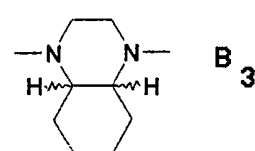
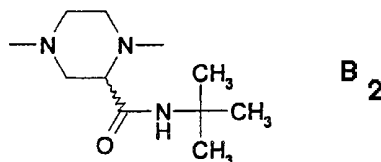
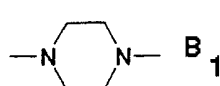
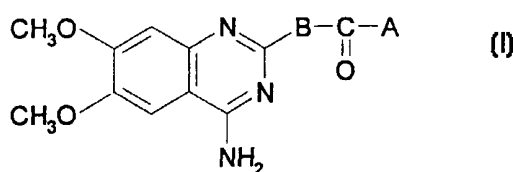




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00	A2	(11) International Publication Number: WO 00/67735 (43) International Publication Date: 16 November 2000 (16.11.00)
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(54) Title: USE OF SELECTIVE ANTAGONISTS OF THE α_{1b} -ADRENERGIC RECEPTOR FOR IMPROVEMENT OF SEXUAL DYSFUNCTION



(57) Abstract

Compounds (I) (A=2-furyl, substituted 2-furyl, 2-tetrahydrofuryl, substituted alkoxy or substituted phenoxyalkyl; B=B₁, B₂ or B₃, but if B=B₁ then A=substituted phenoxyalkyl) and their enantiomers, diastereoisomers and pharmaceutically acceptable salts are useful for the preparation of a medicament for the treatment of sexual dysfunction in males and females. Compounds II (I:B=B₃, A ≠ 2-furyl) are novel and are claimed per se. Pharmaceutical compositions containing compounds II are also claimed, as are pharmaceutical compositions containing compounds I and one or more of a prostaglandin, a direct vasodilator and a 5 cGMP phosphodiesterase inhibitor (e.g. sildenafil). Compounds which bind to mammalian α_{1b} adrenergic receptors with an affinity of at least about 10^{-8} M and which bind to mammalian α_{1b} adrenergic receptors with an affinity at least 10-fold higher than the affinity with which the compound binds to mammalian α_{1a} or α_{1d} or α_{1L} adrenergic receptors are also useful for the preparation of a medicament for the treatment of sexual dysfunction in males and females. A method of identifying such compounds is also disclosed and claimed.

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TITLE

Use of Selective Antagonists of the α_{1b} -Adrenergic Receptor for Improvement of Sexual Dysfunction

DESCRIPTION**Field of the Invention**

The invention relates to novel selective antagonists of the α_{1b} -adrenergic receptor and to the use of those and other selective antagonists of the α_{1b} -adrenergic receptor in the preparation of medicaments for the treatment of human sexual dysfunction. The invention further relates to pharmaceutical compositions containing the selective antagonists of the α_{1b} -adrenergic receptor and optionally also containing prostaglandins, direct vasodilators or 5 cGMP phosphodiesterase inhibitors. Finally, the invention relates to a method of identifying compounds useful in the treatment of patients suffering from sexual dysfunction.

Background of the Invention

Sexual dysfunction arises from different mechanisms in males and females. In males impotence is the inability to obtain and sustain an erection sufficient for intercourse. Erection is achieved as a result of blood inflow into the corpora cavernosa of the penis, which produces engorgement of the corpora cavernosa, and subsequent penile erection. It is estimated that as many as 30 million American men experience some degree of erectile dysfunction, the prevalence of which increases with age.

The causes of impotence can be divided into two subcategories: 1) organic and 2) psychological. The organic aspects of impotence are caused by underlying vascular disease such as that associated with hypertension, diabetes mellitus and prescription medications. About half of all cases of impotence are of vascular origin. Because the physiologic process of erection is initiated by an increase in blood flow through the penile arteries and shunting of blood into the vascular spaces of the corpora cavernosa,

erectile dysfunction can result from the inability of the arteries of the penis to dilate, thereby inhibiting the flow of blood into the erectile tissue.

The sympathetic pathways play a primary role in the neural control of penile erection. It is generally accepted that, in the detumescent state, release of noradrenaline (NA), acting on postjunctional α_1 -receptors on the cavernous arteries and on the corpora cavernosa contributes to keep the penile smooth muscle contracted. Conversely, intracavernous injection of α_1 -antagonists like phenoxybenzamine, phentolamine and moxisylyte produces tumescence and erection.

The erectile response to transurethral prazosin in human males has been recently reported, as well as the relaxing effect of this antagonist on human male, dog and rat isolated penile tissues and vessels.

In females the sexual response initiates with a stimulation which causes vasocongestion and results in lubrication of the vagina in preparation for penis insertion. Lubrication is due to formation of an exudate which, together with genital congestion, produces the so-called orgasmic platform which preludes to orgasm. In brief, female sexual dysfunction may be due to interference with the different stages of intercourse and can be related to either organic or functional causes, or both.

Several reasons including stress, anxiety, depression, fatigue, interpersonal conflicts between the partners or more simply ageing, can lead to failure of the vasocongestive response, thereby inhibiting normal vaginal lubrication. Women in this condition may be incapable of achieving a normal sexual response without appropriate treatments. It has been recently confirmed that both vaginal vasocongestion and clitoral erection depend on increased blood flow. Moreover, as has been reported for the male sexual organ, it has been demonstrated that a local injection in the vagina of α_1 -adrenergic antagonists such as phentolamine can increase blood flow and intravaginal pressure up to levels comparable with those achieved by stimulation of the pelvic nerve. These data

clearly indicate that noradrenaline plays an important role in maintaining flaccidity of the organ concerned in the female sexual tract too.

It is thus important to identify new products having an α_1 -adrenoceptor antagonistic activity, which can be useful in promoting vasodilatation of the arteries in the vaginal walls and clitoris, thereby improving lubrication and helping continuation of the sexual act.

Pharmacological, biochemical and radioligand binding studies has shown three different α_1 -receptors subtypes with a high affinity for prazosin, namely α_{1A} -(α_{1a} -), α_{1B} -(α_{1b} -) and α_{1D} -(α_{1d} -), with lower case subscripts being used for recombinant receptors and upper case subscripts for receptors in native tissues. In functional studies α_1 -receptors with a low affinity for prazosin have also been identified and termed α_{1L} -.

