HU000025869T2

(19) **HU**

(11) Lajstromszám: **E 025 869**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 05 755563**
(22) A bejelentés napja: **2005. 06. 21.**

(96) Az európai bejelentés bejelentési száma:
EP 20050755563
(97) Az európai bejelentés közzétételi adatai:
EP 1758886 A1 **2006. 01. 05.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 1758886 B1 **2015. 03. 04.**

(51) Int. Cl.: ***C07D 401/06*** *(2006.01)*
A61K 314/96 *(2006.01)*
A61P 15/06 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/EP 05/006760
(87) A nemzetközi közzétételi szám:
WO 06000399

(30) Elsőbbségi adatok:
0414093 **2004. 06. 23.** **GB**

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(54) **Piperazindionok mint oxitocin receptor antagonisták**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 758 886 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
04.03.2015 Bulletin 2015/10

(21) Application number: **05755563.3**

(22) Date of filing: **21.06.2005**

(51) Int Cl.:
C07D 401/06 *(2006.01)* ***A61K 31/496*** *(2006.01)*
A61P 15/06 *(2006.01)*

(86) International application number:
PCT/EP2005/006760

(87) International publication number:
WO 2006/000399 (05.01.2006 Gazette 2006/01)

(54) **PIPERAZINEDIONES AS OXYTOCIN RECEPTOR ANTAGONISTS**

PIPERAZINDIONE ALS OXYTOCINREZEPTORANTAGONISTEN

PIPERAZINEDIONES UTILISES EN TANT QU'ANTAGONISTES DU RECEPTEUR DE L'OXYTOCINE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
HR LV

(30) Priority: **23.06.2004 GB 0414093**

(43) Date of publication of application:
07.03.2007 Bulletin 2007/10

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(56) References cited:
WO-A-99/47549 **WO-A-03/053443**
WO-A-2005/000311 **WO-A-2005/000840**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 1 758 886 B1

Description

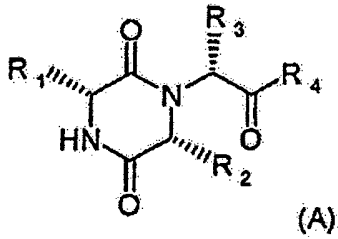
[0001] This invention relates to a novel diketopiperazine derivative having a potent and selective antagonist action at the oxytocin receptor, to processes for its preparation, pharmaceutical compositions containing it and to its use in medicine.

[0002] The hormone oxytocin is a potent contractor of the uterus and is used for the induction or augmentation of labour. Also the density of uterine oxytocin receptors increases significantly by >100 fold during pregnancy and peaks in labour (pre-term and term).

[0003] Pre-term births/labour (between 24 and 37 weeks) causes about 60% of infant mortality/morbidity and thus a compound which inhibits the uterine actions of oxytocin e.g. oxytocin antagonists, should be useful for the prevention or control of pre-term labour.

[0004] International patent application WO 99/47549 describes diketopiperazine derivatives including 3-benzyl-,5-diketopiperazine derivatives as inhibitors of fructose 1,6-bisphosphate (FBPase).

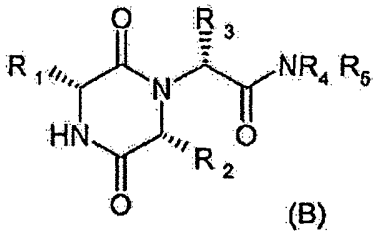
[0005] International patent application WO 03/053443 describes a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor. A preferred class of compounds described therein is represented by the formula (A)



(A)

[0006] Such compounds include those wherein inter alia R_1 is 2-indanyl, R_2 is C_{3-4}alkyl, R_3 is a 5 or 6 membered heteroaryl group linked to the rest of the molecule via a carbon atom in the ring, R_4 represents the group NR_5R_6 wherein Rs and R_6 each represent alkyl e.g. methyl, or R_5 and R_6 together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen.

[0007] International patent application WO 2005/000840 describes diketopiperazine derivatives of formula (B)

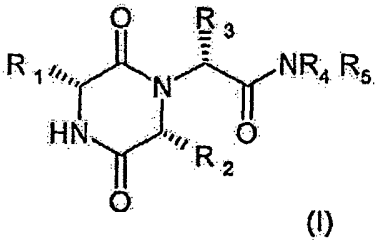


(B)

wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2-methyl-1,3-oxazol-4-yl and R_4 and R_5 together with the nitrogen atom to which they are attached represent morpholino.

[0008] We have now found a novel group of selective oxytocin receptor antagonists which exhibit a particularly advantageous pharmacokinetic profile.

[0009] The present invention thus provides a compound of formula (I)



(I)

wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2,6-dimethyl-3-pyridyl, R_4 and R_5 together with the nitrogen atom

to which they are attached represent morpholino, or a pharmaceutically acceptable acid addition salt thereof, in which the acid is selected from: hydrochloric, hydrobromic, nitric, phosphoric, sulphuric, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric and maleic acid.

[0010] It will be appreciated that the compound of formula (I) possesses the absolute stereochemistry depicted at the asymmetric carbon atoms bearing groups R_1, R_2 and R_3, ie the stereochemistry at these positions is always (*R*). Nevertheless, it should also be appreciated that although such compounds are substantially free of the (*S*)-epimer at each of R_1, R_2 and R_3, each epimer may be present in small amounts, for example 1 % or less of the (S)-epimer may be present.

[0011] It will also be appreciated that the group R_2 contains an asymmetric carbon atom and that the invention includes both the (*R*)- and (*S*)-epimers thereof.

[0012] In one embodiment of the invention, R_2 Is (1*S*)-1-methylpropyl. In another embodiment of the invention, R_2 is (1*R*)-1-methylpropyl.

[0013] A further embodiment of the invention is the compound the preparation of which is specifically described in example 3.

[0014] In one aspect, the compound of formula (I) is (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-((1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-((1*S*)-1-methylpropyl]-2,6-piperazinedione or a pharmaceutically acceptable acid addition salt thereof, in which the acid is selected from: hydrochloric, hydrobromic, nitric, phosphoric, sulphuric, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric and maleic acid.

[0015] Solvates of the compounds of formula (I) are also disclosed, for example hydrates, or solvates with pharmaceutically acceptable solvents including, but not limited to, alcohols, for example ethanol, *iso*-propanol, acetone, ethers, esters, e.g. ethyl acetate.

[0016] The compound of the invention may also be used in combination with other therapeutic agents. A combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent is provided.

[0017] When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. The compound of the present invention may be used In combination with tocolytics or prophylactic medicines. These include, but are not limited to, beta-agonists such as terbutaline or ritodrine, calcium channel blockers, e.g. nifedepine, non-steroidal anti-inflammatory drugs, such as indomethacin, salts of magnesium, such as magnesium sulphate, other oxytocin antagonists, such as atosiban, and progesterone agonists and formulations. In addition the compound of the present invention may be used in combination with antenatal steroids including betamethasone and dexamethasone, prenatal vitamins especially folate supplements, antibiotics, including but not limited to ampicillin, amoxicillin/clavulanate, metronidazole, clindamycin, and anxiolytics.

[0018] The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient are disclosed. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

[0019] When administration is sequential, either the compound of the invention or the second therapeutic agent may be administered first. When administration Is simultaneous, the combination may be administered either In the same or different pharmaceutical composition.

[0020] When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

[0021] The compound of formula (I) has a high affinity for the oxytocin receptors on the uterus of rats and humans and this may be determined using conventional procedures. For example the affinity for the oxytocin receptors on the rat uterus may be determined by the procedure of Pettibone et al, Drug Development Research 30. 129-142 (1993). The compounds of the invention also exhibit high affinity at the human recombinant oxytocin receptor in CHO cells and this may be conveniently demonstrated using the procedure described by Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p1301-1305.

[0022] The compound of the invention exhibits an advantageous pharmacokinetic profile including good bioavailability coupled with good aqueous solubility. In one aspect, the compound of the invention exhibit good potency and low intrinsic clearance. In another aspect, the compound of the invention exhibit low intrinsic clearance.

[0023] The compound of the invention is therefore useful in the treatment or prevention of diseases and/or conditions mediated through the action of oxytocin. Examples of such diseases and/or conditions include pre-term labour, dysmen-

orrhea, endometriosis and benign prostatic hyperplasia.

[0024] The compound may also be useful to delay labour prior to elective caesarean section or transfer of the patient to a tertiary care centre, treatment of sexual dysfunction (male and female), particularly premature ejaculation, obesity, eating disorders, congestive heart failure, arterial hypertension, liver cirrhosis, nephritic or ocular hypertension, obsessive-compulsive disorder and neuropsychiatric disorders. The compound of the Invention may also be useful for improving fertility rates in animals, e.g. farm animals.

[0025] The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable acid addition salt as described above for use in therapy, particularly for use in human and veterinary therapy, and in particular use as medicine for antagonising the effects of oxytocin upon the oxytocin receptor.

