(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2007 (15.02.2007)

PCT

(10) International Publication Number
WO 2007/017752 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *A61P 15/12* (2006.01)
A61K 31/497 (2006.01)

(21) International Application Number:
PCT/IB2006/002225

(22) International Filing Date: 31 July 2006 (31.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/707,433 10 August 2005 (10.08.2005) US

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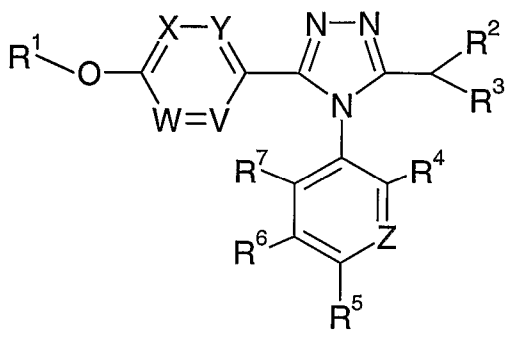
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED TRIAZOLE DERIVATIVES AS OXYTOCIN ANTAGONISTS



(I)

(57) Abstract: The present invention relates to a class of substituted triazoles of formula (I) with activity as oxytocin antagonists, uses thereof, processes for the preparation thereof and compositions containing said inhibitors. These inhibitors have utility in a variety of therapeutic areas including sexual dysfunction, particularly premature ejaculation (P.E.).

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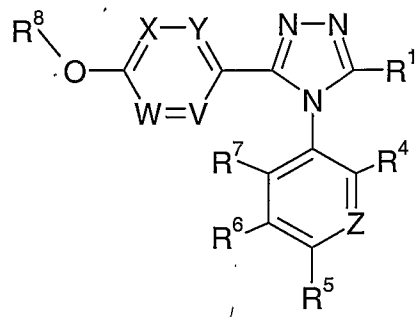
Substituted Triazole Derivatives as Oxytocin Antagonists

The present invention relates to a class of substituted triazoles with activity as oxytocin antagonists, uses thereof, processes for the preparation thereof and compositions containing said inhibitors. These inhibitors have utility in a variety of therapeutic areas including sexual dysfunction, particularly premature ejaculation (P.E.).

The present invention provides for compounds of formula (I):



(I)

wherein:

V, W, X and Y, which may be the same or different, represent CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3, C-CN, C-NH(C_1-C_6)alkyl, C-N((C_1-C_6)alkyl)$_2$, C-C(O)(C_1-C_6)alkyl, C-C(O)O(C_1-C_6)alkyl, C-C(O)NH(C_1-C_6)alkyl, C-C(O)N((C_1-C_6)alkyl)$_2$, C-C(O)OH, C-O(C_1-C_6)alkyl, C-C(O)NH_2 or N;

Z is CH or N;

R^1 is H or CHR^2R^3;

R^2 is selected from:

(i) H;

(ii) (C_1-C_6)alkyl, which is optionally substituted by O(C_1-C_6)alkyl or phenyl;

(iii) O(C_1-C_6)alkyl, which is optionally substituted by O(C_1-C_6)alkyl;

(iv) NH(C_1-C_6)alkyl, said alkyl group being optionally substituted by O(C_1-C_6)alkyl;

(v) N((C_1-C_6)alkyl)$_2$, wherein one or both of said alkyl groups may be optionally substituted by O(C_1-C_6)alkyl;

(vi) a 5 to 8 membered N-linked saturated or partially saturated heterocycle containing 1 to 3 heteroatoms, each independently selected from N, O and S, wherein at least one heteroatom is N and said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, C(O)(C_1-C_6)alkyl, C(O)NH(C_1-C_6)alkyl, C(O)N((C_1-C_6)alkyl)$_2$, C(O)OH, C(O)NH_2 and C(O)OCH_2Ph; and

(vii) a 5 to 7 membered N-linked aromatic heterocycle containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is

N; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1$-$C_6)$alkyl, $O(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$, $C(O)(C_1$-$C_6)$alkyl, $C(O)NH(C_1$-$C_6)$alkyl, $C(O)N((C_1$-$C_6)alkyl)_2$, C(O)OH, $C(O)NH_2$ and $C(O)OCH_2Ph$;

R^3 is selected from H, $(C_1$-$C_6)$alkyl and $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl;

R^4, R^5, R^6 and R^7 are each independently selected from H, halo, CN, $(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$ and $O(C_1$-$C_6)$alkyl; and

R^8 is phenyl or naphthyl, each of which is optionally substituted with one or more substituents independently selected from halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, cyano, CF_3, $S(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$, $CO(C_1$-$C_6)$alkyl, $C(O)NH(C_1$-$C_6)$alkyl, $C(O)N((C_1$-$C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer,
with the proviso that the compound of formula (I) is not 4-(2-methoxy-phenyl)-3-methyl-5-(4-phenoxy-phenyl)-4H-[1,2,4]triazole.

Unless otherwise indicated, alkyl and alkoxy groups may be straight or branched and contain 1 to 6 carbon atoms and preferably 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, pentyl and hexyl. Examples of alkoxy include methoxy, ethoxy, isopropoxy and n-butoxy. Halo means fluoro, chloro, bromo or iodo and is preferably fluoro.

A heterocycle may be saturated, partially saturated or aromatic. Examples of heterocyclic groups are tetrahydrofuranyl, thiolanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, sulfolanyl, dioxolanyl, dihydropyranyl, tetrahydropyranyl, piperidinyl, pyrazolinyl, pyrazolidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, azepinyl, oxazepinyl, thiazepinyl, thiazolinyl and diazapanyl. Examples of aromatic heterocyclic groups are pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Examples of bicyclic aromatic heterocyclic groups are benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, quinolinyl and isoquinolinyl.

Unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

Preferred embodiments of the compounds of formula (I) according to the above definition are those that incorporate one or more of the following preferences.

Preferably, V, W, X and Y are each independently selected from CH, C-(C_1-C_6)alkyl, C-O(C_1-C_6)alkyl, C-halo, C-CF_3 and N.
More preferably, V, W, X and Y are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-OCH_3, C-F, C-Cl, C-CF_3 and N.
Most preferably, X and V represent N, and W and Y represent CH.

Preferably, Z is N.

Preferably, R^1 is CHR^2R^3.

Preferably, R^2 is selected from:

(i) H;
(ii) (C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl;
(iii) O(C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl;
(iv) NH(C_1-C_3)alkyl, said alkyl group being optionally substituted by O(C_1-C_3)alkyl;
(v) N((C_1-C_3)alkyl)$_2$, wherein one or both of said alkyl groups may be optionally substituted by O(C_1-C_3)alkyl;
(vi) a 5 to 6 membered N-linked saturated heterocycle containing 1 to 2 nitrogen atoms; said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted by $C(O)NH_2$ or $C(O)OCH_2Ph$; and
(vii) a 5 to 6 membered N-linked aromatic heterocycle containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein at least two heteroatoms are N.

More preferably, R^2 is selected from:

(i) H;
(ii) (C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl; and
(iii) O(C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl.

Yet more preferably, R^2 is selected from H, methyl, methoxy and ethoxy.
Most preferably, R^2 is H.

Preferably, R^3 is H or (C_1-C_3)alkyl.
More preferably, R^3 is H or CH_3.
Most preferably, R^3 is H.

Preferably, R^4, R^5, R^6 and R^7 are each independently selected from H, halo, (C_1-C_3)alkyl and O(C_1-C_3)alkyl.

More preferably, R^4, R^5, R^6 and R^7 are each independently selected from H, chloro, fluoro, methyl and methoxy.
Most preferably, R^4, R^6 and R^7 are H, and R^5 is methoxy.