Several studies have demonstrated the presence of these α_1 -adrenergic receptor subtypes in the animal and human cavernous tissues. In situ hybridization with specific oligonucleotide probes and protection assays techniques has demonstrated that human and rat corpus cavernosum tissues expressed all three cloned α_1 -adrenergic receptor subtypes.

On the other hand, functional studies in male human penile tissue are controversial, suggesting the involvement of all three cloned α_1 -ADR subtypes, or that the α_{1L} -ADR subtype is the main mediator of NA-induced contraction in this tissue. Conversely, nothing is known so far about vaginal vessels.

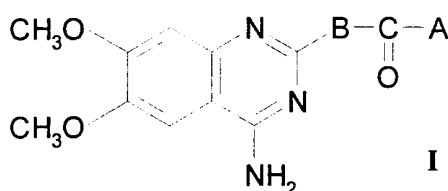
Pharmacological evidence for the univocal presence of a well defined α_1 -adrenergic receptor subtype(s) in the penile or vaginal tissue would represent a major advance in the field of male and female sexual dysfunction treatment, allowing the possibility of the use of selective α_1 -antagonists.

The α -antagonists currently being used for the treatment of predominantly male impotence suffer from unwanted side effects, such as priapism, a painful erection of exceeding long duration which may result in fibrosis of cavernous tissue. Other side effects are penile pain and hypotension.

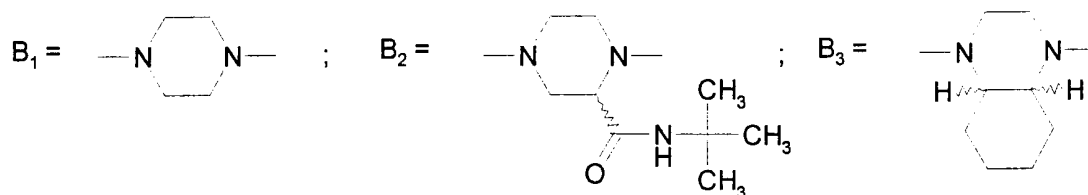
The invention has as its object the satisfaction of the perceived need for selective α_1 -antagonists which do not subject the impotent male to the side effects of known treatments, notably of the cardiovascular type.

Summary of the Invention

The invention is directed to the treatment of sexual dysfunction. To this end, the invention provides the use of a compound having the general formula I



wherein A represents a 2-furyl, substituted 2-furyl, 2-tetrahydrofuryl, substituted alkoxy or substituted phenoxyalkyl group, and B represents one of the following groups of the formula B₁, B₂ or B₃:

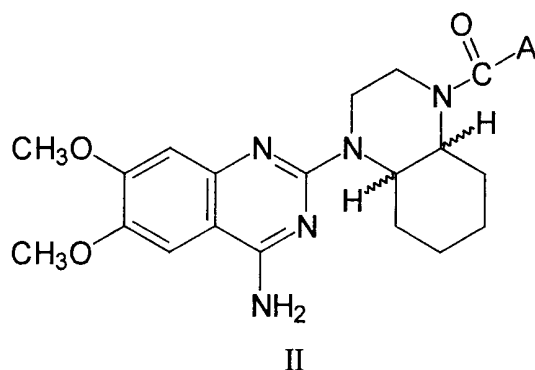


with the proviso that if B represents the group B₁ then A represents a substituted phenoxyalkyl group,

or of an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound,

for the preparation of a medicament for the treatment of sexual dysfunction. The medicament may also contain a prostaglandin, a direct vasodilator or a 5 cGMP phosphodiesterase inhibitor.

Some of the compounds I are novel. Accordingly the invention also provides compounds having the general formula II



wherein A represents a 2-tetrahydrofuryl, substituted 2-furyl, substituted alkoxy or substituted phenoxyalkyl group,
and enantiomers, diastereoisomers and pharmaceutically acceptable salts of such compounds.

Pharmaceutical compositions containing a compound II, or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound, and a pharmaceutically acceptable diluent or carrier are also included in the invention. So too are pharmaceutical compositions containing a compound I, or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound, and a prostaglandin, a direct vasodilator or a 5 cGMP phosphodiesterase inhibitor, and a pharmaceutically acceptable diluent or carrier.

In another aspect, the invention provides use of a compound which

(a) binds to mammalian α_{1b} adrenergic receptors with an affinity of at least about 10^{-8}

M and

- (b) binds to mammalian α_{1b} adrenergic receptors with an affinity at least 10-fold higher than the affinity with which the compound binds to mammalian α_{1a} or α_{1d} or α_{1L} adrenergic receptors

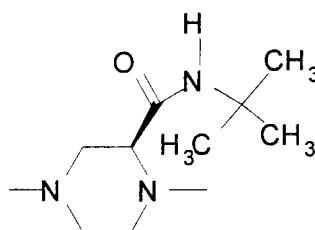
for the preparation of a medicament for the treatment of sexual dysfunction.

In a further aspect, the invention provides a method for identifying a compound useful for treating sexual dysfunction. The method comprises the steps of

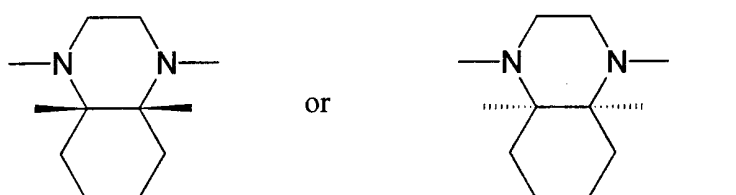
- (a) individually measuring the binding affinity of test compounds for a mammalian α_{1b} adrenergic receptor and a mammalian α_{1a} or α_{1d} adrenergic receptor by radioreceptor binding techniques,
- (b) measuring the affinity for a mammalian α_{1L} adrenergic receptor by antagonizing the contractile effect on α_1 adrenergic receptors on selected mammalian tissue, and
- (c) identifying those compounds which
- (1) bind to a α_{1b} adrenergic receptor with an affinity of at least 10^{-8} M, and
 - (2) bind to a α_{1b} adrenergic receptor with an affinity at least 10-fold higher than the affinity with which the compound binds to mammalian α_{1a} or α_{1d} or α_{1L} adrenergic receptors.