[0026] The invention also provides for the use of a compound of formula (I) or a pharmaceutically acceptable acid addition salt as described above for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

[0027] A method for antagonising the effects of oxytocin upon the oxytocin receptor, comprising administering to a patient in need thereof an antagonistic amount of at least one chemical entity selected from a compound of formula (I) and/or pharmaceutically acceptable derivatives thereof is also provided.

[0028] It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

[0029] It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 1000 mg per day, dependent upon the route of administration.

[0030] Thus for parenteral administration a daily dose will typically be in the range 2 to 50mg, preferably 5 to 25mg per day. For oral administration a daily dose will typically be within the range 10 to 1000 mg, e.g. 50 to 500 mg per day.

[0031] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0032] While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

[0033] The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable acid addition salt as described above together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0034] The compositions of the Invention include those in a form especially formulated for oral, buccal, parenteral, inhatation or insufflation, implant, vaginal or rectal administration.

[0035] Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

[0036] For buccal administration the composition may take the form of tablets or lozenges formulated in the conventional manner.

[0037] The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

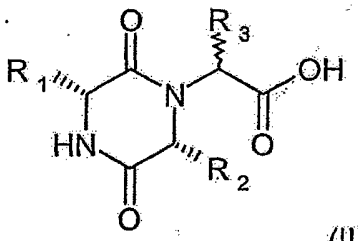
[0038] The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 1-50% for tablets and capsules and 3-50% for liquid preparations.

[0039] The advantageous pharmacokinetic profile of the compounds of the invention is readily demonstrated using

conventional procedures for measuring the pharmacokinetic properties of biologically active compounds.

[0040] The compounds of the invention and pharmaceutically acceptable derivatives thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of the invention unless otherwise stated.

[0041] Compounds of formula (I) may be prepared by reaction of the carboxylic acid (II), wherein R_1, R_2 and R_3 have the meanings defined in formula (I), and the chirality at R_3 is either R or S, or a mixture thereof,



(II)

or an activated derivative thereof with the amine HNR_4R_5, wherein R_4 and R_5 have the meaning defined in formula (I), under standard conditions for preparing amides from a carboxylic acid or an activated derivative thereof and an amine.

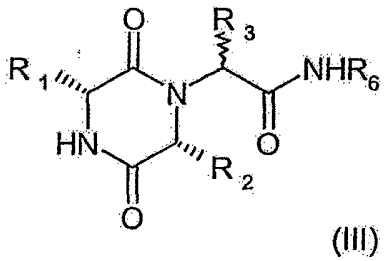
[0042] It will be appreciated that the mixture of diastereomers of compounds of formula (I) obtained from the above reaction may be separated using standard resolution techniques well known in the art, for example column chromatography.

[0043] Thus the amide of formula (I) may be prepared by treating the carboxylic acid of formula (II) with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride), oxalyl chloride or 1,1'-carbonyldiimidazole in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed, ie the activated derivative of the compound of formula (II), with the amine HNR_4R_5,

[0044] Alternatively the amide of formula (I) may be prepared by reacting a mixed anhydride derived from the carboxylic acid (II), wherein R_1, R_2 and R_3 have the meanings defined in formula (I) with the amine HNR_4R_5 in an aprotic solvent such as tetrahydrofuran. Conveniently the reaction is carried out at low temperatures, for example 25°C to - 90°C, conveniently at approximately-78°C.

[0045] The mixed anhydride is conveniently prepared by reacting the carboxylic acid (II) with a suitable acid chloride e.g. pivalolyl chloride in an aprotic solvent such as ethyl acetate in the presence of a tertiary organic base such as a trialkylamine e.g. triethylamine and at low temperatures, for example 25°C to - 90°C, conveniently at approximately -78°C.

[0046] Compounds of formula (I) may also be prepared by reacting a compound of formula (III)



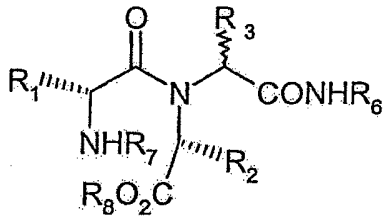
(III)

wherein R_1, R_2 and R_3 have the meanings defined in formula (I) and R_6 is 2-hydroxyphenyl, with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the products thus formed with the amine HNR_4R_5.

[0047] Compounds of formula (II) may be prepared from a compound of formula (III) wherein R_6 is 2-hydroxyphenyl by reaction with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.

[0048] Compounds of formula (III) wherein R_6 is 2-hydroxyphenyl may be prepared from the corresponding compounds of formula (III) wherein R_6 is a 2-benzyloxyphenyl group by hydrogenolysis using hydrogen and a palladium catalyst.

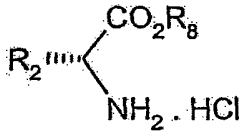
[0049] Alternatively compounds of formula (III) wherein R_6 is a 2-hydroxyphenyl may be prepared from the compound of formula (IV)



(IV)

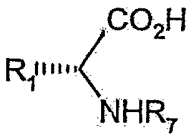
wherein R_2 and R_3 have the meanings defined in formula (I), R_6 is 2-benzyloxyphenyl, R_7 is benzyloxycarbonyl and R_8 is C_{1-6}alkyl, by the reaction with hydrogen in the presence of a palladium on charcoal catalyst and acetic acid. This reaction is conveniently carried out in a solvent such as ethanol, trifluoroethanol or mixtures thereof.

[0050] Compounds of formula (IV) may be prepared by reacting the amino ester hydrochloride (V)



(V)

wherein R_1 has the meaning defined in formula (I) and R_8 is C_{1-6}alkyl, with an aldehyde R_3CHO (VI) wherein R_3 has the meaning defined in formula (I), in the presence of triethylamine and in a solvent such as trifluoroethanol and then reacting the resultant product with a compound of formula (VII)



(VII)

wherein R_1 has the meaning defined in formula (I) and R_7 is t-butyloxycarbonyl or benzyloxycarbonyl and the isocyanide CNR_6 (VIII) wherein R_6 is a 2-benzyloxyphenyl group, in a solvent such as trifluoroethanol.

[0051] Compounds of formula (III) wherein R_6 is a 2-benzyloxyphenyl group may be prepared from a compound of formula (IV) wherein R_1, R_2 and R_3 have the meanings defined in formula (I), R_6 Is 2-benzyloxyphenyl and R_7 is t-butyloxycarbonyl by the reaction with hydrogen chloride in dioxan followed with triethylamine in a solvent such as dichloromethane.

[0052] The compound of formula (IV) wherein R_7 is t-butyloxycarbonyl may be prepared by the route described above using a compound of formula (VII) wherein R_7 is t-butyloxycarbonyl.

[0053] The R_2 substituent is a 1-methylpropyl group and the compound of formula (I) wherein R_2 is a 1-methylpropyl group having an (*S*) or (*R*) configuration may be prepared by starting with the aminoester hydrochloride (V) wherein the R_2 group has the required (S) or (R) configuration.

[0054] Aminoester hydrochloride (V), wherein R_1 has the meaning defined in formula (I) and R_8 is C_{1-6} alkyl, may be prepared from the corresponding commercially available amino acids, D-alloisoleucine or D-isoleucine, by the method of Schmidt, U; Kroner, M; Griesser, H. Synthesis (1989), (11), 832-5.

[0055] Aldehydes R_3CHO (VI), wherein R_3 has the meaning defined in formula (I), are either commercially available or may be prepared by literature methods (Comins, Daniel L.; Weglarz, Michael A.; J.Org.Chem.; 53; 19; 1988; 4437-4442).

[0056] The aminoacid derivative (VII) wherein R_1 has the meaning defined in formula (I) and R_7 is t-butyloxycarbonyl is commercially available; the aminoacid derivative (VII) wherein R_1 has the meaning defined in formula (I) and R_7 is benzyloxycarbonyl may be prepared from the corresponding commercially available amino acid (R)-$R_1CH(NH_2)CO_2H$ (IX), wherein R_1 has the meaning defined in formula (I), by treatment with N-(benzyloxycarbonyloxy)succinimde and triethylamine in a solvent such as dioxane in water.

[0057] The isocyanide CNR_6 (VIII) may be prepared according to literature methods (Obrecht, Roland; Herrmann, Rudolf; Ugi, Ivar, Synthesis, 1985,4, 400-402).

[0058] Acid addition salts of the compound of formula (I) may be prepared by conventional means, for example, by treating a solution of the compound in a suitable solvent such as dichloromethane or acetone, with a suitable solution of the appropriate inorganic or organic acid.

[0059] The following examples are illustrative, but not limiting of the embodiments of the present invention.

Experimental

Nomenclature

[0060] All intermediates and examples were named using ACD Name Pro 6.02 in ISISDraw.

Abbreviations

[0061]

CV: Column volume. One column volume is defined as the volume occupied by the sorbent in the packed column. This can be approximately calculated from the mass and density of the particular sorbent being used (1CV= mass divided by density).