Preferably, R^8 is phenyl, which is optionally substituted with one or more substituents independently selected from halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, cyano, CF_3 and $S(C_1\text{-}C_6)$alkyl.
More preferably, R^8 is phenyl, which is optionally substituted with one or more substituents independently selected from chloro, fluoro, methyl, ethyl, isopropyl, methoxy, cyano, CF_3 and SCH_3.
Most preferably, R^8 is as defined in the examples.

Pharmaceutically acceptable salts of the compounds of formula (I) comprise the acid addition and base salts thereof.
Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.
Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.
Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).
Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;
(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) using the desired acid or base; or
(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

As indicated, so-called 'pro-drugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in "Pro-drugs as Novel Delivery Systems", Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and "Bioreversible Carriers in Drug Design", Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include

(i) where the compound of formula I contains a carboxylic acid functionality, an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by (C_1-C_8)alkyl; and

(ii) where the compound of formula (I) contains a primary or secondary amino functionality, an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references. Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof (-CH_3 -> -CH_2OH):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof (-NR'R" -> -NHR' or –NHR");

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof (-NHR' -> -NH_2);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof (-$CONH_2$ -> COOH).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, a keto group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

The present invention includes all crystal forms of the compounds of formula (I) including racemates and racemic mixtures (conglomerates) thereof. Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Also within the scope of the invention are intermediate compounds as hereinafter defined, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for compounds of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

When preparing compounds of formula (I) in accordance with the invention, it is open to a person skilled in the art to routinely select the form of intermediate which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products or may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in "Remington's Pharmaceutical Sciences", 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents

may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula (I) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (I) may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis,

sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection. Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 2 to 30mg of the compound of formula (I). The overall daily dose will typically be in the range 50 to 100mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for
example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis. Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like. The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

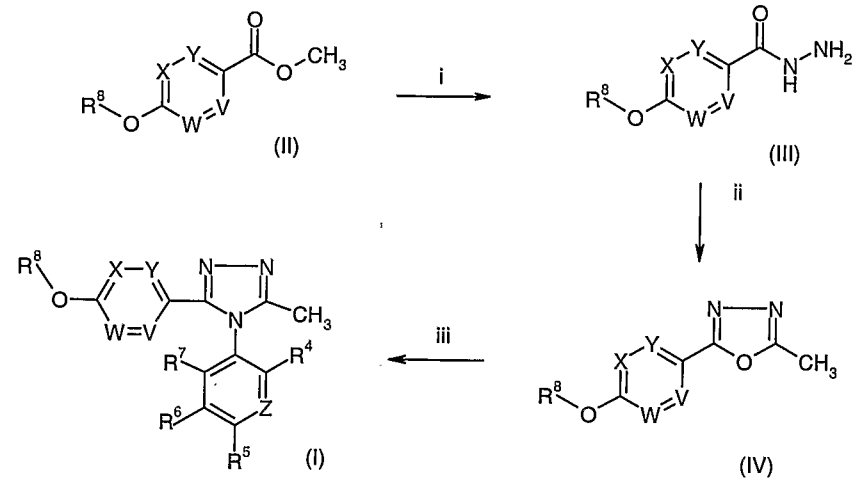
For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 50mg to 100mg depending, of course, on the mode of administration and efficacy. For example, oral administration may require a total daily dose of from 50mg to 100mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Accordingly in another aspect the invention provides a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable diluent or carrier.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

Processes

Compounds of general formula (I) where X is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; R^1 is CH_3; and where R^4, R^5, R^6, R^7, R^8, V, W, Y and Z are as described herein may be prepared according to reaction scheme 1.



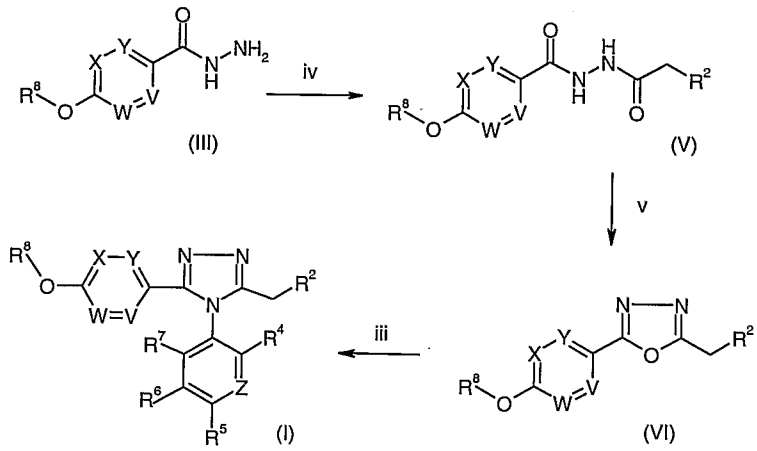
Scheme 1

Compounds of formula (III) are either commercially available or can be prepared from compounds of formula (II) by process step (i), which comprises reaction with hydrazine monohydrate in a suitable solvent such as methanol or ethanol heated to reflux. Typical conditions comprise heating 1 equivalent of aryl ester (II) and 3 equivalents of hydrazine monohydrate in methanol at 75°C for 48 hours.

Compounds of formula (IV) may be prepared from compounds of formula (III) by process step (ii), which comprises reaction with N,N-dimethylacetamide dimethyl acetal (*ex* Aldrich) in a suitable solvent such as N,N-dimethylformamide, N-methyl pyrrollidine or toluene followed by the addition of a suitable acid catalyst such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid. Typical conditions comprise heating 1 equivalent of aryl hydrazine (III) and 1.3 equivalents of N,N-dimethylacetamide dimethyl acetal in N,N-dimethylformamide at 60°C for 2 hours, followed by concentration *in vacuo*, addition of toluene and 0.025 equivalents of *para*-toluenesulfonic acid and heating at reflux for 2 hours.

Compounds of formula (I) may be prepared from compounds of formula (IV) by process of step (iii), which comprises reaction with a suitable aniline or aminopyridine in the presence of a suitable acid, such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid in a suitable solvent, such as xylene or toluene by heating at elevated temperature. Typical conditions comprise heating 1 equivalent of 1,2,4-oxidiazole (IV), 3 equivalents of aniline or aminopyridine and 0.04 equivalents of *para*-toluenesulfonic acid in xylene at 150°C for 22 hours.

Compounds of general formula (I) where R^1 is CH_2R^2; X is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; Y is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; and where R^2, R^4, R^5, R^6, R^7, R^8, V, W and Z are as described herein may alternatively be prepared according to reaction scheme 2.



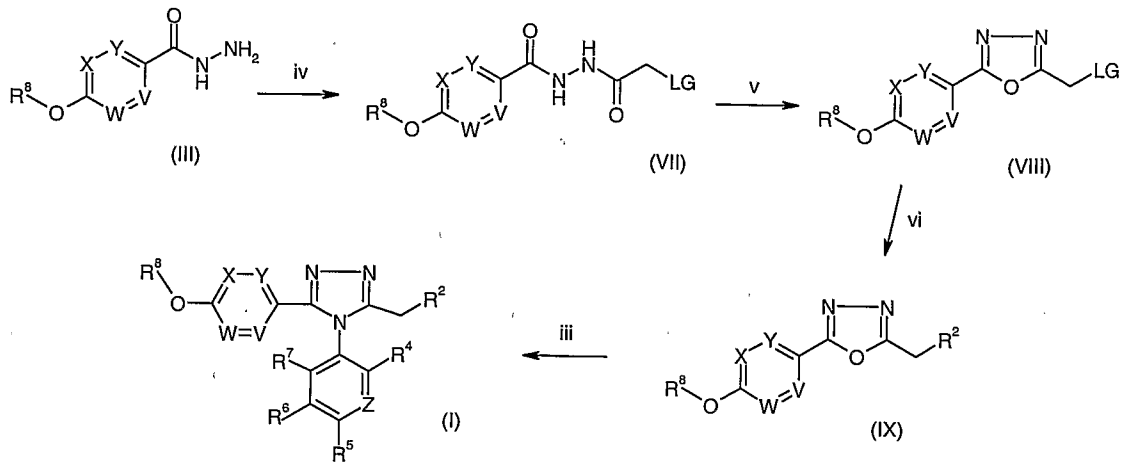
Scheme 2

Compounds of formula (V) can be prepared from the aryl hydrazides of formula (III) by process step (iv), which comprises reaction with an acid chloride, such as $R^2CH_2C(O)Cl$, in the presence of base such as triethylamine, N-methylmorpholine, sodium carbonate or potassium hydroxide. Typical conditions comprise reacting 1.0 equivalents of aryl hydrazide (III), 1.0-1.3 equivalents of acid chloride ($R^2CH_2C(O)Cl$) and 1.2-2.0 equivalents of N-methyl morpholine in dichloromethane at 25°C.