Detailed Description of the Invention

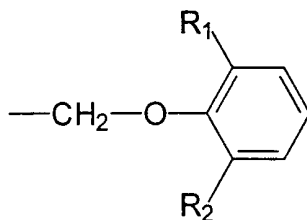
In the Compounds I, the group B₂ preferably has the following stereochemistry



and the group B₃ preferably has a *cis* stereochemistry, with the junctional hydrogen atoms having the same orientation:



the former being preferred. Also in the Compounds I, the preferred substituted phenoxyalkyl groups A have the formula



wherein R₁ represents a linear or branched alkyl chain having from 1 to 5 carbon atoms and R₂ represents an alkoxy group having from 1 to 4 carbon atoms; the most preferred substituted phenoxyalkyl group is the 6-isopropyl-2-methoxyphenoxyethyl group.

The most preferred Compounds I include:

- 4-amino-6,7-dimethoxy-2-[4-[(2-methoxy-6-isopropylphenoxyacetyl)-1-piperazinyl]-quinazoline (Compound A),
- 4-amino-6,7-dimethoxy-2-[(4aR,8aS)-4-(2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline (Compound B) and
- 4-amino-6,7-dimethoxy-2-[3(S)-3-(*t*-butyl-carbamoyl)-4-(2-furoyl)-1-piperazinyl]-quinazoline (Compound C).

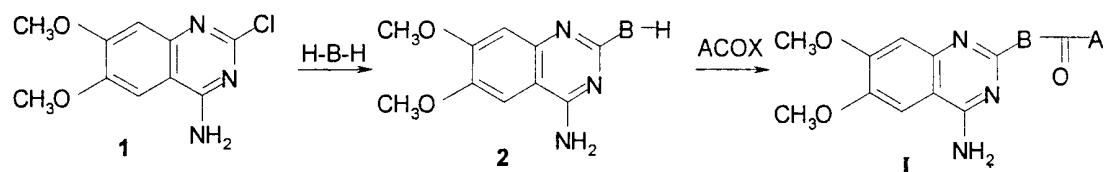
In the Compounds II, the octahydroquinoxaline ring preferably has the (4aR, 8aS) configuration. The preferred substituted phenoxyalkyl groups A are the same as those preferred in Compounds I. Substituted alkoxy is suitably benzyloxy and substituted 2-furyl is preferably 5-methyl-2-furyl. In particular the following Compounds II are preferred:

- 4-amino-6,7-dimethoxy-2-[(±)-4-(2-methoxy-6-isopropylphenoxyacetyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline,
- 4-amino-6,7-dimethoxy-2-[(±)-4-(5-methyl-2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline,
- 4-amino-6,7-dimethoxy-2-[(±)-4-(2-tetrahydrofuroyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline, and

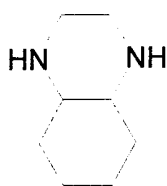
- 4-amino-6,7-dimethoxy-2-[(±)-4-benzoyloxycarbonyl-*cis*-octahydro-1-quinoxaliny]-quinazoline.

The methods of preparation of the quinazoline derivatives of formula **I** are disclosed in the following references: WO 95/25726; Giardinà D. et al., *J. Med. Chem.* **39**, 4602-7 (1996); WO 97/11698.

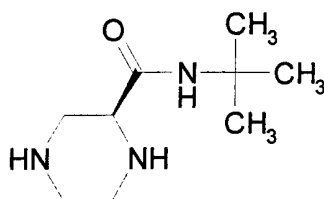
The synthesis of the compounds of formula **I** can be performed according to the following scheme:



The starting material **1** is commercially available (e.g. from Lancaster Synthesis Ltd, Eastgate, White Lund, Morecambe, Lancashire, LA3 3DY, England) or alternatively can be prepared as described by Althuis et al., *J. Med. Chem.* **20**, 146-149 (1977). The amines H-B-H can be in the form of the racemate or homochiral where appropriate and can be commercially available, such as piperazine, or can be prepared according to methods described in the literature. For example, the amine

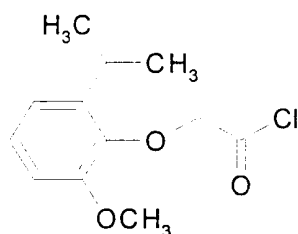


can be prepared as described by Brill et al., *J. Org. Chem.* **28**, 1135-1138 (1963) or by stereoselective synthesis as described by Brill et al., *J. Org. Chem.* **29**, 579-581 (1964), and the amine



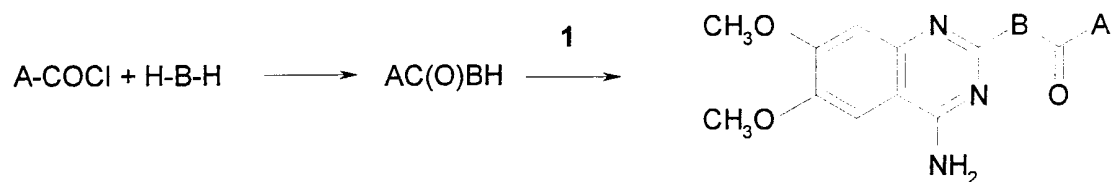
can be prepared starting from 2-pyrazinecarboxylic acid by amidification followed by reduction and resolution as described in *Tetr. Lett.* **35**, 673-676 (1994). The reaction is performed at 150-200°C without solvent or in the presence of a suitable polar solvent, such as *i*-amyl alcohol or *n*-butyl alcohol, at reflux temperature.

Intermediates ACOX are commercially available or can be prepared, when A = phenoxyalkyl, starting from the corresponding phenol derivative, by reaction with a haloalkylacid ester, followed by hydrolysis and chlorination, by the methods known to those skilled in the art and described in Example 1 for



The condensation to give **I** may be carried out by reaction of **2** with ACOX, where X represents a halogen atom (e.g. chlorine), in a chlorinated solvent, such as chloroform or dichloromethane, or in an aprotic polar solvent, such as dimethylformamide, in the presence of a base, such as triethylamine or diisopropylamine, at 0°C to 40°C. Alternatively, when X represents a hydroxyl group the condensation may be carried out in a chlorinated or aprotic polar solvent as above reported, in the presence of a condensing agent, such as dicyclohexylcarbodiimide, and of a promoting agent, such as 4-dimethylaminopyridine at a temperature of 0°C to 40°C, or other equivalent.