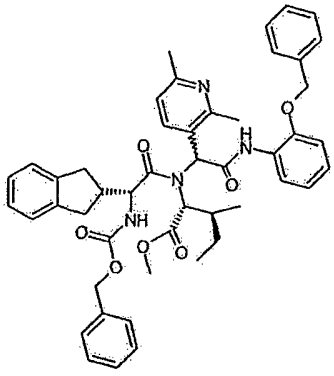
General purification and analytical methods

[0062] Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H and 5% water in acetonitrile (solvent B), using the either elution gradient 1, 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 0%B or elution gradient 2, 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-4.6 minutes 100%B, 4.6-4.8 minutes 0%B at a flow rate of 3 ml/minute. Retention times (Rt) are quoted in minutes. The mass spectra (MS) were recorded on a Waters ZQ 2000 mass spectrometer using electrospray positive [ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative [ES-ve to give $(M-H)^-$ molecular ion] modes. ^1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

[0063] Purification using silica cartridges refers to chromatography carried out using a Combiflash® Companion™ with Redisep® cartridges supplied by Presearch. Hydrophobic frits refer to filtration tubes sold by Whatman. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd. TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F_{254}.

Intermediate 1

[0064]



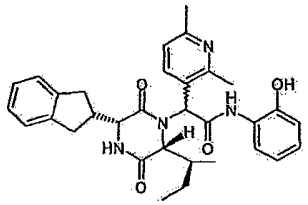
Methyl *N*-[(2*R*)-2-(2,3-dihydro-1*H*-inden-2yl)-2-({[(phenylmethyl)oxy]carbonyl} amino)acetyl]-*N*-[1-(2,6-dimethyl-3-pyridinyl)-2-oxo-2-({2-[(phenylmethyl)oxy] phenyl}amino)ethyl]-D-alloisoleucinate

[0065] 2,6-dimethylpyridine-3-carboxaldehyde (Aurora Feinchemie GmbH) (2.00g, 16.1 mmol) and (D)-alloisoleucine methyl ester hydrochloride (2.93g, 16.1mmol) in methanol (50mL) and 2,2,2-trifluoroethanol (50mL) were treated with triethylamine (2.24mL, 16.1mmol) and the mixture was stirred under nitrogen at room temperature for 20 h. (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(phenylmethyl)oxy]carbonyl}amino)ethanoic acid (5.24g, 16.1 mmol) and 2-benzyloxyphenylisonitrile (3.37g, 16.1 mmol) were added and the mixture was stirred at room temperature under nitrogen for 4 days. The mixture was concentrated under reduced pressure then partitioned between ethyl acetate (150mL) and water

(150mL) plus saturated aqueous sodium hydrogen carbonate (6mL). The aqueous phase was back-extracted with ethyl acetate (50mL) and the combined organic extracts were washed successively with semi-saturated aqueous solutions of sodium hydrogen carbonate, ammonium chloride and sodium chloride (100mL each), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give the crude product (12.01g). This was purified on a Redisep silica column (330g) eluted with 20-50% ethyl acetate in cyclohexane to afford 7.46g of the title compound as a pair of diastereomers.
HPLC Rt = 3.88 and 3.96 minutes (gradient 1); m/z $[M+H]^+$ = 797

Intermediate 2

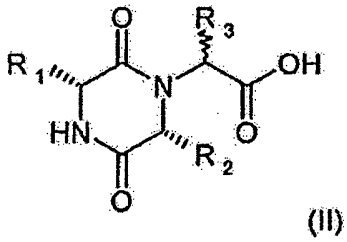
[0066]



[0067] The advantageous pharmacokinetic profile of the compound of the invention is readily demonstrated using conventional procedures for measuring the pharmacokinetic properties of biologically active compounds.

[0068] The compound of the invention and pharmaceutically acceptable acid addition salts as described above may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of the invention unless otherwise stated.

[0069] Compounds of formula (I) may be prepared by reaction of the carboxylic acid (II), wherein R_1, R_2 and R_3 have the meanings defined in formula (I), and the chirality at R_3 is either R or S, or a mixture thereof,



(II)

or an activated derivative thereof with the amine HNR_4R_5, wherein R_4 and R_5 have the meaning defined in formula (I), under standard conditions for preparing amides from a carboxylic acid or an activated derivative thereof and an amine.

[0070] It will be appreciated that the mixture of diastereomers of compounds of formula (I) obtained from the above reaction may be separated using standard resolution techniques well known in the art, for example column chromatography.

[0071] Thus the amide of formula (I) may be prepared by treating the carboxylic acid of formula (II) with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), TBTU (2-(1H-benzotriaxol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride), oxalyl chloride or 1,1'-carbonyldiimidazole in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed, ie the activated derivative of the compound of formula (II), with the amine HNR_4R_5.

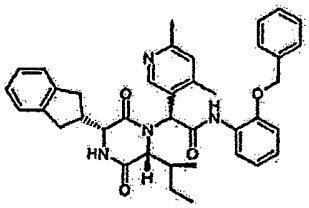
2-((3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(2,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide

[0072] The crude methyl *N*-[(2*R*)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-({[(phenylmethyl) oxy]carbonyl}amino)acetyl]-*N*-[1-(2,6-dimethyl-3-pyridinyl)-2-oxo-2-({2-[(phenylmethyl)oxy]phenyl}amino)ethyl]-D-alloisoleucinate (intermediate 1) (7.46g) was dissolved in ethanol (150mL) and acetic acid (10mL) and the mixture was hydrogenated at 1 atmosphere of H_2 over 10% palladium on carbon (Degussa type) (1.8g wetted with water 1:1 w:w) for 18h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water with saturated aqueous sodium hydrogen carbonate added until the aqueous phase was basic (pH 8). The aqueous phase

was extracted with ethyl acetate and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate:water 3:1 (100mL) then with saturated brine before being dried over anhydrous magnesium sulphate and evaporated under reduced pressure. The crude product was purified on a Redisep silica column (120g) eluted with 0-10% methanol in ethyl acetate to give the title compound as a pair of diastereomers (2.94g).
HPLC Rt = 2.75 and 2.81 minutes (gradient 2); m/z $[M+H]^+$ = 541

Comparative Intermediate 3

[0073]



2-{(3*R*,6R)-3-(2,3-Dihydro-1*H*-Inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyrridinyl)-*N*-{2-[(phenylmethyl)oxy]-phenyl}acetamide

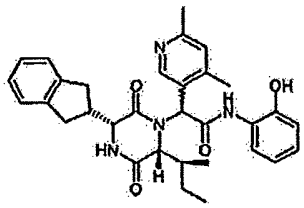
[0074] 4,6-Dimethyl-3-pyridinecarbaldehyde[1] (2.52g) and methyl D-alloisoleucinate hydrochloride (3.4g) were dissolved in 2,2,2-trifluoroethanol (50ml). To this was added triethylamine (2.61ml) and the reaction mixture was left to stand for 18 hours. (2*R*)-2,3-Dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]-carbonyl}amino)ethanoic acid (5.44g) and 2-[(phenylmethyl)oxy]phenyl isocyanide (4.18g) with methanol (10ml) were added to the reaction mixture and the solution was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the residue was separated between dichloromethane and water. The organic phase was passed through a hydrophobic frit and evaporated *in vacuo.* The residue was dissolved in 4N hydrogen chloride in dioxan (50ml) and the reaction mixture was left to stand for 4 hours. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (200ml). To this was added triethylamine (20ml) and the reaction mixture was left to stand for 20 hours. The reaction mixture was separated between dichloromethane and water. The organic phase was passed through a hydrophobic frit and evaporated *in vacuo.* The residue was applied to 4x90g Biotage columns and eluted with cyclohexane/ethyl acetate (1:1, 1:2 v/v) and ethyl acetate. The required fractions were combined and evaporated in vacuo to give 2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-{2-[(phenylmethyl)oxy]phenyl}acetamide (5.55g, 47%) as a tan foam.
HPLC Rt = 3.43, 3.45 minutes gradient 1); m/z $[M+H]^+$ = 631

[0075] Ref:

1.Comins, Daniel L.; Weglarz, Michael A.; J.Org.Chem.; 53; 19; 1988; 4437-4442.

Comparative Intermediate 4

[0076]



2-{(3*R*,6*R*-)3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide

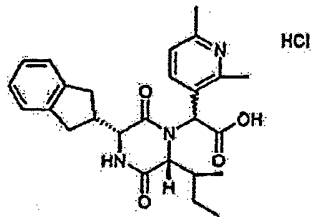
[0077] 2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-{2-[(phenylmethyl)oxy]phenyl}acetamide (intermediate 3) (3.30g) was dissolved In ethanol (75ml) and hydrogenated over palladium on charcoal (wet 10% Pd, 0.50g) for 20 hours. The catalyst was removed by filtration and

washed with dichloromethane. The combined filtrate and washings were evaporated *in vacuo.* The residue was applied to a 90g Biotage column and eluted with ethyl acetate. The required fractions were combined and evaporated *in vacuo* to give 2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide (2.43g, 87%) as a pale yellow solid.
HPLC Rt = 2.86 minutes (gradient 1); m/z $[M+H]^+$ = 541.

