.) EI	(DMSO): 10.20(s,1H); 8.05(s,1H); 6.66(d,1H); 6.51(d,1H); 4.68(d,1H); 3.75(m,2H); 3.69(s,3H); 2.91(m,1H); 2.82(m,2H); 2.40-2.20(m,3H); 2.25(s,3H); 2.08(dd,1H); 1.95(m,2H); 1.82(d,1H); 1.74(s,3H); 1.65(ddd,1H); 1.25(d,12H).
12	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisopropylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride	Me	H	OMe	-O-			$CON(i\text{-}Pr)_2$	Me	-378.1	291 dec.	463 (M+.) EI	(DMSO): 11.10(s,2H); 6.80(d,1H); 6.70(d,1H); 5.55(s,1H); 3.97(d,1H); 3.70(s,3H); 3.67(m,2H); 3.25(d,1H); 3.22(m,1H); 3.07-2.92(m,2H); 2.85(d,3H); 2.29-2.12(m,1H); 2.40-2.20(m,2H); 1.95(dd,1H); 1.77(s,3H); 1.68(dd,1H); 1.24(d,12H)

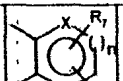
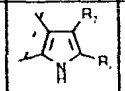
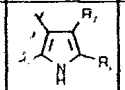
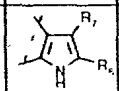
SUBSTITUTE SHEET (RULE 26)



Ex.	name	R_1	R_2	R_3	R_4	R 5		R_6	R_7	$[\alpha]_D^{20}$ C=0.1, MeOH	MP (° C)	m/z	NMR
13	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-8a(9H)-ol hydrochloride	Me	OH	OMe	-O-			$CONEt_2$	Me	-358.8	204 dec.	451 (M+.) EI	(DMSO): 11.20(s,1H); 9.22(s br,1H); 6.83(d,1H); 6.70(d.1H); 6.20(s,1H); 5.49(s,1H); 3.76(d,1H)); 3.70(s,3H); 3.45(d,1H); 3.37(q,4H); 3.29(s,3H); 3.18(dd,1H); 3.10(m,1H); 2.86(d br,3H); 2.75-2.61(m,1H); 2.55(m,1H); 2.52(d,1H); 2.22(d,1H); 1.80(s,3H); 1.73d br,1H).
14	[10R,4bS-(4bβ,9aβ)]-7-Diethylaminocarbonyl 8,14-dimethyl-4-hydroxy-3-methoxy-4b,5,9,9a,10,11 hexahydro-(6H) [2,3 h]pyrrolo[10,4b]imino ethanophenanthrene (*)	Me	H	OMe	OH	H		$CONEt_2$	Me	-340.5	234-235	437 (M+.); EI	(CDCl3): 8.06(s br,1H); 7.25(s,1H); 6.60(ABq,2H); 5.95(s,1H); 4.60(d,1H); 3.79(s,3H); 3.56(dq,2H); 3.40(dq,2H); 3.05(m,1H); 3.00(d,1H); 2.88(dd,1H); 2.52-2.32(m,3H); 2.41(s,3H); 2.25-2.09(m.3H); 1.95(ddd,1H); 1.88(s,3H); 1.80(ddd,1H); 1.12(t,6H).
15	[8R-(4bS*,8α,8aβ,12bβ)]-11-(3-Diethylaminopropyl)aminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline dihydrochloride	Me	H	OMe	-O-			$CONH(CH_2)_3NEt_2$	Me	-381.4	269-271	492 (M+.); EI	
16	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10 dimethyl 5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline (*)	Me	H	H	-O-			$CONEt_2$	Me	-559.2	240-241	405 (M+.); EI	

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Ex.	name	R_1	R_2	R_3	R 4	R 5		R_6	R_7	$[\alpha]_D^{20}$ C=0.1, MeOH	MP (° C)	m/z	NMR
17	[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-1-methoxy-11-(2-methylpropyl)oxycarbonyl-5,6,7,8,12,12b-hexahydro-[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride	Me	H	OMe	-O-			COO-i-Bu	Me	-512.5	278-279 dec.	436.1 (M+.); EI	
18	[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisobutylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro--[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline (*)	Me	H	OMe	-O-			$CON(i\text{-}Bu)_2$	Me	-697.6	141-143	491.0 (M+.); EI	
19	[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-11-isopropylaminocarbonyl-1-methoxy-5,6,7,8,12,12b-hexahydro-[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride	Me	H	OMe	-O-			CONH-iPr	Me	-475.2	257 dec.	421.1 (M+.); EI	

(*) compound transformed in the corresponding free base and, as such, characterised.

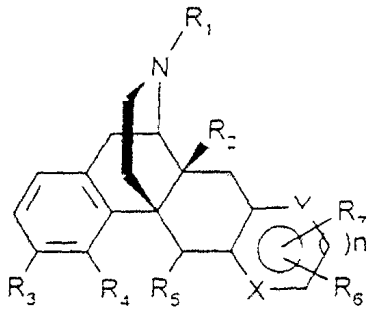
SUBSTITUTE SHEET (RULE 26)

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

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Claims

1 A compound, or salt thereof, of formula (I)



(I)

in which,

R_1 is hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl or furan-2 or 3-yl alkyl or $(CH_2)_mCOR$ wherein m is 1 to 5 and R represents hydroxy, C_{1-5} alkoxy, OC_{3-6} alkenyl or alkylaryl, ~~or R_1 is a group A-B wherein A represents C_{1-10} alkylene and B represents substituted or unsubstituted aryl or heteroaryl.~~

R_2 is hydrogen, hydroxy or C_{1-5} alkoxy, halogen, nitro, NR_8R_9, SR_8, where R_8 and R_9, which may be the same or different, are each hydrogen, C_{1-6} alkyl, or COR_1 where R_1 is defined above;

R_3 is hydrogen, hydroxy, C_{1-5} alkoxy, halogen, SR_8, nitro, NHR_{10}, $NR_{10}R_{11}$, $NHCOR_{10}$, $NHSO_2R_{10}$, where R_{10} and R_{11}, which may be the same or different, are each hydrogen or C_{1-6} alkyl

R_4 and R_5, which may be the same or different, are each independently hydrogen, hydroxy, C_{1-5} alkoxy, or together may form an oxy group (-O-).