Alternatively, the following scheme can be used:



The suitable acyl chlorides are reacted with HBH compounds in polar solvents such as dimethylformamide, acetone or acetonitrile, optionally in the presence of a base such as potassium or cesium carbonate or triethylamine, at 20-100°C.

The intermediates AC(O)BH are then reacted with compound **1** to give compounds **I**. This alkylation may be carried out in a polar protic solvent such as *i*-amyl alcohol and *n*-butyl alcohol or in an aprotic solvent such as dimethylformamide, at 60°C to reflux.

The enantiomers of compounds **I** in which B is B₂ may be obtained starting from the suitable HB₂H enantiomers, that are obtained by salification of the racemate with an optically active acid, such as (S)-10-camphorsulphonic acid in a suitable solvent or solvent mixture, followed by separation of the diastereomeric salts by recrystallisation. Similarly, the enantiomers of compounds **I** in which B is B₃ may be obtained by salification of the racemic intermediate **2** with a suitable optically active acid followed by diastereomeric separation.

Screening candidate compounds to identify those that are useful in practising the invention involves measuring the specific binding activity of the compounds towards different neuronal α_1 adrenergic receptors (such as α_{1a} , α_{1b} and α_{1d} subtypes according to the method of Testa et al., *Pharmacol. Comm.* **6**: 79-86, 1995), that may be achieved by using any of a multiplicity of methods that are well-known in the art, such as competitive binding to native or cloned receptors.

Typically, a biological source of, for example α_{1b} adrenergic receptors is used in which the receptor is present at a sufficiently high concentration so that binding of a labelled ligand is easily measurable. This source may comprise a mammalian tissue or fluid (either in situ or after removal from the animal) or a tissue culture cell. The target receptor may be expressed from either an endogenous (native) gene or from a transfected receptor-encoding recombinant gene. For example the rat liver is a rich (native) source of α_{1B} adrenergic receptors (Taddei et al., *Life Sci.* **53**: PL177-PL181, 1993). Alternatively hamster α_{1b} adrenergic receptor cDNA can be transiently

expressed in COS-7 cells in culture (Cotecchia S. et al., *Proc. Natl. Acad. Sci. USA* **85**: 7159-7163, 1988) and human α_{1b} adrenergic receptor cDNA can be expressed in CHO cells in culture (Testa et al., *Pharmacol. Comm.* **6**: 79-86, 1995).

Furthermore, human α_{1a} and α_{1d} adrenergic receptor cDNA has been expressed in CHO cells (Testa et al., *Pharmacol. Comm.* **6**: 79-86, 1995) whereas bovine α_{1a} (formerly α_{1c}) (Schwinn et al., *J Biol. Chem.* **265**: 8183-8189, 1990) and rat α_{1d} (Lomasney et al., *J. Biol. Chem.* **266**: 6365-6369, 1991) clones of the adrenergic receptor have been transiently expressed in COS-7 cells and can be used to assess selectivity for the α_{1b} adrenergic receptor by a radioreceptor binding technique.

The ability of the test compounds to compete with the appropriate labelled ligand for receptor binding is then measured and a binding constant (K_i) is calculated using the Cheng and Prusoff equation (Cheng et al., *Biochem Pharmacol.* **22**: 3099-3108, 1973) or equivalent computational method well known in the art. A detailed description is given in Example 8 below.

On the contrary, no radioreceptor binding techniques are available for determining the affinity of compounds for the α_{1L} adrenergic receptor subtype, even though this subtype can be studied by functional techniques in a variety of tissues, such as rabbit mesenteric and carotid arteries, rat vas deferens and small mesenteric artery, human prostate (see for review Doherty J.R. *Eur. J. Pharmacol.* **361**: 1-15, 1998), as well as rabbit aorta pretreated with chloroethylclonidine (Testa et al., *J. Pharmacol. Exp. Ther.* **281**: 1284-1293, 1997).

In this approach, the ability of the test compounds to inhibit the NA-induced contraction of the vessels is measured and the dissociation constant (K_b) is estimated (Arunlakshana et al., *Br. J. Pharmacol. Chemother.* **14**: 45-58, 1959), or equivalent computational method well known in the art. A detailed description is given in Example 9 below.

As discussed above the compounds useful in practising the invention bind to the α_{1b} adrenergic receptor with a K_i of at least 10^{-8} M and have an affinity for the α_{a1} , α_{1b} and α_{1L} adrenergic receptors at least 10-fold lower. Once a compound is identified as possessing the above characteristics, its pharmacological activity can be confirmed using one or more animal model systems for studying male erection. Useful animal model systems include increase of intracavernous pressure in anesthetized rats and/or dogs.

In such methods, compounds are administered into corpus cavernosum and the intracavernous pressure developed is measured, simultaneously to blood pressure. The efficacy of the compounds is better measured by evaluating the ratio between intracavernous and blood pressure, which are strictly correlated. In this way an activity index is obtained which is expressed as a percent value and reflects the percent of ICP with respect to blood pressure, which can reach a maximum value of 100%. These methods are described in detail in Examples 10 and 11 below.

As measured using the above in vivo models, useful compounds induce a significant increase with regard to vehicle in the ICP/BP ratio when administered locally at a dose of 10-1000 μ g with a blood pressure decrease lower than 20% (30% only at the highest dosage). A model to measure the effects of the products of the invention on vaginal and clitoral pressure is described in Example 12.

Therapeutic Applications

The invention encompasses the pharmaceutical formulations comprising the α_{1b} adrenergic receptor antagonists listed above for treatment of male and female sexual dysfunction, in particular that due to vascular origin.

Without wishing to be bound by theory, the neural sympathetic control maintains the penis and the vaginal wall, as well as the clitoris, in their flaccid state and antagonising the effect of sympathetic mediators in these tissues with selective α_{1b} adrenergic receptor antagonists allows this negative control to be overcome, with relaxation of the

penile smooth muscle and vasodilatation of the cavernous arteries in the male and vasocongestion in the female. As a result, in the male blood flow into the trabecular spaces of the corpora cavernosa is increased, causing engorgement of the penis (tumescence). Expansion of the trabecular walls against the tunica albuginea compresses subtunical venules and impedes venous outflow, resulting in sustained tumescence, i.e. an erection. In females, vasocongestion allows vaginal lubrication, thus a satisfactory sexual activity.