Intermediate 5

{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl)(2,6-dimethyl-3-pyridinyl)acetic acid hydrochloride

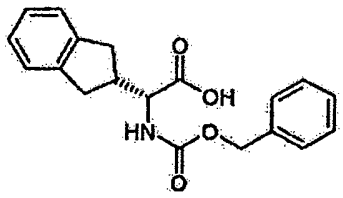
[0078]



[0079] 2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(2,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide (24.25g, 45mmol) (intermediate 2) and 1,1'-carbonyidiimidazole (11.7g, 72mmol) were dissolved in dry dichloromethane (200ml) and left to stand under nitrogen for 20 hours. The solvent was removed *in vacuo* and the residue was dissolved in acetone (200ml) and 2N hydrochloric acid (20ml). After stirring for 20 hours the solvent was removed *in vacuo* and the residue was dissolved in methanol (50ml). The solution was applied to an aminopropyl cartridge (2x70g) and eluted with methanol (250ml) and then 10% acetic acid in methanol (250ml). The required fractions were combined and evaporated *in vacuo.* The residue was treated with 2N hydrochloric acid and the resulting solution evaporated *in vacuo* to give the title compound {(3R,6R)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2,6-dimethyl-3-pyridinyl)acetic acid hydrochloride as a tan solid (12.21g, 56%).
HPLC Rt = 2.48 minutes (gradient 2); m/z $[M+H]^+$ = 450.

Comparative Intermediate 6

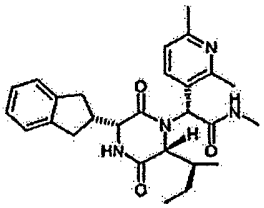
[0080]



[0081] (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(phenylmethyl)oxy]carbonyl}amino)ethanoic acid (2*R*)-amino(2,3-dihydro-1*H*-inden-2-yl)ethanoic acid (1.91g, 10mmol) was suspended in dioxane (10ml) and water (10ml). To this was added triethylamine (1.7ml) and N-(benzyloxycarbonyloxy)-succinimde (2.54g) and the reaction mixture was stirred rapidly at room temperature for 2 days. The reaction mixture was poured into water (50ml) and extracted with chloroform (100ml). The organic phase was washed with 1N hydrochloric acid (50ml) and water (50ml). This was dried over magnesium sulphate and the solvent removed *in vacuo* to give the title compound (3.06g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.40-7.29 (m, 5H), 7.21-7.11 (m, 4H), 5.28 (d, 1H, J=8.6hZ), 5.11 (s, 2H), 4.57 (m, 1H), 3.14-2.79 (m, 5H); LCMS m/z 326 (MH^+), Rt 3.35min (gradient 2)

Comparative Example 1

[0082]



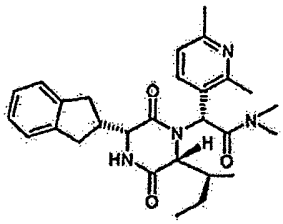
(2*R*)-2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(2,6-dimethyl-3-pyridinyl)-*N*-methylethanamide

[0083] 2-{(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(2,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide (intermediate 2) (0.400g, 0.74mmol) and 1,1'-carbonyldiimidazole (0.192g, 1.18mmol) in dry dichloromethane (10mL) were stirred at room temperature under N_2 for 7 hrs. The mixture was treated with a 2M solution of methylamine in tetrahydrofuran (1.849mL, 3.70mmol) and left to stand overnight at room temperature. The solvents were blown down under N_2 and the residue was purified on a Redisep silica column (35g) eluted with 0-10% methanol in ethyl acetate followed by further purification on a Kromasil KR100-10-C18 reverse-phase column eluted with aqueous acetonitrile (20-46% MeCN) containing 0.1% formic acid. This gave the title compound as a white lyophilisate (30%) after freeze-drying from 1,4-dioxane.
HPLC Rt = 2.44 minutes (gradient 1); m/z $[M+H]^+$ = 463
^{1}H NMR ($CDCl_3$) δ 7.63 (d, 1H), 7.25-7.15 (m, 4H), 7.05 (d, 1H), 6.79 (d, 1H), 5.96 (q, 1H), 5.35 (s, 1H), 4.07 (dd, 1H), 3.88 (d, 1H), 3.19-2.88 (m, 4H), 2.85 (d, 3H), 2.81-2.73 (m, 1H), 2.56 (s, 3H), 2.55 (s, 3H), 1.82-1.67 (m, 2H), 1.20-1.08 (m, 1H), 0.99 (d, 3H), 0.90 (t, 3H).

[0084] Similarly prepared from intermediate 2 and dimethylamine (2.0M in tetrahydrofuran):

Comparative Example 2

[0085]

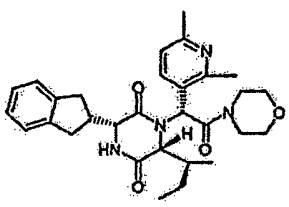


[0086] (2*R*)-2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(2,6-dimethyl-3-pyridinyl)-*N*,*N*-dimethylethanamide as a white lyophilisate (33%) after freeze-drying from 1,4-dioxane HPLC Rt = 2.69 minutes (gradient 1); m/z $[M+H]^+$ = 477
^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H), 7.27-7.15 (m, 4H), 7.08 (d, 1H), 6.66 (s, 1H), 6.30 (d, 1H), 4.10 (dd, 1H), 4.05 (d, 1H), 3.22-3.08 (m, 3H), 2.99-2.84 (m, 4 H), 2.80-2.70 (m, 4H), 2.63 (s, 3H), 2.58 (s, 3H), 1.65-1.53 (m, 1H), 0.97-0.78 (m, 2H), 0.71 (t, 3H), 0.46 (d, 3H).

[0087] Similarly prepared from intermediate 2 and morpholine (3.7mmol):

Example 3 (Method A)

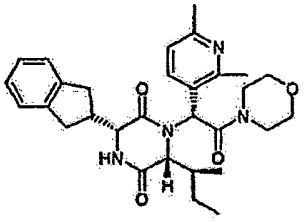
[0088]



[0089] (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl}-1-[(1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-9-methylpropyl]-2,5-piperazinedione as a white lyophilisate (88mg, 23%) after freeze-drying from 1,4-dioxane
HPLC Rt = 2.70 minutes (gradient 2); m/z $[M+H]^+$ = 519
^1H NMR ($CDCl_3$) δ 7.49 (d, 1H), 7,27-7,15 (m, 4H), 7.10 (d, 1H), 6.68 (s, 1H), 6.40 (d, 1H), 4.10 (dd, 1H), 4.01 (d, 1H), 3.74-3.52 (m, 5H), 3.28-3.07 (m, 5H), 2.97-2.84 (m, 2H), 2.79-2.71 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.65-1.53 (m, 1H), 0.98-0.80 (m, 2H), 0.70 (t, 3H), 0.45 (d, 3H).

Example 3 (Method B)

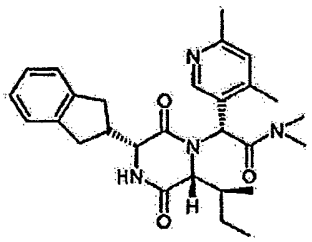
[0090]



[0091] (3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-1-methylproply]-2,5-piperazinedione A suspension of {(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2,6-dimethyl-3-pyridinyl)acetic acid hydrochloride (5.0g, 10.3mmol) (intermediate 5) In dry dichloromethane (50ml) was treated with 1,1-carbonyldiimidazole (2.6g, 16mmol) and the reaction mixture was stirred under nitrogen for 18 hours. Morpholine (4.8ml, 55mmol) was added and the resultant solution was left to stand under nitrogen for 18 hours. The solvent was removed *in vacuo* and the residue was separated between ethyl acetate and water. The organic phase was washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane. This was applied to a basic alumina cartridge (240g) and eluted using a gradient of 0-7.5% methanol in diethyl ether (9CV), 7.5-10% methanol in diethyl ether (1CV) and 10% methanol in diethyl ether (1CV). The required fractions were combined and *evaporated in vacuo* to give (3*R*,6*R*)-3-(2,3-dlhydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-1-methylpropyl]-2,5-piperazinedione as a white solid (2.4g, 45%).
HPLC Rt = 2.72 minutes (gradient 2); m/z $[M+H]^+$ = 519

Comparative Example 4

[0092]



(2*R*)-2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*,*N*-dimethylethanamide

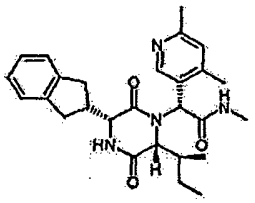
[0093] 2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-(2-hydroxyphenyl)acetamide (intermediate 4) (0.700g) and 1,1'-carbonyldiimidazole (0.324g) were dissolved in dry dichloromethane (20ml) and left to stand for 20 hours. To one half of this solution (10ml) was added a 2.0M solution of dimethylamine in tetrahydrofuran (5ml) and the reaction mixture was left to stand for 3 days. The reaction mixture was separated between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic phase was passed through a hydrophobic frit and evaporated *in vacuo.* The residue was applied to a silica cartridge (10g) and eluted with ethyl acetate then 5% methanol in ethyl acetate. The required fractions were evaporated In vacuo and the residue was purified further using Mass Directed AutoPrep. This gave (2R)-2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-

6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*,*N*-dimethylethenamide (0,10g, 32%) as a white foam.
HPLC Rt = 2.82 minutes (gradient 1); m/z $[M+H]^+$ = 477
^1H NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.26-7.15 (m, 4H), 7.08 (s, 1H), 6.71 (s, 1H), 6.16 (d, 1H), 4.17 (d, 1H), 4.10 (dd, 1H), 3.22-3.06 (m, 3H), 2.98 (s, 3H), 2.91 (m, 1H), 2.74 (dd, 1H), 2.67 (s, 3H), 2.57 (s, 3H), 2.39 (s, 3H), 1.56 (m, 1H), 0.93 (m, 1H), 0.85 (m, 1H), 0.68 (t, 3H), 0.45 (d, 3H).