Compounds of formula (VI) can be prepared from diacylhydrazines of formula (V) by process step (v), which comprises reaction with a suitable dehydrating agent such as phosphorous oxychloride, trifluoromethanesulfonic anhydride or phosphorous pentachloride at a temperature of 25° to 110°C. Typical conditions comprise heating 1.0 equivalents of diacylhydrazine (V) in phosphorous oxychloride at 110°C for 4 hours.

Compounds of formula (I) may be prepared from compounds of formula (VI) by process step (iii), which comprises reaction with a suitable aniline or aminopyridine in the presence of a suitable acid such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid, in a suitable solvent such as xylene or toluene, by heating at elevated temperature. Typical conditions comprise heating 1 equivalent of 1,2,4-oxidiazole (V), 3 equivalents of aniline or aminopyridine and 0.04 equivalents of *para*-toluenesulfonic acid in xylene at 150°C for 22 hours.

Compounds of general formula (I) where R^1 is CH_2R^2; R^2 is NR^9R^{10} or OR^{11} and wherein R^9, R^{10} and R^{11} are the substituents on the N-linked and O-linked R^2 groups as described herein; and where R^4, R^5, R^6, R^7, R^8, W, V, X, Y and Z are described herein may alternatively be prepared according to reaction scheme 3.



Scheme 3

Compounds of formula (VII) can be prepared from aryl hydrazides of formula (III) by process step (iv), which comprises reaction with an acid chloride LG-$CH_2C(O)Cl$ as described in scheme 2, where LG is a leaving group such as halo or mesylate.

Compounds of formula (VIII) can be prepared from compounds of formula (VII) by process step (v) as described previously in scheme 2.

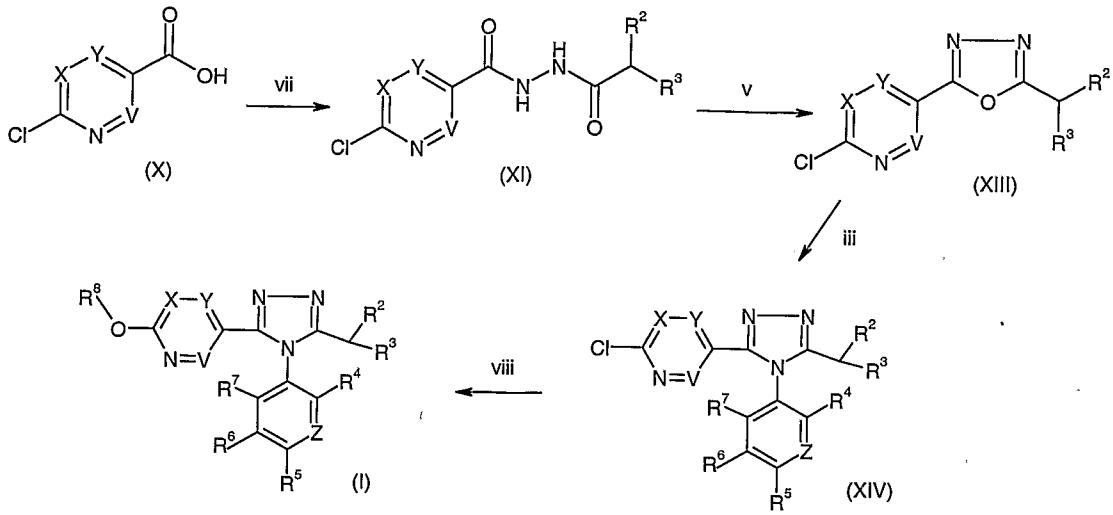
Compounds of formula (IX) can be prepared from alkyl chlorides of formula (VIII) by process step (vi), which;

(a) when R^2 is NR^9R^{10}, comprises reaction with a suitable primary or secondary amine (HNR^9R^{10}), optionally in the presence of a base such as potassium carbonate, sodium carbonate or cesium carbonate, in a suitable solvent such as acetonitrile or N,N-dimethylformamide by heating at 25°C-50°C for 2-18 hours. Typical conditions comprise heating 1 equivalent of alkyl halide (VIII), 1.5 equivalents of amine and 2 equivalents of potassium carbonate in acetonitrile for 18 hours at 25°C; or

(b) when R^2 is OR^{11}, compounds of formula (IX) can be prepared by the reaction of alkyl halide (VIII) with a suitable alkoxide salt such as $R^{11}ONa$, optionally generated *in situ*, in a suitable solvent such as tetrahydrofuran or $R^{11}OH$, by stirring at room temperature for 2-18 hours. Typical conditions comprise stirring 1 equivalent of alkyl halide (VIII), 1.5 equivalents of alcohol ($R^{11}OH$) and 2 equivalents of sodium hydride in tetrahydrofuran at room temperature for 2 hours.

Compounds of formula (I) can be prepared from compounds of formula (IX) by process step (iii) as described previously in scheme 1.

Compounds of general formula (I) where W is N; R^1 is CHR^2R^3 and where R^2, R^3, R^4, R^5, R^6, R^7, R^8, V, X, Y and Z are described herein may alternatively be prepared according to reaction scheme 4.



Scheme 4

Compounds of formula (X) are commercially available.

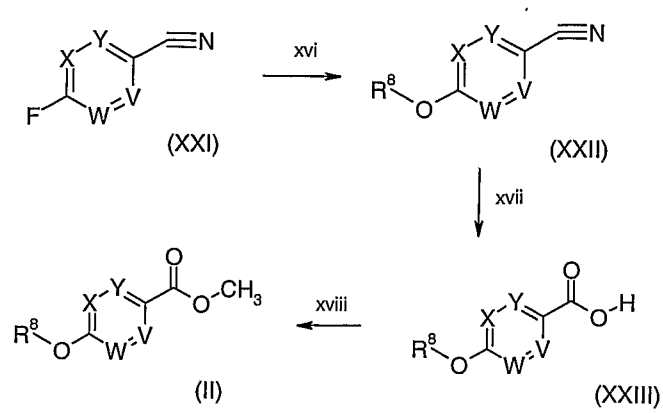
Compounds of formula (XI) may be prepared from compounds of formula (X) by process step (vii), which comprises reaction with acetyl hydrazine in the presence of a suitable coupling reagent such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and a suitable base such as triethylamine, in a suitable solvent such as N,N-dimethylformamide. Typical conditions comprise stirring 1.0 equivalent of chloronicotinic acid (X), one equivalent of acetyl hydrazine, one equivalent of HBTU and one equivalent of triethylamine in N,N-dimethylformamide at 25°C for 48 hours.

Compounds of formula (XIII) can be prepared from compounds of formula (XI) by process step (v) as described previously in scheme 2.

Compounds of formula (XIV) can be prepared from compounds of formula (XIII) by process step (iii) as described in scheme 1.

