

SUBSTITUTED DIKETOPIPERAZINES AS OXYTOCIN ANTAGONISTS

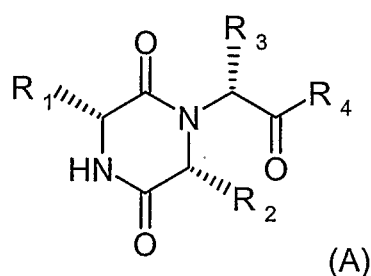
This invention relates to novel diketopiperazine derivatives having a potent and selective antagonist action at the oxytocin receptor, to processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

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).

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.

International patent application WO 99/47549 describes diketopiperazine derivatives including 3-benzyl-2,5-diketopiperazine derivatives as inhibitors of fructose 1,6-bisphosphate (FBPase).

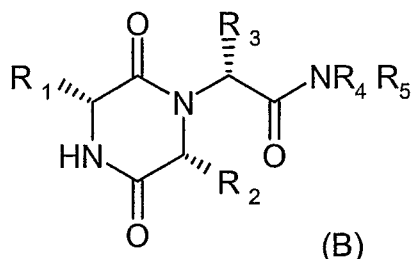
International patent application WO 03/053443 describes a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor. A preferred class of compounds described therein is represented by the formula (A).



Such compounds include those wherein inter alia R_1 is 2-indanyl, R_2 is C_{3-4} alkyl, R_3 is an optionally substituted 6,5 fused bicyclic ring e.g. 1H-indazol-5-yl linked to the rest of the molecule via a carbon atom in the ring, R_4 represents the group NR_5R_6 wherein R_5 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.

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



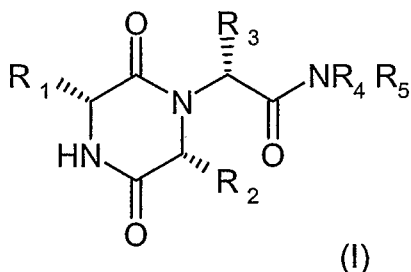
wherein R₁ is 2-indanyl, R₂ is 1-methylpropyl, R₃ is 2-methyl-1,3-oxazol-4-yl and R₄ and R₅ together with the nitrogen atom to which they are attached represent morpholino.

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

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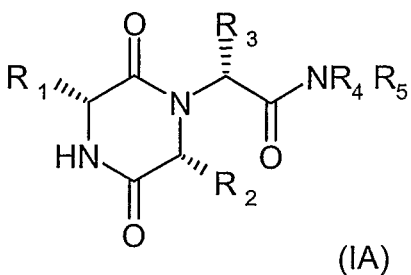
The present invention thus provides at least one chemical entity selected from compounds of formula (I)



wherein R₁ is 2-indanyl, R₂ is 1-methylpropyl, R₃ is 1-methyl-indazol-5-yl, R₄ represents methyl and R₅ represents hydrogen and pharmaceutically acceptable derivatives thereof.

20

Alternatively, the present invention provides at least one chemical entity selected from compounds of formula (IA)



wherein R₁ is 2-indanyl, R₂ is 1-methylpropyl, R₃ is 1-methyl-indazol-5-yl, R₄ represents methyl and R₅ represents hydrogen or methyl, and pharmaceutically acceptable derivatives thereof.

- 5 It will be appreciated that the compounds of formula (I) and formula (IA) possess the absolute stereochemistry depicted at the asymmetric carbon atoms bearing groups R₁, R₂ and R₃, 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 R₁, R₂ and R₃, each epimer may be present in small
10 amounts, for example 1% or less of the (*S*)-epimer may be present.

It will also be appreciated that the group R₂ contains an asymmetric carbon atom and that the invention includes both the (*R*)- and (*S*)-epimers thereof.

- 15 In one embodiment of the invention, R₂ is (1*S*)-1-methylpropyl. In another embodiment of the invention, R₂ is (1*R*)-1-methylpropyl.

In one embodiment of the invention, R₅ represents hydrogen. In another embodiment of the invention, R₅ represents methyl.

20

In one embodiment of the invention is the compound the preparation of which is specifically described in example 1. In another embodiment of the invention is the compounds the preparation of which is specifically described in examples 1 and 2.

- 25 In one aspect, chemical entities useful in the present invention may be at least one chemical entity selected from:

(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]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide, and

- (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]-*N,N*-dimethyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide,
30 and pharmaceutically acceptable derivatives thereof.

- As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use. Salts and solvates of compounds of the invention
35 which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope

of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable salts and solvates.