An "effective amount" of the compound for treating sexual dysfunction is an amount that results in measurable amelioration of erection. In the male, an additional parameter is the duration of erection, while in the female the effective amount is that which produces a measurable amount of blood flow in the clitoris and vaginal wall.

The effective amount for treating sexual dysfunction can be determined by experimentation using methods known in the art, such as by establishing a matrix of dosages and frequencies and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient may vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter may be determined by a physician skilled in the art or reported by the patient to the physician. It will be understood that any significant clinical or statistical improvement is within the scope of this invention. Clinically significant improvement is defined as an improvement perceptible to the patient and or to the physician.

Preferably, the compounds of the invention are employed in combination with a suitable pharmaceutical carrier prior to administration. Such compositions comprise a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier or excipient. For example, when administration is by injection, an aqueous solution acceptable by intracavernosal injection into the penis is prepared. In this instance, the carriers include but are not limited to water, saline, buffered saline, salts, glycerol and ethanol, either alone or in combination. Also, a non-

irritant preservative such as, for example, benzalkonium chloride may be added to the compositions.

In the case of intraurethral, subcutaneous or topical administration, the pharmaceutical carrier includes but is not limited to gels such as petroleum gels, ointments, creams, solutions, sprays, powders, foams and liposome formulations. The carrier is water-soluble, non-irritating, and does not sensitise the skin. In a preferred embodiment, the carrier for this type of administration has a semi-soft cream-like consistency. This can be obtained by the use of a hydrogel such as hydroxypropylmethylcellulose.

For intravaginal administration in a vaginal douche, carriers include but are not limited to water, saline, buffered saline, salts, glycerol and ethanol, either alone or in combination. Moreover, a non-irritating preservative including, for example, benzalkonium chloride may be added to the compositions.

The carriers for administration in a cream or vaginal ovule include but are not limited to propylene glycol, hydrogenated lanolin, sweet almond oil, polyglycol esters of fatty acids, cetyl alcohol, glyceryl monostearate, sodium edetate, triglycerides of fatty acids, gelatine, glycerine, titanium dioxide, parabens.

The pharmaceutical compositions according to the invention may optionally comprise other active agents which enhance or complement the sexual-act improving effects of the compounds of the invention. Such active agents include, but are not limited to, prostaglandins, for example prostaglandin E₂; direct vasodilators, for example papaverine; and type-V phosphodiesterase inhibitors, for example 1-{[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[3,4-d]pyrimidin-5-yl)-4-ethoxyphenyl]-4-methylpiperazine also known as sildenafil. These compounds supplement the direct action of the compounds of the invention in producing the desired amelioration effects. The use of a compound according to the invention together with sildenafil may also allow the dosage of the latter to be reduced, minimising its undesirable side effects by

administering the combination orally or intravenously or also by one of the methods discussed in the next paragraphs.

Preferably, the compounds of the invention are administered according to one of following methods. The compounds of the invention may be administered by injection wherein the compounds of the invention are dissolved in saline at a concentration ranging from 0.2 to 20 mg/ml. A volume of 0.5 ml is injected intracavernously. In another example of a preferred method of use, the compounds of the invention are formulated in a petrolatum gel, which is then applied externally to an intraurethral catheter. The dosage of the compounds of the invention is in the range of 1 to 10 percent of the weight of gel applied. The catheter is inserted into the urethra in order to administer the compounds of the invention intraurethrally and to produce the vasodilatation required for erection.

Any amount of the above described compounds which is effective in relieving human sexual dysfunction may be administered by injection. A range of about 0.1 to 10 mg/dose is used in a single dose. Preferably about 0.3 mg/dose to about 3 mg/dose is used in a single dose.

For a vaginal douche, concentration may range from 0.2% to 5%, while for a vaginal cream concentration may range from 1% to 10%. The amount which can be administered by means of a vaginal ovule may range from 1 to 100 mg.

The invention is illustrated by the following Examples and by the Tables and Figures to which reference is made therein.

Example 1**4-Amino-6,7-dimethoxy-2-[4-(2-methoxy-6-isopropylphenoxyacetyl)-1-piperazinyl]-quinazoline hydrochloride****(I: A = 2-methoxy-6-isopropylphenoxyethyl, B = B₁) (Compound A)****2-Methoxy-6-isopropylphenoxyacetic acid (1A)**

A solution of 11.1 ml of ethyl bromoacetate in 10 ml of toluene was added dropwise at room temperature over about 15 minutes into a mixture of 20 g of NaOH, 30 ml of H₂O, 1.1 g of triethylbenzylammonium chloride, 8.4 g of 2-isopropyl-6-methoxyphenol (prepared according to Johnson et al., *Tetrahedron*, **38**, 1397-1404 (1982)) and 40 ml of toluene. The mixture was stirred vigorously at the same temperature for 2 h and thereafter for 2 h at 60-65°C and for 6.5 h under reflux. During this last step a solution of 6 ml of ethyl bromoacetate in 10 ml of toluene was added. In the end the mixture was diluted with 250 ml of H₂O. The aqueous phase was separated off and treated with concentrated HCl; the emulsified precipitate was extracted with Et₂O (3 x 50 ml) and the organic phase was washed with water. Another extraction was performed with 40 ml of 20% Na₂CO₃ and the slightly alkaline solution was treated with concentrated HCl and extracted with Et₂O (3 x 40 ml). The extracts were pooled and the solvent was evaporated off, giving 8 g (72%) of the title compound; b.p. 190°C/0.7 mmHg.

4-Amino-6,7-dimethoxy-2-[4-(2-methoxy-6-isopropylphenoxyacetyl)-1-piperazinyl]-quinazoline hydrochloride

3.6 ml of SOCl₂ was added dropwise into a boiling solution of 6 g of intermediate 1A in 30 ml of CCl₄ and the mixture was stirred under reflux for 2 h. The oily residue, obtained by evaporation of the reaction mixture, was dissolved in 26 ml of CHCl₃ and the solution was added dropwise over 30 minutes into a stirred solution of 7.75 g of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)-quinazoline and 4.1 ml of Et₃N in 50 ml of DMF. After stirring for 2 hours, the solvents were evaporated off to dryness. The residue was dissolved in 250 ml of CHCl₃. The solution was washed with 2.5% NaHCO₃ and then with H₂O, and finally evaporated to dryness. The purification was performed by column chromatography using CHCl₃/MeOH 100:3 as eluting mixture.