[0094] Similarly prepared from intermediate 4 and methylamine:

Comparative Example 5

[0095]

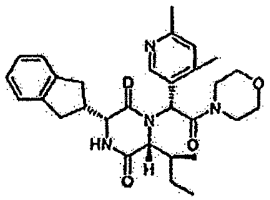


[0096] (2*R*)-2-{(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}-2-(4,6-dimethyl-3-pyridinyl)-*N*-methylethanamide HPLC Rt = 2.60 minutes (gradient 1); m/z $[M+H]^+$ = 463 ^1H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.25-7.14 (m, 4H), 7.04 (s, 1H), 6.72 (d, 1H), 6.07 (q, 1H), 5.45 (s, 1 H), 4.07 (dd, 1 H), 3.90 (d, 1 H), 3.17-3.04 (m, 3H), 2.92 (m, 1H), 2.86 (d, 3H), 2.76 (dd, 1H), 2.53 (s, 3H), 2.33 (s, 3H), 1.70 (m, 2H), 1.12 (m, 1H), 0.94 (d, 3H), 0.87 (t, 3H).

[0097] Similarly prepared from intermediate 4 and morpholine:

Comparative Example 6

[0098]



[0099] (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(4,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-1-methylpropyl]-2,5-piperazinedione HPLC Rt = 2.94 minutes (gradient 2); m/z $[M+H]^+$ = 519 ^1H NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.25-7.15 (m, 4H), 7.09 (s, 1H), 6.71 (s, 1H), 6.21 (d, 1H), 4.14-4.07 (m, 2H), 3.73-3.47 (m, 5H), 3.23-3.05 (m, 5H), 2.95-2.83 (m, 2H), 2.74 (dd, 1H), 2.58 (s, 3H), 2.38 (s, 3H), 1.56 (m, 1H), 0.94 (m, 1H), 0.86 (m, 1H), 0.68 (t, 3H), 0.44 (d, 3H).

Biological Activity

[0100] Examples 1-6 of the present invention were tested in all of the assays described below. Results for each of the compounds are shown in Table 1 below. Table 1 also includes a compound X for comparison.

Assay 1

Determination of antagonist affinity at human Oxytocin-1 receptors using FLIPR

Cell Culture

[0101] Adherent Chinese Hamster Ovary (CHO) cells, stably expressing the recombinant human Oxytocin-1 (hOT) receptor, were maintained in culture in DMEM:F12 medium (Sigma, cat no D6421), supplemented with 10% heat inac-

tivated foetal calf serum (Gibco/Invitrogen, cat. no.01000-147), 2mM L-glutamine (Gibco/Invitrogen, cat. no. 25030-024) and 0.2mg/ml G418 (Gibco/Invitrogen, cat no. 10131-027). Cells were grown as monolayers under 95%:5% air:CO_2 at 37°C and passaged every 3-4 days using TrypLE™ Express (Gibco/Invitrogen, cat no. 12604-013).

Measurement of $[Ca^{2+}]_i$ using the FLIPR™

[0102] CHO-hOT cells were seeded into black walled clear-base 384-well plates (Nunc) at a density of 10,000 cells per well in culture medium as described above and maintained overnight (95%:5% air:CO_2 at 37°C). After removal of culture medium, cells were incubated for 1h at 37°C in Tyrode's medium (NaCl, 145mM; KCl, 2.5mM; HEPES, 10mM; Glucose, 10mM; $MgCl_2$, 1.2mM; $CaCl_2$, 1.5mM) containing probenacid (0.7mg/ml), the cytoplasmic calcium indicator, Fluo-4 (4uM; Teflabs, USA) and the quenching agent Brilliant Black (250uM; Molecular Devices, UK). Cells were then incubated for an additional 30min at 37°C with either buffer alone or buffer containing OT antagonist, before being placed into a FLIPR™ (Molecular Devices, UK) to monitor cell fluorescence (λ_{ex} = 488nm, λ_{EM} = 540nm) before and after the addition of a submaximal concentration of oxytocin (EC80).

Data Analysis

[0103] Functional responses using FLIPR were analysed using Activity Base Version 5.0.10.

Assay 2

Oxytocin Binding Assay

Preparations

[0104] Membranes were prepared from CHO cells expressing human recombinant oxytocin receptors. The membrane preparation was frozen in aliquots at -70°C until used.

Binding Assay Protocol

[0105] Membranes (~50 ug) were incubated in 200 ul of assay buffer (50 mM Tris, 10 mM $MgCl_2$, and 0.1% bovine serum albumin, pH 7.5) containing ~ 2.4 nM of [3H]-oxytocin in the absence (total binding) or presence (non-specific binding) of 1 uM unlabeled oxytocin and increasing concentrations of the compounds in Examples 1 to 6 or comparator compounds. Incubations were performed at room temperature for 60 minutes. The reactions were stopped with 3 ml of ice cold buffer and filtered through Whatman GF/C filter paper presoaked in 0.3% polyethylenimine. The filters were washed 4 times with 3 ml buffer using a Brandel cell harvester. The filters were counted in 3 ml Ready Safe scintillation fluid (Beckman).

[0106] Specific binding represented approximately 90% of total binding.

Data Analysis

[0107] IC_{50} values were determined from competition binding experiments using non-linear regression analysis (GraphPad) and converted to Ki using the method of Cheng and Prusoff, 1974. Data are reported as mean values.

Assay 3

Determination of In vitro Intrinsic Clearance in Microsomes

[0108] NADP regeneration buffer for use in incubations was prepared fresh on the assay day. It contained 7.8mg glucose-6-phosphate (mono-sodium salt), 1.7mg NADP and 6 Units glucose-6-phosphate dehydrogenase per 1mL of 2% sodium bicarbonate. Microsomes (human, female; cynomolgus monkey, female; dog, female; rat, female) were prepared in pH7.4 phosphate buffer and contained 0.625mg protein/mL. Unless stated, all subsequent steps were performed by a Tecan Genesis 150/8 RSP. A 1.25mM stock solution of the compounds was prepared in Acetonitrile/water (1:1). 25ul of the 1.25mM stock solution was added to 600ul of Acetonitrile/water (1:1) to give a 50uM solution. For each species, the 50uM solutions (10uL) were added to microsomes (790uL) in a microplate (Porvair, 96 deepwell, square). 400uL of the microsomal solution containing the compound was transferred to a microplate (Porvair, 96 deepwell, round) and was pre-warmed at 37°C for five minutes prior to initiation of incubations. All incubations were initiated by addition of 100uL of NADP regeneration system to the pre-warmed microsomes. The mixtures were incubated at 37°C in a

Techne heating block. Following 0, 3, 6, 12 and 30 minutes incubation, 20uL aliquots were taken and added to 100uL of acetonitrile containing internal standard.

[0109] For determination of the rate of metabolism, incubations were performed at a compound concentration of 0.5uM and a protein concentration of 0.5mg/mL. The concentration of solvent in the incubation was 0.5%.

[0110] Test compound concentrations were determined by LC/MS/MS; results were reported as analyte:internal standard peak area ratios.

[0111] The rate of disappearance was calculated by fitting a single exponential decay to the concentration-time curve using Excel and intrinsic clearance was calculated using the following formula:

$$Cli = \frac{[rate\,(1/min) * 52.5\ mg\ protein/g\ liver]}{0.5\ mg\ protein/mL}$$

Results

[0112] Examples 1 to 6 of the present Invention and also a comparator compound X = (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-methylpyridin-3-yl)ethenamide (Example 209 in WO 03/053443) were tested in the above assays.

[0113] Comparator compound X when tested in assays 1 and 2 showed a similar potency to that exhibited by Compounds 1 to 6 of the present invention, in fact each of these compounds exhibited fpKi's of between 8.1 and 9.2 (Assay 1) and pKi's of between 8.8 and 10.5 (Assay 2).