- 5 As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's
10 Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. In one aspect, pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. In another aspect, pharmaceutically acceptable
15 derivatives are salts, solvates and esters. In one aspect, pharmaceutically acceptable derivatives are physiologically acceptable salts. In a further aspect, pharmaceutically acceptable derivatives are solvates and esters. In another aspect, pharmaceutically acceptable derivatives are solvates.
- 20 Suitable physiologically acceptable salts of compounds of the present invention include acid addition salts formed with physiologically acceptable inorganic acids or organic acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulphuric acid, sulphonic acids e.g. methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic, citric acid, tartaric acid,
25 lactic acid, pyruvic acid, acetic acid, succinic acid, fumaric acid and maleic acid.

The present invention also relates to solvates of the compounds of formula (I) or formula (IA), for example hydrates, or solvates with pharmaceutically acceptable solvents including, but not limited to, alcohols, for example ethanol, *iso*-propanol,
30 acetone, ethers, esters, e.g. ethyl acetate.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative
35 thereof together with a further therapeutic agent.

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

5 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 compounds of the present invention may be used in combination with tocolytics or prophylactic medicines.

10 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 compounds of the present invention may be used in combination with

15 antenatal steroids including betamethasone and dexamethasone, prenatal vitamins especially folate supplements, antibiotics, including but not limited to ampicillin, amoxicillin/clavulanate, metronidazole, clindamycin, and anxiolytics.

In one aspect, the combinations referred to above may be presented for use in the

20 form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any

25 convenient route.

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

30 pharmaceutical composition.

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

35 any convenient formulation, conveniently in such manner as are known for such compounds in the art.

The compounds of formula (I) and formula (IA) have 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
5 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.

10 The compounds of the invention exhibit an advantageous pharmacokinetic profile including good bioavailability and low intrinsic clearance. In one aspect, the compounds of the invention exhibit good potency and low intrinsic clearance. In another aspect, the compounds of the invention exhibit low intrinsic clearance.

15 The compounds of the invention are 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, dysmenorrhea, endometriosis and benign prostatic hyperplasia.

20 The compounds 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.

25 The compounds of the invention may also be useful for improving fertility rates in animals, e.g. farm animals.

The invention therefore provides for at least one chemical entity selected from compounds of formula (I) or formula (IA) and pharmaceutically acceptable derivatives
30 thereof for use in therapy, particularly for use in human or veterinary therapy, and in particular for use as a medicine for antagonising the effects of oxytocin upon the oxytocin receptor.

The invention also provides for the use of at least one chemical entity selected from
35 compounds of formula (I) or formula (IA) and pharmaceutically acceptable derivatives thereof for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

According to a further aspect, the invention also provides for 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
5 chemical entity selected from compounds of formula (I) or formula (IA) and pharmaceutically acceptable derivatives thereof.

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.

10 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
15 adult human treatment will typically be in the range of 2 to 1000 mg per day, dependent upon the route of administration.

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

The desired dose may 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.

25 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.

30 The invention thus further provides a pharmaceutical formulation comprising at least one chemical entity selected from compounds of formula (I) or formula (IA) and pharmaceutically acceptable derivatives thereof 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
35 compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant, vaginal or rectal administration.

- 5 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;
- 10 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
- 15 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
- 20 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
- 25 or other glycerides.

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

- 30 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
- 35 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.

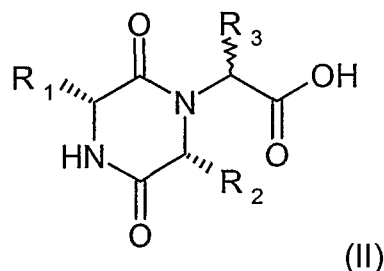
The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 1-50% for tablets and capsules and 3-50% for liquid preparations.

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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.

10 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.

15 Thus, compounds of formula (I) or formula (IA) 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 formula (IA), and the chirality at R_3 is either *R* or *S*, or a mixture thereof,



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

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

Thus the amide of formula (I) or formula (IA) may be prepared by treating the carboxylic acid of formula (II) with an activating agent such as BOP (benzotriazol-1-
30 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 .

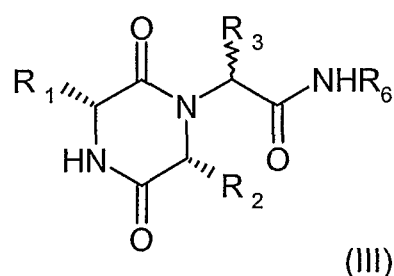
- 5 Alternatively the amide of formula (I) or formula (IA) may be prepared by reacting a mixed anhydride derived from the carboxylic acid (II) with the amine HNR_4R_5 in an aprotic solvent such as tetrahydrofuran. Conveniently the reaction is carried out at low temperatures, for example 25°C to -90°C , more conveniently at approximately -78°C .