The residue was suspended into 100 ml of boiling ethanol, and ethanolic HCl was then added in a slight excess until dissolution. After cooling, the hydrochloride salt was collected by suction and recrystallized from ethanol to give 6.4 g (45%) of the product; m.p. 252-254°C.

Example 2

4-Amino-6,7-dimethoxy-2-[(4aR,8aS)-4-(2-furoyl)-*cis*-octahydro-1-quinoxalinyll]-quinazoline hydrochloride

(I: A = 2-furyl, B = B₃) (Compound B)

(±)-(2-Furoyl)-*cis*-octahydroquinoxaline (2A)

1.44 g of 48% hydrobromic acid was added dropwise to a solution of 3.85 g of *cis*-octahydroquinoxaline (prepared as described in Brill et al., *J. Org. Chem.* **28**, 1135-1138, (1963)) in 26 ml of ethanol and 4 ml of H₂O stirred at 40-45°C. 1.16 g of 2-furoyl chloride was added dropwise over 15 minutes into the resulting solution and stirring was continued for 3 h at 80°C. The solution was concentrated to low volume, diluted with water and extracted with chloroform. The residue obtained after solvent evaporation was purified by flash chromatography eluting with petroleum ether : ethyl acetate : methanol : 28% aqueous ammonia 8 : 6 : 2 : 0.2 to give 2.35 g (40%) of the desired compound. M.p. 178°C dec.

(+)-1-(2-Furoyl)-*cis*-octahydroquinoxaline (2B)

A solution of 2.35 g of the above intermediate 2A in 22 ml of methanol was treated with a solution of 1.54 g of (S)-(+)-mandelic acid in 22 ml of methanol. The mixture was evaporated to dryness to give a residue which was crystallized by dissolving the solid in 265 ml of hot ethyl acetate and then reducing the volume by evaporation to about 130 ml. The precipitate was recrystallized another six times with the same solvent to give 0.4 g of the (+)-mandelate salt; m.p. 188-190°C, $[\alpha]_D^{20} = +79.4^\circ$ (c=1, MeOH). The salt was dissolved in water, the ice-cooled solution made basic with 2 N NaOH, and the resulting mixture extracted with chloroform (3 x 22 ml). Removal of the dried

solvent gave 0.21 g of the desired compound as a waxy solid; m.p. 47-50°C, $[\alpha]_D^{20} = +70.1^\circ$ (c=1, MeOH).

4-Amino-6,7-dimethoxy-2-[(4aR,8aS)-4-(2-furoyl)-cis-octahydro-1-quinoxaliny]-quinazoline hydrochloride

A mixture of 0.21 g of the above intermediate 2B, 0.18 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline and 0.2 g of N,N-diisopropylethylamine in 13 ml of isoamyl alcohol was heated at reflux for 72 h. After cooling, the mixture was left at 0°C overnight. The solid was then collected, triturated with cold 2N NaOH, filtered, washed with water, and transformed into the hydrochloride salt. Crystallisation from MeOH/15% EtOH gave 0.06 g of the title compound. M.p. 262-264°C, $[\alpha]_D^{20} = +74.4^\circ$ (c=1, MeOH).

Example 3

4-Amino-6,7-dimethoxy-2-[(3S)-3-(*t*-butylcarbamoyl)-4-(2-furoyl)-1-piperazinyl]-quinazoline

(I: A = 2-furyl, B = B₂) (Compound C)

4-Amino-6,7-dimethoxy-2-[(3S)-3-(*t*-butyl-carbamoyl)-1-piperazinyl]-quinazoline (3A)

A mixture of 0.36 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline, 1.08 g of (S)-N-*tert*-butyl-2-piperazinecarboxamide bis-(1S)-(+)-10-camphorsulfonate, prepared as described in US 5,700,364, and 0.94 ml of diisopropylethylamine in 10 ml of isoamyl alcohol was heated at reflux for 9 h. After cooling to room temperature, the solvent was evaporated in vacuo and 50 ml of dichloromethane was added to the residue. The mixture was washed with water (3 x 20 ml), 5% aqueous Na₂CO₃ (30 ml), water (3 x 20 ml), dried (Na₂SO₄) and evaporated to dryness. The residue was purified by flash chromatography eluting with chloroform : 2N methanolic ammonia 100:3 to give 0.173 g (30%) of the desired compound.

¹H-NMR (CDCl₃, δ): 1.35 (s, 9H, C(CH₃)₃), 1.65-2.10 (m, 1H, piperazine NH), 2.30-3.40 (m, 5H, piperazine CHs), 3.95 (s, 6H, OCH₃), 4.45 (d, 1H, piperazine CH), 4.68

(dd, 1H, piperazine CH), 6.00-6.45 (m, 2H, NH₂), 6.85-7.10 (m, 2H, CONH and quinazoline H8), 7.18 (s, 1H, quinazoline H5).

4-Amino-6,7-dimethoxy-2-[(3S)-3-(*t*-butylcarbamoyl)-4-(2-furoyl)-1-piperazinyl]-quinazoline

A mixture of 0.243 g of the above intermediate 3A, 0.17 ml of diisopropylethylamine, 0.08 ml of 2-furoyl chloride in 10 ml of dichloromethane was stirred at room temperature for 10 hours. The solution was diluted with dichloromethane (10 ml), washed with water (4 x 10 ml), 2N NaOH (4 x 10 ml) and water (4 x 10 ml), dried (Na₂SO₄) and evaporated to dryness. The residue was purified by flash chromatography eluting with petroleum ether : ethyl acetate 100 : 2 to give 0.2 g (68%) of the title compound as an ivory solid.

¹H-NMR (DMSO-d₆, δ): 1.14 (s, 9H, C(CH₃)₃), 3.08-3.22 (m, 1H, piperazine CH), 3.32-3.47 (m, 2H, piperazine CHs), 3.77 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 4.10-4.25 (m, 1H, piperazine CH), 4.35-4.50 (m, 1H, piperazine CH), 4.82-4.98 (m, 2H, piperazine CHs), 6.61-6.66 (m, 1H, furan H4), 6.69 (s, 1H, furan H3), 6.95-7.18 (m, 3H, CONH and NH₂), 7.42 (s, 1H, quinoline H8), 7.55 (s, 1H, quinoline H5), 7.85 (s, 1H, furan H5).