[0114] However, the compounds of the present Invention exhibited a surprising improvement in *in vitro* intrinsic clearance in microsomes (Assay 3) when compared with comparator compound X.

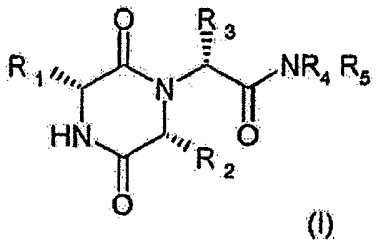
Table 1

Assay 3	Microsomal Cl (ml/min/g)			
	Rat	Dog	Cynomolgus monkey	Human
Comparator X	+	+	++++	++
Comparative Example 1	+	+	+	+
Comparative Example 2	+	+	++, +++	+, +
Example 3	+	+	+	+
Comparative Example 4	+, +	+, +	+++++, +++++	++, +
Comparative Example 5	+	+	+++	+
Comparative Example 6	+	+	+++	+

Key to Table 1
+ corresponds to 1-8 ml/min/mg
++ corresponds to 9-15 ml/min/mg
+++ corresponds to 16-20 ml/min/mg
++++ corresponds to 21-30 ml/min/mg
+++++ corresponds to > 31 ml/min/mg

Claims

1. A compound of formula (I)



(I)

wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2,6-dimethyl-3-pyridyl, R_4 and R_5 together with the nitrogen atom to which they are attached represent morpholino, or a pharmaceutically acceptable acid addition salt thereof, In which the acid is selected from: hydrochloric, hydrobromic, nitric, phosphoric, sulphuric, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic, citric, tartaric, lactic, pyruvic; acetic, succinic, fumaric and maleic acid.

2. A compound according to claim 1, which Is (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione or a pharmaceutically acceptable acid addition salt thereof, in which the acid Is selected from: hydrochloric, hydrobromic, nitric, phosphoric, sulphuric, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric and maleic acid.

3. A compound according to claim 1, which is (3*R*,6*R*)-3-(2,3-dihydro-1*H*-Inden-2-yl)-1-[(1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-1-methylpropyl]-2,5-piperazinedione.

4. A compound according to claim 1, which is (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1*S*)-1-methylpropyl]-2,5-piperazinedione benzenesulfonate salt.

5. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4, together with one or more pharmaceutically acceptable carriers.

6. A compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4 for use in therapy.

7. A compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4 for use in therapy in humans.

8. Use of a compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4 for the manufacture of a medicament for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

9. Use of a compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4 for the manufacture of a medicament for the treatment of one or more diseases or conditions selected from pre-term labour, dysmenorrhea, endometriosis, benign prostatic hyperplasia, sexual dysfunction, premature ejaculation, obesity, congestive heart failure, arterial hypertension, liver cirrhosis, nephritic or ocular hypertension, obsessive-compulsive disorder and neuropsychiatric disorders.

10. Use according to claim 9 wherein said one or more diseases or conditions are selected from pre-term labour and premature ejaculation.

11. Use according to claim 9 wherein said one or more diseases or conditions is endometriosis.

12. Use according to claim 9 wherein said one or more diseases or conditions is benign prostatic hyperplasia.

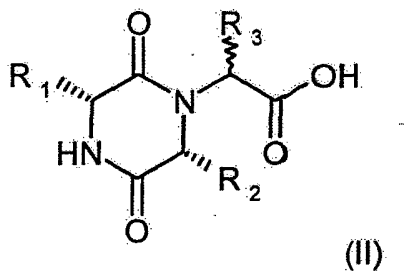
13. Use according to claim 9 wherein said one or more diseases or conditions is congestive heart failure.

14. Use according to claim 9 wherein said one or more diseases or conditions is dymenorrhea.

15. Use of a compound or a pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4 for the manufacture of a medicament for treating or preventing diseases or conditions mediated through the action of oxytocin.

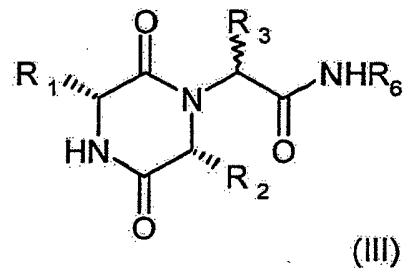
16. A process for the preparation of compounds of formula (I) as claimed in claim 1 which comprises:

(a) reacting a compound of formula (II)



(II)

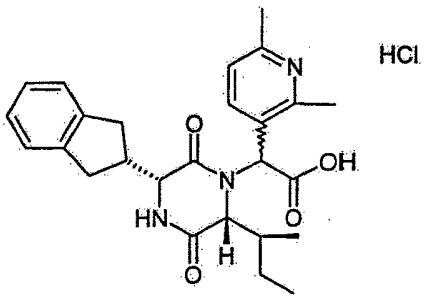
wherein R_1, R_2 and R_3 have the meanings defined in claim 1 and the chirality at R_3 is either R or S or a mixture thereof, or an activated derivative thereof, with the amine HNR_4R_5 wherein R_4 and R_5 have the meaning defined in claim 1 under standard conditions for preparing amides from a carboxylic acid or an activated derivative thereof and an amine; or
(b) reacting a compound of formula (III)



(III)

wherein R_1, R_2 and R_3 have the meanings defined in claim 1 and R_6 is 2-hydroxyphenyl with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with amine HNR_4R_5 wherein R_4 and R_5 have the meanings defined in claim 1.

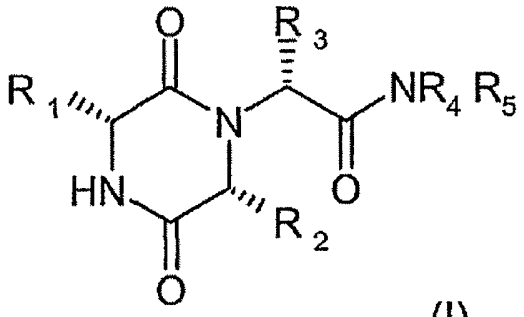
17. A compound which is {(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2,6-dimethyl-3-pyridinyl)acetic acid hydrochloride



HCl

Patentansprüche

1. Eine Verbindung der Formel (I)



(I)

wobei R_1 2-Indanyl ist, R_2 1-Methylpropyl ist, R_3 2,6-Dimethyl-3-pyridyl ist, R_4 und R_5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, Morpholin darstellen, oder ein pharmazeutisch verträgliches Säureadditionssalz davon, in dem die Säure ausgewählt ist aus: Salzsäure, Bromwasserstoffsäure, Salpetersäure, Phosphorsäure, Schwefelsäure, Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Zitronensäure, Weinsäure, Milchsäure, Brenztraubensäure, Essigsäure, Bernsteinsäure, Fumarsäure und Maleinsäure.

2. Eine Verbindung gemäß Anspruch 1, die (3R,6R)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-[(1R)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazindion oder ein pharmazeutisch verträgliches Säureadditionssalz davon ist, in dem die Säure ausgewählt ist aus: Salzsäure, Bromwasserstoffsäure, Salpetersäure, Phosphorsäure, Schwefelsäure, Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Zitronensäure, Weinsäure, Milchsäure, Brenztraubensäure, Essigsäure, Bernsteinsäure, Fumarsäure und Maleinsäure.

3. Eine Verbindung gemäß Anspruch 1, die (3R,6R)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-[(1R)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazindion ist.

4. Eine Verbindung gemäß Anspruch 1, die (3R,6R)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-[(1R)-1-(2,6-dimethyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazindion-Benzolsulfonatsalz ist.

5. Eine pharmazeutische Zusammensetzung, die eine Verbindung oder ein pharmazeutisch verträgliches Säureadditionssalz davon gemäß einem der Ansprüche 1 bis 4 zusammen mit einem oder mehreren pharmazeutisch verträglichen Trägern umfasst.

6. Eine Verbindung oder ein pharmazeutisch verträgliches Säureadditionssalz davon gemäß einem der Ansprüche 1 bis 4 zur Verwendung in der Therapie.

7. Eine Verbindung oder ein pharmazeutisch verträgliches Säureadditionssalz davon gemäß einem der Ansprüche 1 bis 4 zur Verwendung in der Therapie bei Menschen.

8. Verwendung einer Verbindung oder eines pharmazeutisch verträglichen Säureadditionssalzes davon gemäß einem der Ansprüche 1 bis 4 für die Herstellung eines Medikaments zur Antagonisierung der Wirkungen von Oxytocin am Oxytocin-Rezeptor.

9. Verwendung einer Verbindung oder eines pharmazeutisch verträglichen Säureadditionssalzes davon gemäß einem der Ansprüche 1 bis 4 für die Herstellung eines Medikaments zur Behandlung einer oder mehrerer Erkrankungen oder Zustände, ausgewählt aus vorzeitigen Wehen, menstrueller Dystonie, Endometriose, gutartiger Prostata-Hyperplasie, Sexualstörung, vorzeitiger Ejakulation, Fettsucht, Stauungsinsuffizienz, arteriellem Bluthochdruck, Leberzirrhose, nephritischem oder okulärem Bluthochdruck, Zwangsstörung und neuropsychiatrischen Störungen.