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The mixed anhydride is conveniently prepared by reacting the carboxylic acid (II) with a suitable acid chloride e.g. pivaloyl 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 .

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Compounds of formula (I) or formula (IA) may also be prepared by reacting a compound of formula (III)

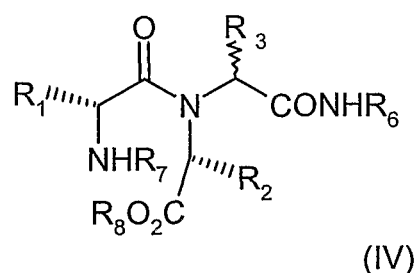


- 20 wherein R_1 , R_2 and R_3 have the meanings defined in formula (I) and formula (IA) and R_6 is 2-hydroxyphenyl, with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the products thus formed with the amine HNR_4R_5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

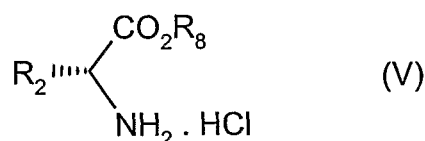
- 25 Compounds of formula (II) may be prepared from a compound of formula (III) wherein R_6 is 2-hydroxyphenyl by reaction with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.

- 30 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.

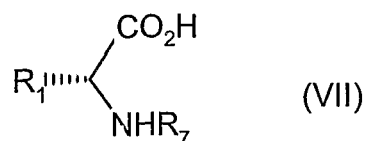
Compounds of formula (III) wherein R_6 is a 2-benzyloxyphenyl group may be prepared from a compound of formula (IV)



- 5 wherein R_1 , R_2 and R_3 have the meanings defined in formula (I) and formula (IA), R_6 is 2-benzyloxyphenyl, R_7 is t-butyloxycarbonyl and R_8 is C_{1-6} alkyl by reaction with hydrogen chloride in a solvent such as dioxan, followed by treatment with a base such as triethylamine in methanol.
- 10 Compounds of formula (IV) may be prepared by reacting the amino ester hydrochloride (V),



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



- wherein R_1 has the meaning defined in formula (I) and formula (IA), 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.
- 20

- 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) and formula (IA), 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.
- 25

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.

5

The R_2 substituent is a 1-methylpropyl group and the compound of formula (I) and formula (IA) 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.

10

Aminoester hydrochloride (V), wherein R_1 has the meaning defined in formula (I) and formula (IA) 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.

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Aldehyde R_3CHO (VI), wherein R_3 has the meaning defined in formula (I) and formula (IA), may be prepared from the commercially available bromo compound R_3Br , wherein R_3 has the meaning defined in formula (I) and formula (IA), by the method of V. Auwers; Lange; *Chem.Ber.*; 55; 1922; 1141, 1157. Alternatively, aldehyde R_3CHO (VI) may be prepared from the commercially available nitrile compound R_3CN , wherein R_3 has the meaning defined in formula (I) and formula (IA), by the method of Halley, Frank; Sava, Xavier. *Synthesis of 5-cyanoindazole and 1-methyl and 1-aryl-5-cyanoindazoles. Synthetic Communications* (1997), 27(7), 1199-1207.

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The aminoacid derivative (VII) wherein R_1 has the meaning defined in formula (I) and formula (IA) and R_7 is t-butyloxycarbonyl is commercially available; the aminoacid derivative (VII) wherein R_1 has the meaning defined in formula (I) and formula (IA) 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) and formula (IA), by treatment with N-(benzyloxycarbonyloxy)succinimide and triethylamine in a solvent such as dioxane in water.

30

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

35

Acid addition salts of the compound of formula (I) and formula (IA) 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.

5

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

Experimental

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Abbreviations

DIBAL – diisobutylaluminium chloride

Nomenclature

15 All intermediates and examples were named using ACD Name Pro 6.02 in ISISDraw.

General purification and analytical methods

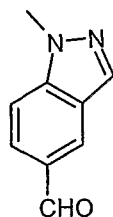
Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H and 5% water in acetonitrile (solvent B), using the either
20 elution gradient 1, 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 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 (R_t) are quoted in minutes. The mass spectra (MS) were
25 recorded on a Waters ZQ 2000 mass spectrometer using electrospray positive [ES+ve to give MH⁺ and M(NH₄)⁺ 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.

30 Purification using silica cartridges refers to chromatography carried out using a Combiflash® CompanionTM 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
35 coated with silica gel 60 F₂₅₄.