Example 4

4-Amino-6,7-dimethoxy-2-[(±)-4-(2-methoxy-6-isopropylphenoxyacetyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride · 2.5 H₂O

(I: A = 2-methoxy-6-isopropylphenoxyethyl, B = B₃)

4-Amino-6,7-dimethoxy-2-[(±)-*cis*-octahydro-1-quinoxaliny]-quinazoline dihydrochloride · 2.5 H₂O (4A)

A mixture of 7.85 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline, 13.3 g of triethylamine, 0.4 g of dimethylaminopyridine, 11.5 g of *cis*-decahydroquinoxaline and 80 ml of *i*-amyl alcohol was stirred at reflux for 72 hours. After cooling to room temperature, the solvent was evaporated off and the residue was purified by flash

chromatography, eluting with petroleum ether : ethyl acetate : methanol : 28% ammonium hydroxide 8 : 6 : 2 : 0.2. The residue obtained was transformed into the hydrochloride salt and crystallized from *i*-propanol : methanol 1:1 to give 14.7 g (73%) of the desired compound; m.p. 290-295°C.

4-Amino-6,7-dimethoxy-2-[4-chloroacetyl-(±)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride (4B)

A solution of 0.26 g of chloroacetyl chloride in 6 ml of dichloromethane was added dropwise over 15 minutes at 0°C to a stirred mixture of 0.5 g of the above intermediate 4A and 0.21 g of diisopropylethylamine in 15 ml of dichloromethane. After 4 h stirring at room temperature and 72 h resting in a refrigerator, the solid was collected by suction and purified by crystallization from chloroform to give 0.12 g (33%) of the desired product; m.p. >270°C.

¹H-NMR (CDCl₃, δ): 1.30-2.35 (m, 8H, octahydroquinoxaline CHs at position 5, 6, 7 and 8), 3.70-4.18 (m, 10H, octahydroquinoxaline CHs at position 2 and 3 and 2 OCH₃), 4.20-4.36 (m, 1H, octahydroquinoxaline H4a), 4.47 (s, 2H, CH₂Cl), 4.60-4.78 (m, 1H, octahydroquinoxaline H8a), 7.48 (s, 1H, quinoline H8), 7.75 (s, 1H, quinoline H5), 8.66 (br, 1H, NH), 8.90 (br, 1H, NH), 11.95 (br, 1H, NH).

4-Amino-6,7-dimethoxy-2-[(±)-4-(2-methoxy-6-isopropylphenoxyacetyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride · 2.5 H₂O

10 ml of a freshly prepared 0.095 M EtONa solution was added to a stirred solution of 0.16 g of 2-isopropyl-6-methoxyphenol in 5 ml of ethanol and stirring was continued for 0.5 hours at room temperature. The resulting solution was added dropwise in 15 minutes into a stirred solution 0.2 g of the above intermediate 4B in 50 ml of ethanol under nitrogen atmosphere. The mixture was stirred for 5 hours at room temperature and was then refluxed for 20 hours. The residue, obtained after solvent evaporation, was converted into the hydrochloride salt and crystallized from *i*-propanol to give 0.64 g (21%) of the title compound; m.p. 208-209°C.

Example 5

4-Amino-6,7-dimethoxy-2-[(±)-4-(5-methyl-2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride · 2.5 H₂O

(I: A = 5-methyl-2-furyl, B = B₃)

5-Methyl-2-furoyl chloride (5A)

A solution of 0.31 g of SOCl₂ in 2 ml of benzene was added dropwise at 0°C under nitrogen atmosphere to a solution of 0.22 g of 5-methylfuroic acid, prepared following the method described by Robert et al., *Eur. J. Med. Chem.* **30**, 915-924 (1995), in 5 ml of benzene. The mixture was stirred at 80°C for 1 hour and the excess SOCl₂ was then distilled off. The residue (0.24 g, 97% of theoretical) was utilised for the next step without further purification.

4-Amino-6,7-dimethoxy-2-[(±)-4-(5-methyl-2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride · 2.5 H₂O

A solution of 0.24 g of the above intermediate 5A in 5 ml of dichloromethane was added dropwise at 0°C to a stirred solution of 0.56 g of intermediate 4A and 0.25 g of triethylamine in 10 ml of dichloromethane. The mixture was stirred at room temperature for 3 hours and then kept at 0-4°C overnight. The precipitate was collected by suction and purified by flash chromatography eluting with petroleum ether : ethyl acetate : methanol : 28% ammonium hydroxide 8 : 8 : 2 : 0.2. The pure base was transformed into the hydrochloride salt and crystallized from *i*-propanol to give 0.2 g (27%) of the title compound; m.p. 268-270°C.

Example 6

4-Amino-6,7-dimethoxy-2-[(±)-4-(2-tetrahydrofuroyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline hydrochloride · 2.5 H₂O

(I: A = 2-tetrahydrofuryl, B = B₃)

2-Tetrahydrofuroyl chloride (6A)

A mixture of 0.22 g of 2-tetrahydro-2-furoic acid and 0.5 ml of SOCl₂ in 10 ml of benzene was stirred at 80°C for 1 hour. The excess of SOCl₂ and benzene were distilled off to give 0.25 g of an oily residue which was considered 80% pure and was used for the next step without further purification.

4-Amino-6,7-dimethoxy-2-[(±)-4-(2-tetrahydrofuroyl)-cis-octahydro-1-quinoxalinyll]-quinazoline hydrochloride · 2.5 H₂O

This compound was prepared according to the method described in Example 5, but using the intermediate 6A instead of intermediate 5A and using petroleum ether : ethyl acetate : methanol : 14% ammonium hydroxide 8 : 6 : 2 : 0.1 as the eluant for the flash chromatography. The pure base was transformed into the hydrochloride salt and crystallized from ethanol to give 21% of the title compound; m.p. 220-223°C.

Example 7

4-Amino-6,7-dimethoxy-2-[(±)-4-benzyloxycarbonyl-cis-octahydro-1-quinoxalinyll]-quinazoline hydrochloride · 0.75 H₂O

(I: A = benzyloxy, B = B₃)

This compound was prepared according to the method described in Example 5, but using benzyloxycarbonyl chloride instead of intermediate 5A and using petroleum ether : ethyl acetate : methanol : 14% ammonium hydroxide 8 : 5 : 0.6 : 0.025 as the eluant for the flash chromatography. The pure base was transformed into the hydrochloride salt and crystallized from ethanol to give 14% of the title compound; m.p. 243-245°C.