Compounds of formula (I) may be prepared from compounds of formula (XIV) by process step (viii) – chloride displacement by a phenol in the presence of a suitable base, such as caesium carbonate or potassium carbonate, in a suitable solvent, such as N-methylpyrrolidinone or DMF, heated at between room temperature and 100 °C for between 2-18h hours.

Compounds of general formula (II) where R^8, V, W, X, and Y are described herein may be prepared according to reaction scheme 5.



Scheme 5

Compounds of formula (XXI) are commercially available.

Compounds of general formula (XXII) can be prepared from compounds of formula (XXI) by process step (xvi), which comprises reaction with an alcohol HOR^8 in the presence of a suitable base such as sodium hydride, in a suitable solvent such as tetrahydrofuran or N,N-dimethylformamide. Typical conditions comprise stirring 1 equivalent of halo aryl nitrile (XXI), 1 equivalent of alcohol HOR^8 and 1.0-1.5 equivalents of sodium hydride in tetrahydrofuran for 18 hours at 25°C.

Compounds of general formula (XXIII) can be prepared from compounds of formula (XXII) by process step (xvii) as described in Bioorg Med. Chem.; **10** (3), 557-560; 2002.

Compounds of general formula (II) are prepared from compounds of formula (XXIII) by process step (xviii), which comprises reaction with methanol in the presence of an acid catalyst such as sulphuric acid. Typical conditions comprise heating 1.0 equivalent of aryl carboxylic acid (XXIII), excess methanol and 0.04 equivalents of sulphuric acid at reflux for 48 hours.

All of the above reactions and the preparations of novel starting materials disclosed in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

All of the above reactions and the preparations of novel starting materials disclosed in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

The compounds of the invention are useful because they have pharmacological activity in mammals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which modulation of the levels of oxytocin could provide a beneficial effect. Disease states that may be mentioned include sexual dysfunction, particularly premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, occular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

Accordingly in another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament.

In another aspect the invention provides a method of treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof.

In another aspect the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect.

In another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect.

In another aspect the invention provides a method of treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, occular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

In another aspect the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, wherein the disorder or condition is selected from

sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

In another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

Sexual dysfunction (SD) is a significant clinical problem which can affect both males and females. The causes of SD may be both organic as well as psychological. Organic aspects of SD are typically caused by underlying vascular diseases, such as those associated with hypertension or diabetes mellitus, by prescription medication and/or by psychiatric disease such as depression. Physiological factors include fear, performance anxiety and interpersonal conflict. SD impairs sexual performance, diminishes self-esteem and disrupts personal relationships thereby inducing personal distress. In the clinic, SD disorders have been divided into female sexual dysfunction (FSD) disorders and male sexual dysfunction (MSD) disorders (Melman *et al, J. Urology*, 1999, 161, 5-11).

FSD can be defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several diverse female sexual disorders (Leiblum, S.R. (1998). Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, 10, S104-S106; Berman, J.R., Berman, L. & Goldstein, I. (1999). Female sexual dysfunction: Incidence, pathophysiology, evaluations and treatment options. *Urology*, 54, 385-391). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or psychological problems can cause FSD. Treatments in development are targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998). Definition and classification of female sexual disorders, *Int. J. Impotence Res.*, 10, S104-S106). Desire or libido is the drive for

sexual expression. Its manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. Arousal is the vascular response to sexual stimulation, an important component of which is genital engorgement and includes increased vaginal lubrication, elongation of the vagina and increased genital sensation/sensitivity. Orgasm is the release of sexual tension that has culminated during arousal.

Hence, FSD occurs when a woman has an inadequate or unsatisfactory response in any of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders. Although the compounds of the invention will improve the genital response to sexual stimulation (as in female sexual arousal disorder), in doing so it may also improve the associated pain, distress and discomfort associated with intercourse and so treat other female sexual disorders.

Thus, in accordance with a further aspect of the invention, there is provided the use of a compound of the invention in the preparation of a medicament for the treatment or prophylaxis of hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder, more preferably for the treatment or prophylaxis of sexual arousal disorder, orgasmic disorder, and sexual pain disorder, and most preferably in the treatment or prophylaxis of sexual arousal disorder.

Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants eg SSRIs or antihypertensive agents.

Sexual pain disorders (includes dyspareunia and vaginismus) is characterised by pain resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

The prevalence of FSD is difficult to gauge because the term covers several types of problem, some of which are difficult to measure, and because the interest in treating FSD is relatively recent. Many women's sexual problems are associated either directly with the female ageing process or with chronic illnesses such as diabetes and hypertension.

Because FSD consists of several subtypes that express symptoms in separate phases of the sexual response cycle, there is not a single therapy. Current treatment of FSD focuses principally on psychological or relationship issues. Treatment of FSD is gradually evolving as more clinical and basic science studies are dedicated to the investigation of this medical problem. Female sexual complaints are not all psychological in pathophysiology, especially for those individuals who may have a component of vasculogenic dysfunction (eg FSAD) contributing to the overall female sexual complaint. There are at present no drugs licensed for the treatment of FSD. Empirical drug therapy includes oestrogen administration (topically or as hormone replacement therapy), androgens or mood-altering drugs such as buspirone or trazodone. These treatment options are often unsatisfactory due to low efficacy or unacceptable side effects.

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being:

> "a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked distress or interpersonal difficulty."

The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disturbance causes marked distress and/or interpersonal difficulty.

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post menopausal (±HRT) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and UG disorders.

The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

Male sexual dysfunction (MSD) is generally associated with either erectile dysfunction, also known as male erectile dysfunction (MED) and/or ejaculatory disorders such as premature ejaculation, anorgasmia (unable to achieve orgasm) or desire disorders such as hypoactive sexual desire disorder (lack of interest in sex).

PE is a relatively common sexual dysfunction in men. It has been defined in several different ways but the most widely accepted is the Diagnostic and Statistical Manual of Mental Disorders IV one which states:

> "PE is a lifelong persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration and before the patient wishes it. The

clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or stimulation, and frequency of sexual activity. The disturbance causes marked distress of interpersonal difficulty."

The International Classification of Diseases 10 definition states:

"There is an inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following: (1) occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse); (2) ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged abstinence from sexual activity"

Other definitions which have been used include classification on the following criteria:

- Related to partner's orgasm
- Duration between penetration and ejaculation
- Number of thrust and capacity for voluntary control

Psychological factors may be involved in PE, with relationship problems, anxiety, depression, prior sexual failure all playing a role.

Ejaculation is dependent on the sympathetic and parasympathetic nervous systems. Efferent impulses via the sympathetic nervous system to the vas deferens and the epididymis produce smooth muscle contraction, moving sperm into the posterior urethra. Similar contractions of the seminal vesicles, prostatic glands and the bulbouretheral glands increase the volume and fluid content of semen. Expulsion of semen is mediated by efferent impulses originating from a population of lumber spinothalamic cells in the lumbosacral spinal cord (Coolen & Truitt, *Science*, 2002, 297, 1566) which pass via the parasympathetic nervous system and cause rhythmic contractions of the bulbocavernous, ischiocavernous and pelvic floor muscles. Cortical control of ejaculation is still under debate in humans. In the rat the medial pre-optic area and the paraventricular nucleus of the hypothalamus seem to be involved in ejaculation.

Ejaculation comprises two separate components – emission and ejaculation. Emission is the deposition of seminal fluid and sperm from the distal epididymis, vas deferens, seminal vesicles and prostrate into the prostatic urethra. Subsequent to this deposition is the forcible expulsion of the seminal contents from the urethral meatus. Ejaculation is distinct from orgasm, which is purely a cerebral event. Often the two processes are coincidental.