Intermediate 1 (Method A)1-Methyl-1H-indazole-5-carbaldehyde

A 2.0M solution of n-butyl magnesium chloride in tetrahydrofuran (3.05ml) was added to toluene (20ml) under nitrogen and cooled to -10°C . To this was added a 1.6M solution of n-butyl lithium in hexanes (7.63ml) and after 1 hour the reaction mixture was cooled to -30°C . To this was added a solution of 5-bromo-1-methyl-1H-indazole¹ (2.35g) in tetrahydrofuran (10ml) and the reaction mixture was warmed to -10°C . After 1 hour dimethylformamide (5ml) was added and the reaction mixture was stirred at -10°C for 1 hour. The reaction was quenched using 2N hydrochloric acid (20ml) and the reaction allowed to warm to room temperature. After 30 minutes the reaction mixture was basified with saturated aqueous sodium bicarbonate solution and then extracted using ethyl acetate (2 x 80ml). The organic phase was washed with sodium bicarbonate solution (2 x 100ml) and then 10% lithium chloride in water (2 x 100ml) and then brine. The organic phase was dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The residue was applied to a silica Redisep® cartridge (120g) and eluted with 10-30% ethyl acetate in cyclohexane. The required fractions were combined and evaporated *in vacuo* to give 1-methyl-1H-indazole-5-carbaldehyde (1.43g, 80%) as a white solid.

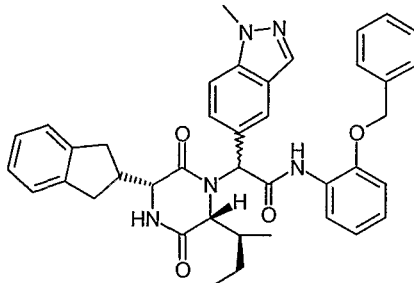
HPLC Rt = 2.2 minutes (gradient 1); m/z $[M+H]^+ = 161$ (gradient 1)

Intermediate 1 (Method B)1-Methyl-1H-indazole-5-carbaldehyde

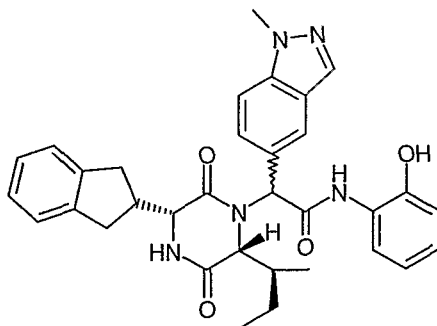
To a solution of 1-methyl-1H-indazole-5-carbonitrile² (7g) in anhydrous toluene (300ml) under nitrogen at -70°C was added a 1.5M solution of DIBAL in toluene (59.4 ml) drop wise over approx 20 minutes. The reaction mixture was allowed to warm to -60°C and stirred at that temperature for 4 hours, the cooling bath removed and then quenched by drop wise addition of acetic acid (30ml) (care evolution of gas). Water (240ml) was added and mixture vigorously stirred for 30 minutes and then extracted with ethyl acetate (200ml). The organic phase was washed with water (100ml) and then brine (100ml) dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to give 1-methyl-1H-indazole-5-carbaldehyde (6.8g, 95%)

as a pale yellow solid, consistent in all respects with that obtained from 5-bromo-1-methyl-1*H*-indazole obtained above.

Intermediate 2



5 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-(1-methyl-1*H*-indazol-5-yl)-*N*-{2-[(phenylmethyl)oxy]phenyl}acetamide
 1-Methyl-1*H*-indazole-5-carbaldehyde (intermediate 1) (1.66g) and methyl D-alloisoleucinate hydrochloride (1.88g) were dissolved in 2,2,2-trifluoroethanol (30ml)
 10 and methanol (30ml). To this was added triethylamine (1.44ml) and the reaction mixture stirred at room temperature under N₂ for 3.5 hours. (2*R*)-2,3-Dihydro-1*H*-inden-2-yl-([(1,1-dimethylethyl)oxy]carbonyl)amino)ethanoic acid (3.01g) and 2-[(phenylmethyl)oxy]phenyl isocyanide (2.16g) were added to the reaction mixture and the solution was left to stand at room temperature for 3 days. The solvent was
 15 removed *in vacuo*. The residue was dissolved in dichloromethane and evaporated *in vacuo*. The residue was dissolved in 4N hydrogen chloride in dioxan (20ml) and the reaction mixture was stirred for 1 hour. The solvent was removed *in vacuo* and co-evaporated with methanol x3. The residue was dissolved in methanol (70ml). To this was added triethylamine (6ml) while the flask stood on dry ice. The reaction mixture
 20 was left to stand for 20 hours at room temperature. The solvent was evaporated *in vacuo* and the residue concentrated from methanol (x1) and dichloromethane (x1). The residue was separated between ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was washed with aqueous sodium bicarbonate solution, water, brine and dried over anhydrous magnesium sulphate. The solvent was
 25 removed *in vacuo* and the residue was applied to a silica cartridge (120g). This was eluted with 30-70% ethyl acetate in cyclohexane. 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-(1-methyl-1*H*-indazol-5-yl)-*N*-{2-[(phenylmethyl)oxy]phenyl}acetamide (4.15g, 62%) as a yellow solid.
 30 HPLC Rt = 3.62, 3.66 minutes (gradient 1) ; m/z [M+H]⁺ = 656.