10. Verwendung gemäß Anspruch 9, wobei die/der ein(e) oder mehreren Erkrankungen oder Zustände ausgewählt sind aus vorzeitigen Wehen und vorzeitiger Ejakulation.

11. Verwendung gemäß Anspruch 9, wobei die/der ein(e) oder mehreren Erkrankungen oder Zustände Endometriose ist.

12. Verwendung gemäß Anspruch 9, wobei die/der ein(e) oder mehreren Erkrankungen oder Zustände gutartige Pro-

stata-Hyperplasie ist.

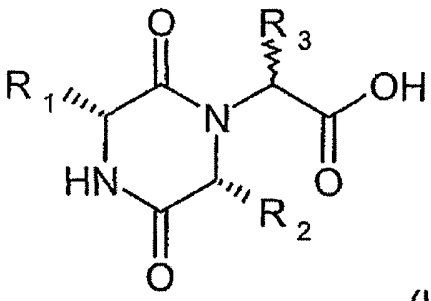
13. Verwendung gemäß Anspruch 9, wobei die/der ein(e) oder mehreren Erkrankungen oder Zustände Stauungsinsuffizienz ist.

14. Verwendung gemäß Anspruch 9, wobei die/der ein(e) oder mehreren Erkrankungen oder Zustände menstruelle Dystonie ist.

15. Verwendung einer Verbindung oder eines pharmazeutisch verträglichen Säureadditionssalzes davon gemäß einem der Ansprüche 1 bis 4 für die Herstellung eines Medikamentes zur Behandlung oder Vermeidung von Krankheiten oder Zuständen, die durch die Wirkung von Oxytocin vermittelt werden.

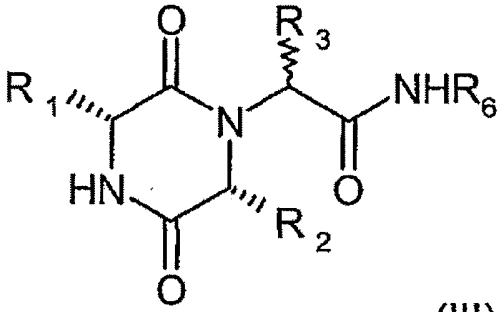
16. Ein Verfahren zur Herstellung von Verbindungen der Formel (I) gemäß Anspruch 1, das umfasst:

(a) Umsetzen einer Verbindung der Formel (II)



(II)

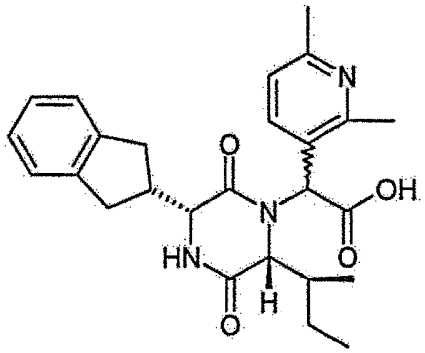
wobei R_1, R_2 und R_3 die in Anspruch 1 definierten Bedeutungen haben und die Chiralität an R_3 entweder R oder S oder ein Gemisch davon ist, oder eines aktivierten Derivats davon, mit dem Amin NHR_4R_5, wobei R_4 und R_5 die in Anspruch 1 definierte Bedeutung haben, unter Standardbedingungen zur Herstellung von Amiden aus einer Carbonsäure oder einem aktivierten Derivat davon und einem Amin; oder
(b) Umsetzen einer Verbindung der Formel (III)



(III)

wobei R_1, R_2 und R_3 die in Anspruch 1 definierten Bedeutungen haben und R_6 2-Hydroxyphenyl ist, mit 1,1'-Carbonyldiimidazol oder 1,1'-Thiocarbonyldiimidazol in einem geeigneten Lösungsmittel und nachfolgendes Umsetzen des so gebildeten Produktes mit Amin NHR_4R_5, wobei R_4 und R_5 die in Anspruch 1 definierten Bedeutungen haben.

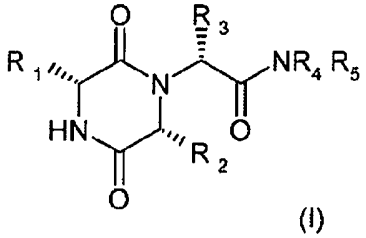
17. Eine Verbindung, die {(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl}(2,6-dimethyl-3-pyridinyl)essigsäure-Hydrochlorid



ist.

Revendications

1. Composé de formule (I)



(I)

dans laquelle R_1 représente un groupe 2-indanyle, R_2 représente un groupe 1-méthylpropyle, R_3 représente un groupe 2,6-diméthyl-3-pyridyle, R_4 et R_5, conjointement avec l'atome d'azote auquel ils sont fixés, représentent un groupe morpholino, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables, dans laquelle l'acide est choisi entre : les acides chlorhydrique, bromhydrique, nitrique, phosphorique, sulfurique, méthanesulfonique, éthane-sulfonique, benzènesulfonique, p-toluènesulfonique, citrique, tartrique, lactique, pyruvique, acétique, succinique, fumarique et maléique.

2. Composé suivant la revendication 1, qui est la (3R,6R)-3-(2,3-dihydro-1H-indène-2-yl)-1-[(1R)-1-(2,6-diméthyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoéthyl]-6-[(1S)-1-méthyl-propyl]-2,5-pipérazinedione ou un de ses sels d'addition d'acides pharmaceutiquement acceptables, dans lequel l'acide est choisi entre : les acides chlorhydrique, bromhydrique, nitrique, phosphorique, sulfurique, méthanesulfonique, éthane-sulfonique, benzènesulfonique, p-toluènesulfonique, citrique, tartrique, lactique, pyruvique, acétique, succinique, fumarique et maléique.

3. Composé suivant la revendication 1, qui est la (3*R*,6*R*)-3-(2,3-dihydro-1*H*-indène-2-yl)-1-[(1*R*)-1-(2,6-diméthyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoéthyl]-6-[(1S)-1-méthyl-propyl]-2,5-pipérazinedione.

4. Composé suivant la revendication 1, qui est le benzènesulfonate de (3*R*,6*R*)-3-(2,3-dihydro-1*H*-indène-2-yl)-1-[(1*R*)-1-(2,6-diméthyl-3-pyridinyl)-2-(4-morpholinyl)-2-oxoéthyl]-6-[(1S)-1-méthylpropyl]-2,5-pipérazinedione.

5. Composition pharmaceutique comprenant un composé ou un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4, conjointement avec un ou plusieurs supports pharmaceutiquement acceptables.

6. Composé ou un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4, pour une utilisation en thérapie.

7. Composé ou un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4, pour une utilisation en thérapie chez les êtres humains.

8. Utilisation d'un composé ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4 pour la production d'un médicament pour antagoniser les effets de l'ocytocine sur le récepteur d'ocytocine.

9. Utilisation d'un composé ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4 pour la production d'un médicament pour le traitement d'une ou plusieurs maladies ou affections choisies entre un accouchement prématuré, la dysménorrhée, l'endométriose, l'hyperplasie prostatique bénigne, un dysfonctionnement sexuel, l'éjaculation précoce, l'obésité, l'insuffisance cardiaque congestive, l'hypertension artérielle, la cirrhose hépatique, l'hypertension néphrétique ou oculaire, un trouble obsessionnel compulsif et des troubles neuropsychiatriques.

10. Utilisation suivant la revendication 9, dans laquelle ladite ou lesdites maladies ou affections sont choisies entre un accouchement prématuré et l'éjaculation précoce.

11. Utilisation suivant la revendication 9, dans laquelle ladite ou lesdites maladies ou affections consistent en l'endométriose.

12. Utilisation suivant la revendication 9, dans laquelle ladite ou lesdites maladies ou affections consistent en l'hyperplasie prostatique bénigne.

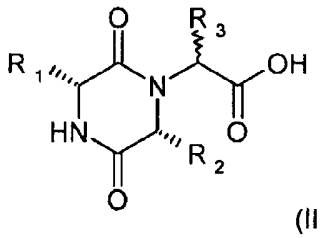
13. Utilisation suivant la revendication 9, dans laquelle ladite ou lesdites maladies ou affections consistent en l'insuffisance cardiaque congestive.

14. Utilisation suivant la revendication 9, dans laquelle ladite ou lesdites maladies ou affections consistent en la dysménorrhée.

15. Utilisation d'un composé ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 4 pour la production d'un médicament pour traiter ou prévenir des maladies ou affections à médiation par l'action de l'ocytocine.