A pulse of oxytocin in peripheral serum accompanies ejaculation in mammals. In man oxytocin but not vasopressin plasma concentrations are significantly raised at or around ejaculation. Oxytocin

does not induce ejaculation itself; this process is 100% under nervous control via α1-adrenoceptor/sympathetic nerves originating from the lumbar region of the spinal cord. The systemic pulse of oxytocin may have a role in the peripheral ejaculatory response. It could serve to modulate the contraction of ducts and glandular lobules throughout the male genital tract, thus influencing the fluid volume of different ejaculate components for example. Oxytocin released centrally into the brain could influence sexual behaviour, subjective appreciation of arousal (orgasm) and latency to subsequent ejaculation.

Accordingly, one aspect of the invention provides for the use of a compound of formula (I) in the preparation of a medicament for the prevention or treatment of sexual dysfunction, preferably male sexual dysfunction, most preferably premature ejaculation.

It has been demonstrated in the scientific literature that the number of oxytocin receptors in the uterus increases during pregnancy, most markedly before the onset of labour (Gimpl & Fahrenholz, 2001, *Physiological Reviews*, 81 (2), 629-683.). Without being bound by any theory it is known that the inhibition of oxytocin can assist in preventing preterm labour and in resolving complications in labour.

Accordingly, another aspect of the invention provides for the use of a compound of formula (I) in the preparation of a medicament for the prevention or treatment of preterm labour and complications in labour.

Oxytocin has a role in feeding; it reduces the desire to eat (Arletti *et al.*, *Peptides*, 1989, 10, 89). By inhibiting oxytocin it is possible to increase the desire to eat. Accordingly oxytocin inhibitors are useful in treating appetite and feeding disorders.

Accordingly, a further aspect of the invention provides for the use of a compound of formula (I) in the preparation of a medicament for the prevention or treatment of appetite and feeding disorders.

Oxytocin is implicated as one of the causes of benign prostatic hyperplasia (BPH). Analysis of prostate tissue have shown that patients with BPH have increased levels of oxytocin (Nicholson & Jenkin, *Adv. Exp. Med. & Biol.*, 1995, 395, 529). Oxytocin antagonists can help treat this condition.

Accordingly, another aspect of the invention provides for the use of a compound of formula (I) in the preparation of a medicament for the prevention or treatment of benign prostatic hyperplasia.

Oxytocin has a role in the causes of dysmenorrhoea due to its activity as a uterine vasoconstrictor (Akerlund, *Ann. NY Acad. Sci.*, 1994, 734, 47). Oxytocin antagonists can have a therapeutic effect on this condition.

Accordingly, a further aspect of the invention provides for the use of a compound of formula (I) in the preparation of a medicament for the prevention of treatment of dysmenorrhoea.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The compounds of the present invention may be coadministered with one or more agents selected from:

1) One or more selective serotonin reuptake inhibitors (SSRIs) such as dapoxetine, paroxetine, 3-[(dimethylamino)methyl]-4-[4-(methylsulfanyl)phenoxy]benzenesulfonamide (Example 28, WO 0172687), 3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzenesulfonamide (Example 12, WO 0218333), *N*-methyl-*N*-({3-[3-methyl-4-(methylsulfanyl)phenoxy]-4-pyridinyl}methyl)amine (Example 38, PCT Application no PCT/IB02/01032).

2) One or more local anaesthetics;

3) one or more α-adrenergic receptor antagonists (also known as α-adrenoceptor blockers, α-receptor blockers or α-blockers); suitable α_1- adrenergic receptor antagonists include: phentolamine, prazosin, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, phenoxybenzamine, rauwolfa alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, Example 19 of WO9830560, terazosin and abanoquil; suitable α_2- adrenergic receptor antagonists include dibenarnine, tolazoline, trimazosin, efaroxan, yohimbine, idazoxan clonidine and dibenarnine; suitable non-selective α-adrenergic receptor antagonists include dapiprazole; further α- adrenergic receptor antagonists are described in PCT application WO99/30697 published on 14th June 1998 and US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference;

4) one or more cholesterol lowering agents such as statins (e.g. atorvastatin/Lipitor- trade mark) and fibrates;

5) one or more of a serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for example 5HT1A, 5HT2A, 5HT2C, 5HT3, 5HT6 and/or 5HT7 receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993;

6) one or more NEP inhibitors, preferably wherein said NEP is EC 3.4.24.11 and more preferably wherein said NEP inhibitor is a selective inhibitor for EC 3.4.24.11, more preferably a selective NEP inhibitor is a selective inhibitor for EC 3.4.24.11, which has an IC_{50} of less than 100nM (e.g. ompatrilat, sampatrilat) suitable NEP inhibitor compounds are described in EP-A-1097719; IC50 values against NEP and ACE may be determined

using methods described in published patent application EP1097719-A1, paragraphs [0368] to [0376];

7) one or more of an antagonist or modulator for vasopressin receptors, such as relcovaptan (SR 49059), conivaptan, atosiban, VPA-985, CL-385004, Vasotocin.

8) Apomorphine - teachings on the use of apomorphine as a pharmaceutical may be found in US-A-5945117;

9) Dopamine agonists (in particular selective D2, selective D3, selective D4 and selective D2-like agents) such as Pramipexole (Pharmacia Upjohn compound number PNU95666), ropinirole, apomorphine, surmanirole, quinelorane, PNU-142774, bromocriptine, carbergoline, Lisuride;

10) Melanocortin receptor agonists (e.g. Melanotan II and PT141) and selective MC3 and MC4 agonists (e.g.THIQ);

11) Mono amine transport inhibitors, particularly Noradrenaline Re-uptake Inhibitors (NRIs) (e.g. Reboxetine), other Serotonin Re-uptake Inhibitors (SRIs) (e.g. paroxetine, dapoxetine) or Dopamine Re-uptake Inhibitors (DRIs);

12) 5-HT_{1A} antagonists (e.g. robalzotan); and

13) PDE inhibitors such as PDE2 (e.g. erythro-9-(2-hydroxyl-3-nonyl)-adenine) and Example 100 of EP 0771799-incorporated herein by reference) and in particular a PDE5 inhibitor such as the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4-d]pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the compounds disclosed in published international application WO95/19978; the compounds disclosed in published international application WO 99/24433 and the compounds disclosed in published international application WO 93/07124; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27112; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27113; the compounds disclosed in EP-A-1092718 and the compounds disclosed in EP-A-1092719.

Preferred PDE5 inhibitors for use with the invention:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756);

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333);

(+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 3-ethyl-5-{5-[4-ethylpiperazin-1-ylsulphonyl]-2-([(1R)-2-methoxy-1-methylethyl]oxy)pyridin-3-yl}-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one (see WO99/54333);

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl}-4-ethylpiperazine (see WO 01/27113, Example 8);

5-[2-*iso*-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 15);

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 66);

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 124);

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 132);

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) - pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1, 3, 7 and 8;

2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 19, 337 and 336 of published international application WO99/24433; and

the compound of example 11 of published international application WO93/07124 (EISAI); and

compounds 3 and 14 from Rotella D P, *J. Med. Chem.*, 2000, 43, 1257.

Still further PDE5 inhibitors for use with the invention include:

4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5- ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a- octahydrocyclopent[4,5]-imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6- carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl) propoxy)-3- (2H)pyridazinone; I-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro- 7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)arnino]-6-chloro-2- quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

The contents of the published patent applications and journal articles and in particular the general formulae of the therapeutically active compounds of the claims and exemplified compounds therein are incorporated herein in their entirety by reference thereto.

More preferred PDE5 inhibitors for use with the invention are selected from the group:
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351);
2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); and
5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one or 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one and pharmaceutically acceptable salts thereof.

A particularly preferred PDE5 inhibitor is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) (also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine) and pharmaceutically acceptable salts thereof. Sildenafil citrate is a preferred salt.