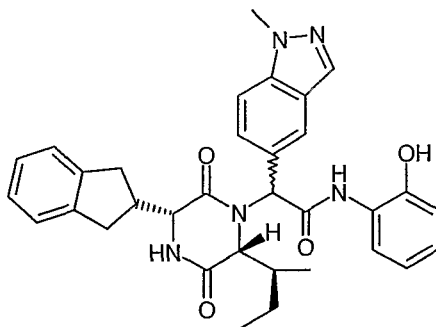
Intermediate 3 (Method A)

2-((3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-N-(2-hydroxyphenyl)-2-(1-methyl-1H-indazol-5-yl)acetamide

- 5 2-((3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-2-(1-methyl-1H-indazol-5-yl)-N-{2-[(phenylmethyl)oxy]phenyl}acetamide (intermediate 2) (0.20g) was dissolved in ethanol (20ml) and hydrogenated over palladium on charcoal (wet 10%Pd, 50mg) for 20 hours. The catalyst was removed by filtration and washed with ethanol/dichloromethane (1:1 v/v). The combined washings and filtrate were evaporated *in vacuo* to give 2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-N-(2-hydroxyphenyl)-2-(1-methyl-1H-indazol-5-yl)acetamide (0.19g, 100%) as a white solid.

Intermediate 3 (Method A)

- 15 2-((3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-N-(2-hydroxyphenyl)-2-(1-methyl-1H-indazol-5-yl)acetamide
2-((3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-2-(1-methyl-1H-indazol-5-yl)-N-{2-[(phenylmethyl)oxy]phenyl}acetamide (3.5g) was dissolved in ethanol (200ml) and hydrogenated over palladium on charcoal (wet 10%Pd, 350mg) for 5 hours. The catalyst was removed by filtration washed and the filtrate concentrated *in vacuo*. This residue was purified on a Redisep ® silica column (120g) eluted with 50-90% ethyl acetate in cyclohexane, to afford 2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-N-(2-hydroxyphenyl)-2-(1-methyl-1H-indazol-5-yl)acetamide (1.54g) as a white solid.
- 25 HPLC Rt = 3.3 minutes (gradient 1); m/z [M+H]⁺ = 566.

Intermediate 3 (Method B)

2-((3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-((1S)-1-methylpropyl)-2,5-dioxo-1-piperazinyl)-N-(2-hydroxyphenyl)-2-(1-methyl-1H-indazol-5-yl)acetamide

5

The methyl *N*-[(2*R*)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-({[(phenylmethyl)oxy]-carbonyl}amino)acetyl]-*N*-[1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-2-({2-[(phenylmethyl)oxy]phenyl}amino)ethyl]-*D*-alloisoleucinate (intermediate 4) (22.6g, 27.5mmol) was dissolved in ethanol (750mL) and acetic acid (70mL) and the mixture was hydrogenated at room temperature at 1 atmosphere of H₂ over 10% palladium on carbon (Degussa type) (7.75g wetted with water 1:1 w:w) for 3.5h. The reaction mixture was filtered then evaporated under reduced pressure and the residue was partitioned between dichloromethane (400ml) and treated with saturated aqueous sodium hydrogen carbonate (400ml, care CO₂). The organic phase was separated by hydrophobic frit and evaporated under reduced pressure to afford the title compound as a pair of diastereomers (15g).

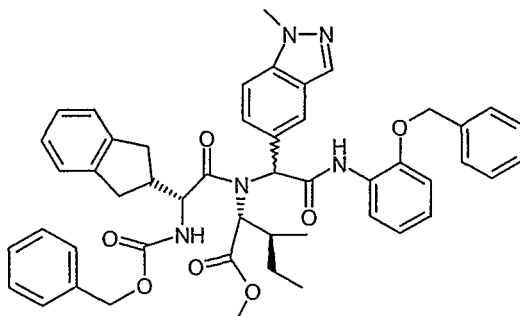
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15