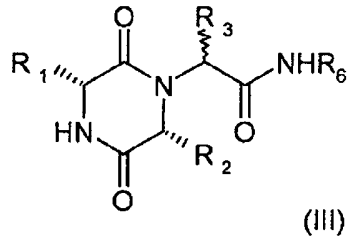
16. Procédé pour la préparation de composés de formule (I) suivant la revendication 1, qui comprend :

(a) la réaction d'un composé de formule (II)



(II)

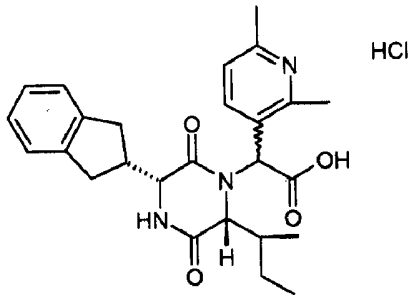
dans laquelle R_1, R_2 et R_3 répondent aux définitions indiquées dans la revendication 1 et la chiralité au niveau de R_3 est la chiralité R ou *S* ou un de leurs mélanges, ou d'un de leurs dérivés activés, avec l'amine HNR_4R_5, dans laquelle R_4 et R_5 répondent aux définitions indiquées dans la revendication 1 dans des conditions classiques pour préparer des amides à partir de l'acide carboxylique ou d'un de ses dérivés activés et d'une amine ; ou
(b) la réaction d'un composé de formule (III)



(III)

dans laquelle R_1, R_2 et R_3 répondent aux définitions indiquées dans la revendication 1 et R_6 représente un groupe 2-hydroxyphényle avec du 1,1'-carbonyldiimidazole ou du 1,1'-thiocarbonyldiimidazole dans un solvant convenable et la réaction ultérieure du produit formé ainsi avec une amine HNR_4R_5, dans laquelle R_4 et R_5 répondent aux définitions indiquées dans la revendication 1.

17. Composé qui est le chlorhydrate d'acide {(3*R*,6*R*)-3-(2,3-dihydro-1*H*-indène-2-yl)-6-[(1*S*)-1-méthylpropyl]-2,5-dioxo-1-pipérazinyl}(2,6-diméthyl-3-pyridinyl)acétique



REFERENCES CITED IN THE DESCRIPTION

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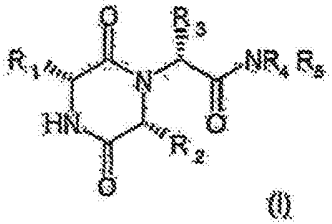
Szabadalmi igénypontok

1. (I) Képletű vegyület



(I)

ahol R_1 jelentése 2-indanil, R_2 jelentése 1-metilpropil, R_3 jelentése 2,6-dimetil-3-piridil, R_4 és R_5 a nitrogénatommal együtt, amelyhez kapcsolódnak, morfolino-csoportot jelent, vagy gyógyszerészetileg elfogadható savaddíciós sója, amelyben a sav az alábbiak közül választott: hidroklórsav, hidrobrómsav, salétromsav, foszforsav, kénsav, metánszulfonsav, etánszulfonsav, benzolszulfonsav, p-toluolszulfonsav, citromsav, borkősav, tejsav, piroszőlősav; ecetsav, borostyánkősav, fumársav és maleinsav.

2. Az 1. igénypont szerinti vegyület, amely a (3R,6R)-3-(2,3-dihidro-1*H*-inden-2-il)-1-[(1R)-1-(2,6-dimetil-3-piridinil)-2-(4-morfolinil)-2-oxoetil]-6-[(1S)-1-metilpropil]-2,5-piperazindion vagy gyógyszerészetileg elfogadható savaddíciós sója, amelyben a sav az alábbiak közül választott: hidroklórsav, hidrobrómsav, salétromsav, foszforsav, kénsav, metánszulfonsav, etánszulfonsav, benzolszulfonsav, p-toluolszulfonsav, citromsav, borkősav, tejsav, piroszőlősav; ecetsav, borostyánkősav, fumársav és maleinsav.

3. Az 1. igénypont szerinti vegyület, amely a (3*R*,6*R*)-3-(2,3-dihidro-1*H*-inden-2-il)-1-[(1*R*)-1-(2,6-dimetil-3-piridinil)-2-(4-morfolinil)-2-oxoetil]-6-[(1*S*)-1-metilpropil]-2,5-piperazindion.

4. Az 1. igénypont szerinti vegyület, amely a (3*R*,6*R*)-3-(2,3-dihidro-1*H*-inden-2-il)-1-[(1*R*)-1-(2,6-dimetil-3-piridinil)-2-(4-morfolinil)-2-oxoetil]-6-[(1*S*)-1-metilpropil]-2,5-piperazindion-benzolszulfonát só.

5. Gyógyszerészeti készítmény, amely tartalmazza az 1-4. igénypontok bármelyike szerinti vegyületet vagy gyógyszerészetileg elfogadható savaddíciós sóját egy vagy több gyógyszerészetileg elfogadható hordozóval együtt.

6. Az 1-4. igénypontok bármelyike szerinti vegyület vagy gyógyszerészetileg elfogadható savaddíciós sója terápiában történő alkalmazásra.

7. Az 1-4. igénypontok bármelyike szerinti vegyület vagy gyógyszerészetileg elfogadható savaddíciós sója terápiában történő alkalmazásra emberben.

8. Az 1-4. igénypontok bármelyike szerinti vegyületnek vagy gyógyszerészetileg elfogadható savaddíciós sójának alkalmazása az oxitocinnak az oxitocin receptoron kifejtett hatásainak antagonizálására szolgáló gyógyszer előállítására.

9. Az 1-4. igénypontok bármelyike szerinti vegyületnek vagy gyógyszerészetileg elfogadható savaddíciós sójának alkalmazása az alábbiak közül választott egy vagy több betegség vagy állapot kezelésére szolgáló gyógyszer előállítására: koraszülés, fájdalmas menstruáció, endometriózis, jóindulatú prosztatanagyobbodás, szexuális diszfunkció, korai magömlés, elhízottság, szívszelhűdés, artériás magas vérnyomás, májcirrózis, nefritiszes vagy okuláris hipertenzió, rögeszmés-kényszeres betegség és neuropszichiátriai rendellenességek.

10. A 9. igénypont szerinti alkalmazás, ahol az egy vagy több betegség vagy állapot a következők közül választott: koraszülés vagy korai magömlés.

11. A 9. igénypont szerinti alkalmazás, ahol az egy vagy több betegség vagy állapot az endometriózis.

12. A 9. igénypont szerinti alkalmazás, ahol az egy vagy több betegség vagy állapot a jóindulatú prosztatanagyobbodás.

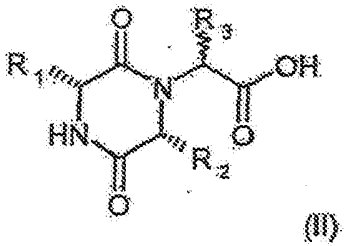
13. A 9. igénypont szerinti alkalmazás, ahol az egy vagy több betegség vagy állapot a szívszélhűdés.

14. A 9. igénypont szerinti alkalmazás, ahol az egy vagy több betegség vagy állapot a fájdalmas menstruáció.

15. Az 1-4. igénypontok bármelyike szerinti vegyületnek vagy gyógyszerészetileg elfogadható savaddíciós sójának alkalmazása oxitocin hatásán keresztül mediált betegségek vagy állapotok kezelésére vagy megelőzésére szolgáló gyógyszer előállítására.

16. Eljárás az 1. igénypont szerinti (I) képletű vegyület előállítására, amely eljárás tartalmazza

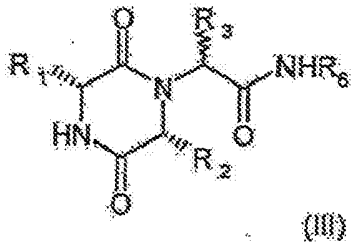
(a) (II) képletű vegyület reagáltatását



(II)

ahol R_1, R_2 és R_3 jelentése az 1. igénypontban meghatározott, és R_3 kiralitása vagy R vagy S vagy ezek keveréke, vagy aktivált származékának reagáltatását, egy következő képletű aminnal: HNR_4R_5, ahol R_4 és R_5 jelentése az 1. igénypontban meghatározott, amidok karbonsavból vagy aktivált származékából és aminból történő előállítására vonatkozó sztenderd körülmények között; vagy

(b) (III) képletű vegyület reagáltatását



(III)

ahol R_1, R_2 és R_3 jelentése az 1. igénypontban meghatározott, és R_6 jelentése 2-hidroxifenil, 1,1'-karbonildiimidazollal vagy 1,1'-tiokarbonildiimidazollal egy megfelelő oldószerben és az így képződött termék ezt követő, HNR_4R_5 aminnal történő reakcióját, ahol R_4 és R_5 jelentése az 1. igénypontban meghatározott.

17. Vegyület, amely a {(3*R*,6*R*)-3-(2,3-Dihidro-1*H*-inden-2-il)-6-[(1*S*)-1-metilpropil]-2,5-dioxo-1-piperazinil}(2,6-dimetil-3-piridinil)ecetsav-hidroklorid