Preferred agents for coadministration with the compounds of the present invention are PDE5 inhibitors, selective serotonin reuptake inhibitors (SSRIs), vasopressin V_{1A} antagonists, α-adrenergic receptor antagonists, NEP inhibitors, dopamine agonists and melanocortin receptor

agonists as described above. Particularly preferred agents for coadministration are PDE5 inhibitors, SSRIs, and V_{1A} antagonists as described herein.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

The present invention provides for a composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier. In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salts, solvates or polymorphs thereof, a pharmaceutically acceptable diluent or carrier, and one or more additional therapeutic agents.

A suitable assay for determining the Oxytocin antagonist activity of a compound is detailed herein below.

Oxytocin Receptor Beta-lactamase Assay:

Materials:

Cell culture/Reagents

A: cell culture
Nutrient Mixture
F12 Ham's
Foetal Bovine Serum (FBS)
Geneticin
Zeocin
Trypsin/EDTA
PBS (phosphate buffered saline)
HEPES

B: reagents
Oxytocin
OT receptor-specific antagonist
Molecular grade Dimethyl Sulphoxide (DMSO)
Trypan Blue Solution 0.4%
CCF4-AM (Solution A)
Pluronic F127s (Solution B)
24%PEG, 18%TR40 (Solution C)
Probenecid (Dissolved at 200mM in 200mM NaOH, Solution D)

Methods:

Cell Culture: Cells used are CHO-OTR/NFAT-β-Lactamase. The NFAT-β-lactamase expression construct was transfected into the CHO-OTR cell line and clonal populations were isolated via fluorescence activated cell sorting (FACS). An appropriate clone was selected to develop the assay.

Growth Medium
90% F12 Nutrient Mix, 15mM HEPES
10% FBS
400µg/ml Geneticin
200 µg/ml Zeocin
2mM L-Glutamine

Assay media
99.5% F12 Nutrient Mix, 15mM HEPES
0.5% FBS

Recovery of cells- A vial of frozen cells is thawed rapidly in 37°C water bath and the cell suspension transferred into a T225 flask with 50ml of fresh growth medium and then incubated at 37°C, 5% CO_2 in an incubator until the cells adhered to the flask Replace media with 50ml of fresh growth media the following day.

Culturing cells- CHO-OTR-NFAT-βLactamase cells were grown in growth medium. Cells were harvested when they reached 80-90% confluence removing the medium and washing with pre-warmed PBS. PBS was then removed and Trypsin/EDTA added (3mls for T225cm^2 flask) before incubating for 5 min in 37°C/5%CO_2 incubator. When cells were detached, pre-warmed growth media was added (7mls for T225cm^2 flask) and the cells re-suspended and mixed gently by pipetting to achieve single cell suspension. The cells were split into T225 flask at 1:10 (for 3days growth) and 1:30 (for 5 days growth) ratio in 35ml growth medium.

β-Lactamase assay Method:

DAY 1

Cell plate preparation

Cells grown at 80-90% confluence were harvested and counted. Suspensions of cells at 2x105 cells/ml in growth medium were prepared and 30µl of cells suspension added in 384-well, black

clear-bottom plates. A blank plate containing diluents from each reagent was used for background subtraction.
Plates were incubated at 37°C, 5% CO_2 overnight.

DAY 2

Cells stimulation

- 10µl antagonist/compound (diluted in assay media containing 1.25% DMSO = antagonist diluent) was added to appropriate wells and incubated for 15 minutes at 37°C, 5% CO_2.
- 10µl oxytocin, made up in assay media, was added to all wells and incubated for 4 hours at 37°C, 5% CO_2.
- A separate 384-well cell plate was used to generate an oxytocin dose response curve. (10 µl antagonist diluent was added to every well.10µl of oxytocin was then added. The cells are then treated as per antagonist/compound cell plates).

Preparation of 1ml of 6x Loading Buffer with Enhanced Loading Protocol (this requires scale-up according to number of plates to be screened)

- 12µl of solution A (1mM CCF4-AM in Dry DMSO) was added to 60µl of solution B (100mg/ml Pluronic-F127 in DMSO + 0.1% Acetic Acid) and vortexed.
- The resulting solution was added to 925µl of solution C (24% w/w PEG400, 18% TR40 v/v in water).
- 75µl of solution D was added (200mM probenecid in 200mM NaOH).
- 10µl of 6x Loading Buffer was added to all wells and incubated for 1.5hrs – 2hrs at room temperature in the dark.
- The plates were read using an LJL Analyst, Excitation 405nm, Emission 450nm and 530nm, gain optimal, lagtime 0.40µs integration, 4 flashes, bottom reading.

Using the assay described above, the compounds of the present invention all exhibit Oxytocin antagonist activity, expressed as a Ki value, of less than 1µM. Preferred examples have Ki values of less than 200nM and particularly preferred examples have Ki values of less than 50nM. The compound of Example 6 has a Ki value of 5.5nM.

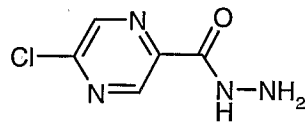
The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

Arbocel®	Filtration agent, from J. Rettenmaier & Sohne, Germany
APCI+	Atmospheric Pressure Chemical Ionisation (positive scan)

$CDCl_3$	Chloroform-d1
d	Doublet
dd	Doublet of doublets
DMSO	Dimethylsulfoxide
ES+	Electrospray ionisation positive scan.
eq	Equivalent
^1H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
MS	(Low Resolution) Mass Spectroscopy
m	Multiplet
m/z	Mass spectrum peak
q	Quartet
s	Singlet
t	Triplet
δ	Chemical shift

Preparation 1

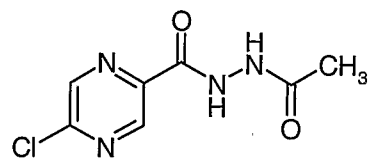
5-Chloropyrazine-2-carboxylic acid hydrazide



5-chloropyrazine-2-carboxylic acid methyl ester (10.02g, 58.25mmol) and hydrazine monohydrate (12.5mL, 250mmol) were dissolved in methanol (400mL) and the reaction mixture heated to reflux for 48 hours. The reaction mixture was then filtered and the precipitate collected dried *in vacuo* to yield the title product, 5.01g (50%). ^1H NMR($CDCl_3$, 400MHz) δ: 4.09(d, 2H), 8.52(s, 1H), 8.66(bs, 1H), 9.14(s, 1H). Microanalysis: $C_5H_5ClN_4O$ requires: C 34.80; H 2.92; N 32.47; found C 34.89; H 2.91, N 32.32. MS APCI+ m/z 173 $[MH]^+$

Preparation 2

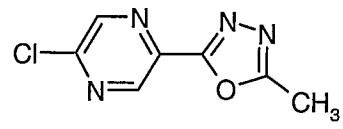
5-Chloropyrazine-2-carboxylic acid N'-acetyl-hydrazide



The product of preparation 1 (2.0g, 29.2mmol) and N-methylmorpholine (1.8mL, 35mmol) were dissolved in dichloromethane (100mL) and the solution treated with acetyl chloride (1.04mL, 11.4mmol). The reaction mixture was stirred at room temperature for 5 hours and then washed with water and *in vacuo* to afford 4.0g, (64%). MS APCI+ m/z 215 $[MH]^+$

Preparation 3

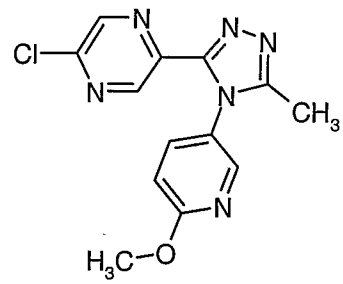
2-Chloro-5-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyrazine



The product of preparation 2 (125g, 435.1mmol) and phosphorous oxychloride (250mL) were combined and heated to 110°C for 4 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate and water. The mixture was neutralised by the addition of 10% sodium carbonate solution and the phases separated. The aqueous phase was extracted with ethyl acetate and the combined organics dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to yield the title product, 30g, (35%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 2.68(s, 3H), 8.71(s, 1H), 9.22(s, 1H). MS APCI+ m/z 197 $[MH]^+$

Preparation 4

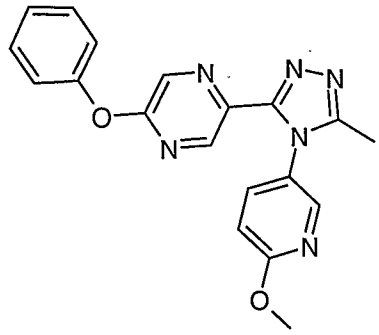
2-Chloro-5-[4-(6-methoxypyridin-3-yl)-5-methyl-4H-[1,2,4]triazol-3-yl]-pyrazine



The product of preparation 3 (8.73g, 32.3mmol), 5-amino-2-methoxypyridine (12g, 96.7mmol) and *para*-toluenesulfonic acid monohydrate (50mg, 0.37mmol) were dissolved in xylene (100mL) and the reaction mixture heated to 150°C for 23 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 90:10 to yield the title product, 4.3g, (44%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 2.36(s, 3H), 3.99(s, 3H), 6.86(d, 1H), 7.45(dd, 1H), 8.02(d, 1H), 8.27(d, 1H), 9.23(d, 1H).

Example 1

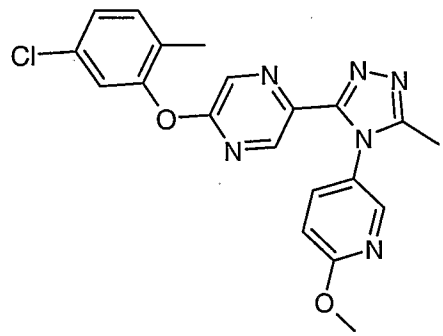
2-[4-(6-Methoxypyridin-3-yl)-5-methyl-4H-[1,2,4]triazol-3-yl]-5-phenoxypyrazine



The chloro compound of preparation 4 (200mg, 0.66mmol), phenol (65mg, 0.69mmol) and caesium carbonate (1.08g, 3.30mmol) in N-methylpyrrolidinone (5mL) were stirred at room temperature for 3hrs then at 80 °C for 2hrs. The reaction mixture was cooled to room temperature and then was taken up in ethyl acetate (25mL) and washed with water (3x25mL). The organic layer was separated and then was dried over magnesium sulfate and concentrated *in vacuo*. The residue was triturated from diethyl ether to yield the title product, 80mg, (34%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 2.40(s, 3H), 4.00(s, 3H), 6.85(d, 1H), 7.15(m, 2H), 7.20(m, 1H), 7.45(m, 3H), 8.05(m, 1H), 8.10(s, 1H), 8.90(s, 1H). MS ES+ m/z 361 $[MH]^+$

Example 2

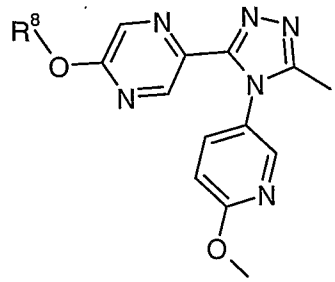
2-(5-Chloro-2-methylphenoxy)-5-[4-(6-methoxypyridin-3-yl)-5-methyl-4H-[1,2,4]triazol-3-yl]pyrazine



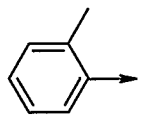
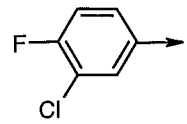
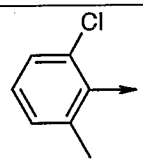
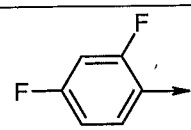
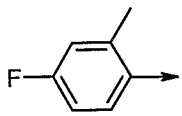
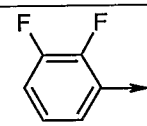
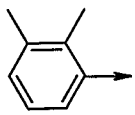
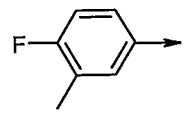
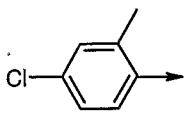
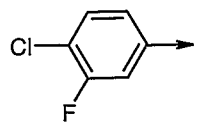
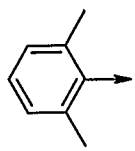
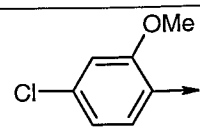
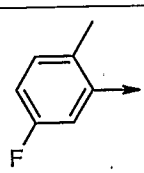
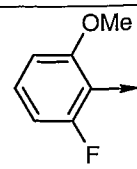
To a 0.5M solution of the chloro compound of preparation 4 (40μmol) in N-methylpyrrolidinone was added a 0.5M solution of 2-methyl-5-chlorophenol (50 μmol) in N-methylpyrrolidinone and the caesium carbonate (1.3mg, 120 μmol) was added. The reaction mixture was shaken at 80 °C for 16 hours then cooled to room temperature. The reaction mixture was diluted with N-methylpyrrolidinone and centrifuged for 10 minutes. The supernatant liquid was decanted off and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to afford the title compound. MS ES+ m/z 409 $[MH]^+$

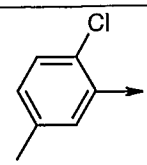
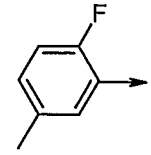
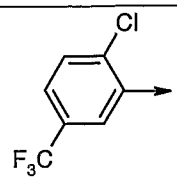
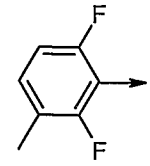
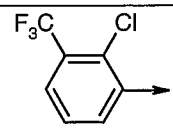
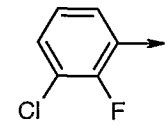
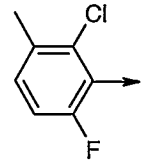
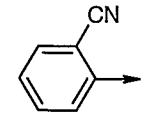
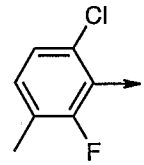
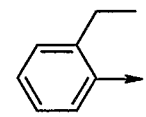
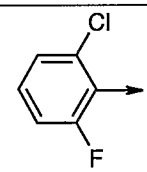
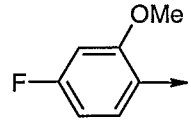
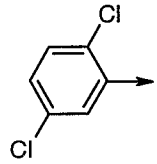
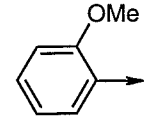
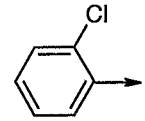
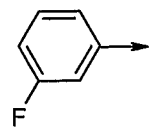
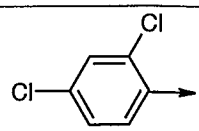
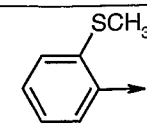
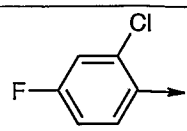
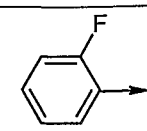
Examples 3-48

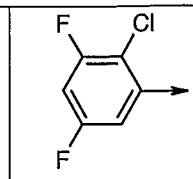
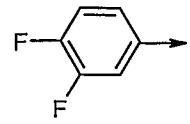
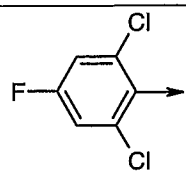
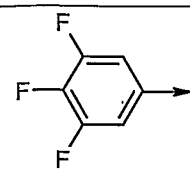
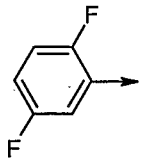
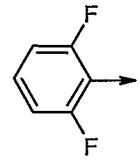
Examples 3-48 were prepared from the compound of preparation 4 and the corresponding phenol (which is either commercially available or known in the literature) using the method of preparation of Example 2.