HPLC Rt = 3.27 minutes (gradient 2); m/z [M+H]⁺ = 566

Intermediate 4

20



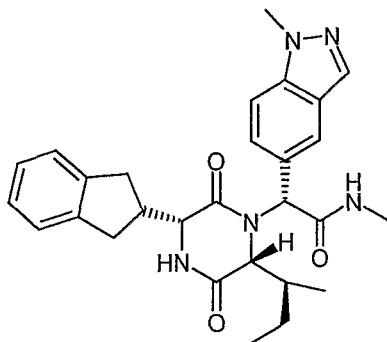
Methyl *N*-[(2*R*)-2-(2,3-Dihydro-1*H*-inden-2-yl)-2-
 ({[(phenylmethyl)oxy]carbonyl}amino)acetyl]-*N*-[1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-2-
 ({2-[(phenylmethyl)oxy]phenyl}amino)ethyl]-*D*-alloisoleucinate

5 1-Methyl-1*H*-indazole-5-carbaldehyde (5.78g, 34mmol) and (*D*)-alloisoleucine
 methyl ester hydrochloride (6.17g, 34mmol) in 2,2,2-trifluoroethanol (100mL) were
 treated with triethylamine (4.74mL, 34mmol) and the mixture was stood under
 nitrogen at room temperature for 18h. (2*R*)-[(Benzyloxycarbonyl)amino](2,3-dihydro-
 1*H*-inden-2-yl)ethanoic acid (11.05g, 34mmol) and 2-benzyloxyphenylisonitrile
 10 (7.52g, 36 mmol) were added and the mixture was stirred at room temperature under
 nitrogen for 3 days. The mixture was concentrated under reduced pressure then
 partitioned between ethyl acetate (750mL) and water (500mL). The aqueous phase
 was back-extracted with ethyl acetate (250mL) and the combined organic extracts
 were washed with sat. sodium chloride (250mL), dried over anhydrous magnesium
 15 sulphate, filtered and evaporated under reduced pressure to give the crude product
 (29.6g). This was purified on a Redisep ® silica column (330g) eluted with 10-50%
 ethyl acetate in cyclohexane to afford 22.6g of the title compound as a pair of
 diastereomers.

HPLC Rt = 4.13 minutes (gradient 2); m/z $[M+H]^+ = 822.6$

20

Example 1



(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)-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide

25 2-((3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-((1*S*)-1-methylpropyl)-2,5-dioxo-1-
 piperazinyl)-*N*-(2-hydroxyphenyl)-2-(1-methyl-1*H*-indazol-5-yl)acetamide
 (intermediate 3) (0.5g) and 1,1'-carbonyldiimidazole (0.23g) were dissolved in dry
 dichloromethane (10ml) and left to stand at room temperature under N₂ for 3 hours. A
 2.0M solution of methylamine in tetrahydrofuran (2.2ml) was added and the reaction
 30 mixture was left to stand for 3 hours. The reaction mixture was evaporated *in vacuo*.

The residue was applied to a silica cartridge (35g) and eluted with a gradient of ethyl acetate to 10% methanol in ethyl acetate. The required fractions were evaporated *in vacuo* and the residue was purified further using a SCX SPE cartridge (5g), washed with methanol and the methanol was concentrated to afford (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]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide as a white solid.

HPLC Rt = 2.9 minutes (gradient 1); m/z [M+H]⁺ = 488.

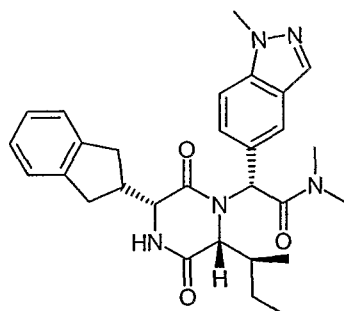
¹H NMR (CDCl₃) δ 7.99 (s, 1H), 7.79 (s, 1H), 7.47 (dd, 1H), 7.42 (d, 1H), 7.25-7.12 (m, 4H), 6.55 (d, 1H), 6.12 (q, 1H), 5.04 (s, 1H), 4.10 (s, 3H), 4.06 (dd, 1H), 3.96 (d, 1H), 3.22-3.05 (m, 3H), 2.97 (m, 1H), 2.85 (d, 3H), 2.76 (dd, 1H), 1.99 (m, 1H), 1.79 (m, 1H), 1.15 (m, 1H), 1.08 (d, 3H), 0.93 (t, 3H).

Example 1

(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]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide

2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-[(1*S*)-1-methylpropyl]-2,5-dioxo-1-piperazinyl]-*N*-(2-hydroxyphenyl)-2-(1-methyl-1*H*-indazol-5-yl)acetamide (15g) and 1,1'-carbonyldiimidazole (6.88g) were dissolved in dry dichloromethane (300mL) under nitrogen and stirred for four hours at room temperature. A 2.0M solution of methylamine in tetrahydrofuran (66.3mL) was added over 10 minutes. then the reaction mixture stirred for 30 minutes, the reaction mixture was then left to stand for 18 hours. The reaction mixture was diluted with dichloromethane (200mL) and washed with 0.1M HCl (400mL). The organic extract was separated by hydrophobic frit and the aqueous extract was washed with further dichloromethane (200ml). The combined organic extracts were concentrated *in vacuo* and the residue was applied to a redisepp[®] silica cartridge (339g) and eluted with a gradient of ethyl acetate to 10% methanol in ethyl acetate. The required fractions were evaporated *in vacuo* and the residue was purified further using a SCX-2 SPE cartridge (50g) conditioning the cartridge with methanol and then loading and eluting the compound with methanol. On concentration of the relevant fractions this gave (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]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide (4.1g, 32%) as a white solid.