R_6 is a group



in which R_3 is defined above, there being up to three R_3 groups in the phenyl ring, or R_6 is a group $C(Z)R_{12}$, in which Z is oxygen or sulphur, R_{12} is C_{1-18} alkyl, C_{1-18} alkoxy or $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different, are hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl ~~or an optionally substituted heterocyclic ring~~ or may form together a C_{3-6} alkyl ring which may be interrupted by an oxygen or a nitrogen

R_7 is hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, or is a group

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in which R_3 is defined above, and,

n is 0 or 1,

when n=0, (i) X is NH, oxygen or sulphur and Y is CH or a R_6 or R_7-substituted carbon; or (ii) X is NH and Y is N; and when n=1, then X and Y are both N, or N and CH.

2. A compound according to claim 1, in which R_1 is methyl, ethyl, propyl, allyl or cyclopropylmethyl.

3. A compound according to claim 1 or 2, in which R_2 is hydrogen or hydroxy.

4. A compound according to any one of claims 1 to 3, in which R_3 is hydrogen, hydroxy or methoxy

5. A compound according to any one of claims 1 to 4, in which each of R_4 and R_5 is hydrogen, hydroxy, methoxy or together they form an oxy group.

6. A compound according to any one of claims 1 to 5, in which R_6 is COO-iPr, $CONEt_2$, CONH-i-Pr, $CON(i\text{-}Pr)_2$, $CONHCH_2Ph$, $CON(\text{-}CH_2\text{-})_4$, $CON(\text{-}C_2H_4OC_2H_4\text{-})$, $CON(i\text{-}Bu)_2$ or $CONH(CH_2)_3NEt_2$.

7. A compound according to claim 1 in which n = 0, X is NH and Y is CH or a R_6- or R_7-substituted carbon atom, where R_6 is a group $-C(Z)-R_{12}$ where R_{12} is $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ alkoxy or $NR_{13}R_{14}$ where R_{13} and R_{14} are as defined in claim 1 and Z is oxygen; and R_7 is methyl.

8. A compound selected from:

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride,

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-10-methyl-7-(2-propenyl)-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride;

[8R-(4bS*,8α,8aβ,12bβ)]-7-Cyclopropylmethyl-11-diethylaminocarbonyl-10-methyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride,

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[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-10-methyl-7-propyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride:

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisopropylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride:

[8R-(4bS*,8α,8aβ,12bβ)]-11-Benzylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride:

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride.

[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-11-pyrrolidinocarbonyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride:

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1(9H)-ol hydrochloride:

[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-11-morpholinocarbonyl-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-1,8a(9H)-diol hydrochloride.

[10R,4bS-(4bβ,9aβ)]-7-Diisopropylaminocarbonyl-8,14-dimethyl-4-hydroxy-3-methoxy-4b,5,9,9a,10,11-hexahydro-(6H)-[2,3-h]pyrrolo[10,4b]imino ethanophenanthrene (*).

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisopropylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride.

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline-8a(9H)-ol hydrochloride.

[10R,4bS-(4bβ,9aβ)]-7-Diethylaminocarbonyl-8,14-dimethyl-4-hydroxy-3-methoxy-4b,5,9,9a,10,11-hexahydro-(6H)-[2,3-h]pyrrolo[10,4b]imino ethanophenanthrene (*).

[8R-(4bS*,8α,8aβ,12bβ)]-11-(3-Diethylaminopropyl)aminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline dihydrochloride.

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diethylaminocarbonyl-7,10-dimethyl-5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline (*);

[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-1-methoxy-11-(2-methylpropyl)oxycarbonyl-5,6,7,8,12,12b-hexahydro-[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride.

[8R-(4bS*,8α,8aβ,12bβ)]-11-Diisobutylaminocarbonyl-7,10-dimethyl-1-methoxy-5,6,7,8,12,12b-hexahydro--[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline (*);

[8R-(4bS*,8α,8aβ,12bβ)]-7,10-Dimethyl-11-isopropylaminocarbonyl-1-methoxy-5,6,7,8,12,12b-hexahydro-[9H]-4,8-methanobenzofuro[3,2-e]pyrrolo[2,3-g] isoquinoline hydrochloride.

9 A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier

10. A method for the manufacture of a medicament for use as an analgesic, immunosuppressant to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agent, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough and respiratory depression, mental illness, epileptic seizures and other neurologic disorders comprising the step of bringing a compound according to any one of claims 1 to 8 into a form suitable for administration.

11. A method for the treatment and/or prophylaxis in mammals, particularly

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humans, of the therapeutic conditions as defined in claim 12, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 8

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/02694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/20 C07D471/08 A61K31/435 C07D495/08 C07D495/20
C07D491/10 //(C07D491/20,307:00,221:00,209:00),(C07D471/08,
221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARCHIV DER PHARMAZIE, vol. 325, no. 10, 1992 WEINHEIM DE, pages 629-636, GOERLITZER ET AL. '1,12-Epoxy-6,12a-iminoethano-naphtho[2,1-g]chinoline' see page 629, column 1, paragraphs 1 and 2 and page 631, compounds 8c-8l	1,9

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1995	- 5. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Alfaro Faus, I

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/EP 95/02694

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/compoisition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.