5

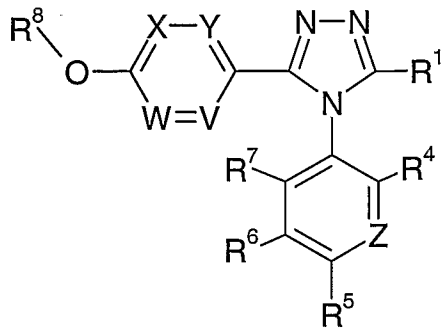
Example	R^8	MS ES+ m/z $[MH]^+$	Example	R^8	MS ES+ m/z $[MH]^+$
3		375	23		413
4		409	24		397
5		393	25		397
6		389	26		393
7		409	27		413
8		389	28		425
9		393	29		409

10		409	30		393
11		463	31		411
12		463	32		413
13		427	33		386
14		427	34		389
15		413	35		409
16		429	36		391
17		395	37		379
18		429	38		407
19		413	39		379

20		431	40		397
21		447	41		415
22		397	42		451

Claims

1. A compound of formula (I):



(I)

wherein:

V, W, X and Y, which may be the same or different, represent CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3, C-CN, C-NH(C_1-C_6)alkyl, C-N((C_1-C_6)alkyl)$_2$, C-C(O)(C_1-C_6)alkyl, C-C(O)O(C_1-C_6)alkyl, C-C(O)NH(C_1-C_6)alkyl, C-C(O)N((C_1-C_6)alkyl)$_2$, C-C(O)OH, C-O(C_1-C_6)alkyl, C-C(O)NH_2 or N;

Z is CH or N;

R^1 is H or CHR^2R^3;

R^2 is selected from:

(i) H;

(ii) (C_1-C_6)alkyl, which is optionally substituted by O(C_1-C_6)alkyl or phenyl;

(iii) O(C_1-C_6)alkyl, which is optionally substituted by O(C_1-C_6)alkyl;

(iv) NH(C_1-C_6)alkyl, said alkyl group being optionally substituted by O(C_1-C_6)alkyl;

(v) N((C_1-C_6)alkyl)$_2$, wherein one or both of said alkyl groups may be optionally substituted by O(C_1-C_6)alkyl;

(vi) a 5 to 8 membered N-linked saturated or partially saturated heterocycle containing 1 to 3 heteroatoms, each independently selected from N, O and S, wherein at least one heteroatom is N and said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, C(O)(C_1-C_6)alkyl, C(O)NH(C_1-C_6)alkyl, C(O)N((C_1-C_6)alkyl)$_2$, C(O)OH, C(O)NH_2 and C(O)OCH_2Ph; and

(vii) a 5 to 7 membered N-linked aromatic heterocycle containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$,

$C(O)(C_1\text{-}C_6)$alkyl, $C(O)NH(C_1\text{-}C_6)$alkyl, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH, $C(O)NH_2$ and $C(O)OCH_2Ph$;

R^3 is selected from H, $(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)alkoxy(C_1\text{-}C_6)$alkyl;

R^4, R^5, R^6 and R^7 are each independently selected from H, halo, CN, $(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)alkyl)_2$ and $O(C_1\text{-}C_6)$alkyl; and

R^8 is phenyl or naphthyl, each of which is optionally substituted with one or more substituents independently selected from halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)alkoxy(C_1\text{-}C_6)$alkyl, cyano, CF_3, $S(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)alkyl)_2$, $CO(C_1\text{-}C_6)$alkyl, $C(O)NH(C_1\text{-}C_6)$alkyl, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer,
with the proviso that the compound of formula (I) is not 4-(2-methoxy-phenyl)-3-methyl-5-(4-phenoxy-phenyl)-4H-[1,2,4]triazole.

2. A compound according to claim 1 wherein V, W, X and Y are each independently selected from CH, $C\text{-}(C_1\text{-}C_6)$alkyl, $C\text{-}O(C_1\text{-}C_6)$alkyl, C-halo, $C\text{-}CF_3$ and N.

3. A compound according to claim 2 wherein X and V represent N, and W and Y represent CH.

4. A compound according to any one of claims 1 to 3 wherein Z is N.

5. A compound according to any one of claims 1 to 4 wherein R^1 is CHR^2R^3.

6 A compound according to claim 5 wherein R^2 and R^3 are both H.

7. A compound according to any one of claims 1 to 6 wherein R^4, R^5, R^6 and R^7 are each independently selected from H, chloro, fluoro, methyl and methoxy.

8. A compound according to claim 7 wherein R^4, R^6 and R^7 are H, and R^5 is methoxy.

9. A compound according to one of claims 1 to 8 wherein R^8 is phenyl, which is optionally substituted with one or more substituents independently selected from halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)alkoxy(C_1\text{-}C_6)$alkyl, cyano, CF_3 and $S(C_1\text{-}C_6)$alkyl.

10. A compound according to claim 9 wherein R^8 is phenyl, which is optionally substituted with one or more substituents independently selected from chloro, fluoro, methyl, ethyl, isopropyl, methoxy, cyano, CF_3 and SCH_3.

11. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 10, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable diluent or carrier.

12. A pharmaceutical composition according to claim 11 including one or more additional therapeutic agents.

13. A compound of formula (I) as claimed in any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament.

14. A method of treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) as claimed in any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or polymorph thereof.

15. Use of a compound of formula (I) as claimed in any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect.

16. A compound of formula (I) as claimed in any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in the treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect.

17. A method according to claim 14, wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

18. Use according to claim 15, wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature

ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

19. A compound according to claim 16, wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

20. A method according to claim 17 wherein the disorder or condition is selected from sexual arousal disorder, orgasmic disorder, sexual pain disorder and premature ejaculation.

21. Use according to claim 18 wherein the disorder or condition is selected from sexual arousal disorder, orgasmic disorder, sexual pain disorder and premature ejaculation.

22. A compound according to claim 19 wherein the disorder or condition is selected from sexual arousal disorder, orgasmic disorder, sexual pain disorder and premature ejaculation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002225

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/497 A61P15/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/028452 A (PFIZER LTD.) 31 March 2005 (2005-03-31) page 40, line 1 - page 47, line 10; claims; examples	1-22
A	WO 03/053437 A (APPLIED RESEARCH SYSTEMS ABS HOLDING) 3 July 2003 (2003-07-03) page 12, line 1 - line 20; claims; examples	1-22
A	AKIO KAKEFUDA ET. AL.: "Discovery of 4,5-Diphenyl-1,2,4-triazole Derivatives as a Novel Class of Selective Antagonists for the Human V1page 1907, tba Receptor." BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 10, 2002, pages 1905-1912, XP002410341 Page 1907, Table 1, compound 9c	1-22

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2006	18/12/2006

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002225

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2005/121152 A (PFIZER LTD) 22 December 2005 (2005-12-22) page 19, line 24 - page 24, line 5; claims; examples	1-22
P,Y	WO 2005/082866 A (PFIZER LTD) 9 September 2005 (2005-09-09) page 37, line 8 - page 44, line 6; claims; examples	1-22

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002225

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14(part), 17(part), 20(part)
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14, 17 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/002225

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			MX	PA06003158 A	05-06-2006
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			AU	2002364291 A1	09-07-2003
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			DE	60207755 T2	27-07-2006
			DK	1458381 T3	20-03-2006
			ES	2249636 T3	01-04-2006
			JP	2005517662 T	16-06-2005
			US	2005187275 A1	25-08-2005
WO 2005121152	A	22-12-2005	NONE		
WO 2005082866	A	09-09-2005	NONE		