HPLC Rt = 2.9 minutes (gradient 1); m/z [M+H]⁺ = 488.

Example 2

(2R)-2-[(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxo-1-piperazinyl]-N,N-dimethyl-2-(1-methyl-1H-indazol-5-yl)ethanamide

- 5 The title compound was similarly prepared from intermediate 3 and dimethylamine.

HPLC R_t = 3.0 minutes; m/z $[M+H]^+$ = 502

- 1H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.82 (s, 1H), 7.53-7.44 (m, 2H), 7.30-7.15 (m, 4H), 6.45 (s, 1H), 6.20 (d, 1H), 4.16-4.10 (m, 5H), 3.19-3.11 (m, 3H), 2.99-2.85 (m, 1H),
 10 2.96 (s, 3H), 2.87 (s, 3H), 2.75 (dd, 1H), 1.50 (m, 1H), 1.05 (m, 1H), 0.78 (m, 1H), 0.60 (t, 3H), 0.39 (d, 3H).

Ref:

1. V. Auwers; Lange; Chem.Ber.; 55; 1922; 1141, 1157.
 15 2: Halley, Frank; Sava, Xavier. Synthesis of 5-cyanoindazole and 1-methyl and 1-aryl-5-cyanoindazoles. Synthetic Communications (1997), 27(7), 1199-1207.

Biological Activity

- 20 Examples 1 and 2 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. The table also includes two compounds X and Y for comparison.

Assay 1

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

Cell Culture

- Adherent Chinese Hamster Ovary (CHO) cells, stably expressing the recombinant
 30 human Oxytocin-1 (hOT) receptor, were maintained in culture in DMEM:F12 medium (Sigma, cat no D6421), supplemented with 10% heat inactivated 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:CO₂ at 37°C and passaged every 3-4 days using TrypLE™ Express (Gibco/Invitrogen, cat no. 12604-013).

5

Measurement of [Ca²⁺]_i using the FLIPR™

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:CO₂ 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; MgCl₂, 1.2mM; CaCl₂, 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 ($\lambda_{\text{ex}} = 488\text{nm}$, $\lambda_{\text{EM}} = 540\text{nm}$) before and after the addition of a submaximal concentration of oxytocin (EC80).

Data Analysis

Functional responses using FLIPR were analysed using Activity Base Version 5.0.10.

Assay 2

Oxytocin Binding Assay

25

Preparations

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

The membrane preparation was frozen in aliquots at -70°C until used.

Binding Assay Protocol

Membranes (~50 ug) were incubated in 200 ul of assay buffer (50 mM Tris, 10 mM MgCl₂, 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 and 2 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).

5

Specific binding represented approximately 90% of total binding.

Data Analysis

IC₅₀ values were determined from competition binding experiments using non-linear regression analysis (GraphPad) and converted to K_i using the method of Cheng and Prusoff, 1974. Data are reported as mean values.

10

Assay 3

Determination of In vitro Intrinsic Clearance in Microsomes

15

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.

20

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).

25

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.

30

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%.

35

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

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:

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

Results

Examples 1 and 2 of the present invention and also two comparator compounds (Comparator compound X = (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-5-yl)-N,N-dimethylethanamide (Example 172 in WO 03/053443) and Comparator compound Y = (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (Example 8 in WO 03/053443) were tested in the above assays, except comparator compound X was not tested in assays 1 and 2.

However, Comparator compound Y was tested in assays 1 and 2 and showed a similar potency to that exhibited by compounds 1 and 2 of the present invention, in fact each of these compounds exhibited fpK_i's of between 8.5 and 8.7 (Assay 1) and pK_i's of between 9.9 and 10.4 (Assay 2).

However, the compounds of the present invention exhibited a surprising improvement in *in vitro* intrinsic clearance in microsomes (Assay 3) when compared with both of the comparator compounds X and Y.

Table 1

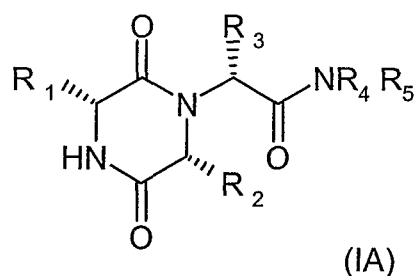
	Assay 3 - Microsomal Cl (ml/min/g)			
	Rat	Dog	Cyno	Human
Comparator compound X	++	+++	+++++	+++++
Comparator compound Y	+	+	++++	+++
Example 1	+	+	++	+
Example 2	+	+	++	+

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
- 5 ++++ corresponds to 21-30 ml/min/mg
- +++++ corresponds to > 31 ml/min/mg

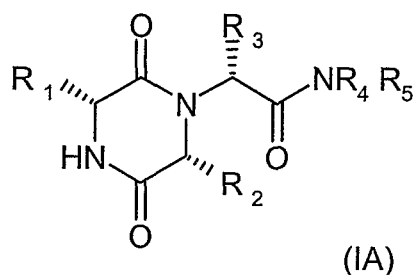
Claims

1. At least one chemical entity selected from a compound of formula (IA)



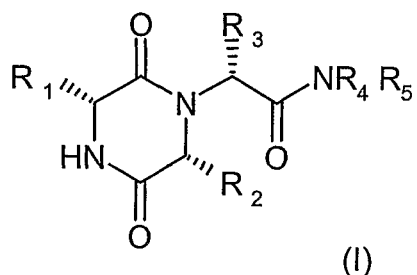
- 5 wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 1-methyl-indazol-5-yl, R_4 represents methyl and R_5 represents hydrogen or methyl, and pharmaceutically acceptable derivatives thereof.

2. At least one chemical entity selected from salts and solvates of compounds of
10 formula (IA)



wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 1-methyl-indazol-5-yl, R_4 represents methyl and R_5 represents hydrogen or methyl.

- 15 3. At least one chemical entity selected from a compound of formula (I)



wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 1-methyl-indazol-5-yl, R_4 represents methyl and R_5 represents hydrogen and pharmaceutically acceptable derivatives thereof.

20

4. At least one chemical entity according to claim 1 or claim 3 wherein R_2 is (1S)-1-methylpropyl.

5. At least one chemical entity according to any one of claims 1, 3 and 4 selected from:

(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-

5 piperazinyl]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide, and pharmaceutically acceptable derivatives thereof.

6. At least one chemical entity according to claim 1 or claim 4 selected from:

(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-

10 piperazinyl]-*N*-methyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide, and

(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]-*N,N*-dimethyl-2-(1-methyl-1*H*-indazol-5-yl)ethanamide,

and pharmaceutically acceptable derivatives thereof.

15 7. A pharmaceutical composition comprising at least one chemical entity according to any one of claims 1 and 3-6 together with one or more pharmaceutically acceptable carriers.

8. At least one chemical entity according to any one of claims 1 and 3-6 for use in
20 therapy.

9. Use of at least one chemical entity according to any one of claims 1 and 3-6 for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

25

10. Use of at least one chemical entity according to any one of claims 1 and 3-6 for the manufacture of a medicament for the treatment of one or more diseases or conditions selected from pre-term labour, dysmenorrhea, endometriosis and benign prostatic hyperplasia.

30

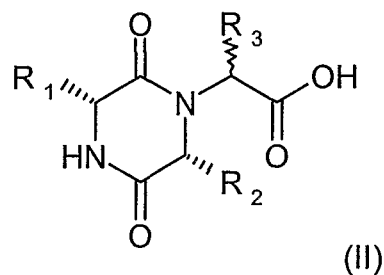
11. A method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in need thereof of an effective amount of at least one chemical entity according to any one of claims 1 and 3-6.

35

12. A method according to claim 11 wherein the disease or condition is selected from pre-term labour, dysmenorrhea, endometriosis and benign prostatic hyperplasia.

- 5 13. A process for the preparation of compounds of formula (I) or of formula (IA) as claimed in claim 1 or claim 3 respectively which comprises:

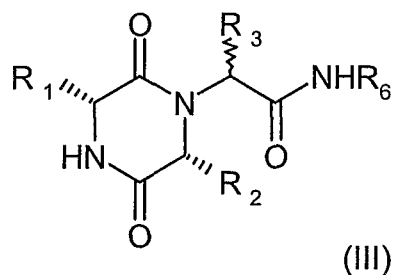
(a) reacting a compound of formula (II)



- 10 wherein R_1 , R_2 and R_3 have the meanings defined in claim 1 or claim 3 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 meanings defined in claim 1 or claim 3 under standard conditions for preparing amides from a carboxylic acid or an activated derivative thereof and an amine, or

15

(b) reacting a compound of formula (III)



- wherein R_1 , R_2 and R_3 have the meanings defined in claim 1 or claim 3, 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 claim 1 or claim 3.
- 20