Example 8

Radioligand Binding Assay at Cloned α₁-adrenoceptors.

[³H]Prazosin binding to bovine α_{1a}, hamster α_{1b} and rat α_{1d}-adrenoceptors was performed in COS-7 cell (CV-1 monkey kidney epithelial cells) membranes expressing transiently bovine α_{1a}, hamster α_{1b} and rat α_{1d}-adrenoceptors. Construction and transfection of individual α₁-adrenoceptors were carried out as previously described (Schwinn et al., *J. Biol. Chem.* **265**: 8183-8189, 1990; Cotecchia S. et al., *Proc. Natl.*

Acad. Sci. USA **85**: 7159-7163, 1988; Lomasney et al., *J. Biol. Chem.* **266**: 6365-6369, 1991).

COS-7 cell membranes (35, 35 and 70 μ g protein/sample for α_{1b} , α_{1a} and α_{1d} , respectively) were incubated in 50 mM Tris, pH 7.4, containing 10 μ M of pargyline and 0.1% of ascorbic acid, with 1.1 nM [3 H]prazosin, in a final volume of 0.22 ml, for 30 minutes at 25°C, in the absence or presence of competing drugs (1 pM-10 μ M). Non-specific binding was determined in the presence of 100 μ M of phentolamine. The incubation was stopped by addition of ice-cold Tris buffer and rapid filtration through 0.2% polyethyleneimine pretreated Whatman GF/B or Schleicher & Schuell GF52 filters.

Binding to cloned human α_1 -adrenoceptor subtypes was performed in membranes from CHO cells (Chinese hamster ovary cells) transfected by electroporation with DNA expressing the gene encoding each α_1 -adrenoceptor subtype. Cloning and stable expression of the human α_1 -adrenoceptor gene was performed as previously described (Testa et al., *Pharmacol. Comm.* **6**: 79-86, 1995). CHO cell membranes (30 μ g of proteins) were incubated in 50 mM of Tris, pH 7.4, with 0.2 nM of [3 H]prazosin in a final volume of 1.02 ml for 30 min at 25°C, in the absence or presence of competing drugs (1pM-10 μ M). Non-specific binding was determined in the presence of 10 μ M of phentolamine. The incubation was stopped by addition of ice-cold Tris buffer and rapid filtration through 0.2% polyethyleneimine pretreated Whatman GF/B or Schleicher & Schuell GF52 filters.

The inhibition of specific binding of the radioligand by the tested drugs was analyzed to estimate the IC₅₀ value by using a non-linear curve-fitting program (De lean et al., *A. J. Physiol.* **235**: E97-E102, 1978). The IC₅₀ value was converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (Cheng et al., *Biochem. Pharmacol.* **22**: 3099-3108, 1973). Data are expressed as mean Ki .

The compounds of Examples 1 to 7 exhibited the desired potency at α_{1b} -adrenoceptor, their Ki values being higher than 1×10^{-8} M (Table 1). Compound A, Compound B and

Compound C were also selective for the α_{1b} -adrenoceptor, their affinity for the other α_1 -subtypes being at least 10-fold lower.

TABLE 1

<i>Affinity (K_i, nM) of the different compounds tested for animal and human recombinant α_1-adrenoceptor subtypes</i>						
	Animal cloned receptors			Human cloned receptors		
	α_{1a}	α_{1b}	α_{1d}	α_{1a}	α_{1b}	α_{1d}
Example 1 - Compound A	7.5	0.45	10.34	-	-	-
Example 2 - Compound B	32.94	0.68	26.9	9.43	0.17	2.63
Example 3 - Compound C	-	-	-	94.12	1.76	25.07
Example 4	-	-	-	-	0.16	-
Example 5	-	-	-	-	0.24	-
Example 7	-	-	-	-	0.65	-
Prazosin	0.72	0.46	1.39	0.61	0.42	0.23
Phentolamine	3.22	89.15	67.05	4.8	33.21	17.26

Example 9

Functional affinity for α_{1L} -adrenergic receptors

The functional α_1 -antagonistic activity of the tested compounds against noradrenaline-induced contractions of rabbit aorta pretreated with chloroethylclonidine (receptor α_{1L}) was evaluated according to the method of Testa (Testa et al., *J. Pharmacol. Exp. Ther.* **281**: 1284-1293, 1997). Adult male New Zealand rabbits were sacrificed by cervical dislocation. The aorta was removed, placed in Krebs-Henseleit buffer and dissected free of adhering tissue. Rings were prepared from each aorta (8 rings per aorta, about 4-5 mm wide) and suspended in 20 ml organ baths containing Krebs bicarbonate buffer of the following composition (mM): NaCl 112.0, KCl 5.0, CaCl₂ 2.5, KH₂PO₄ 1.0, MgSO₄ 1.2, NaHCO₃ 12.0 and glucose 11.1, equilibrated at 37° C with 95% O₂: 5% CO₂. Desmethylinipramine (0.1 μ M) and corticosterone (1 μ M) to block neuronal and extraneuronal uptake of NA, ($\pm$)-propranolol (1 μ M) to block β adrenoceptors and yohimbine (0.1 μ M) to block α_2 -adrenoceptors, were added to the buffer. The tissues were subject to a passive load of 2 g and the developed tension was measured using isometric transducers (Basile 7003).

The preparations were allowed to equilibrate for 60 min and then 10 μ M of NA was added every 30 minutes for three times. The aortic rings were then incubated with the alkylating agent chloroethylclonidine (5×10^{-5} M) for 30 minutes and then washed extensively three times (in 0.5 hours) before constructing the NA concentration-response curve. After washout of NA and re-equilibration of the tissue (45 minutes), the drug to be tested was added and, after 30 minutes, a second NA cumulative concentration-response curve constructed. Each antagonist concentration was tested using 2-3 aortic rings from different rabbits.

Dose ratios (i.e. the ratio between the concentrations of noradrenaline required to produce half-maximal response in the presence and in the absence of the antagonist tested) were calculated at each concentration of the compounds. The logarithm of these dose ratio -1 was plotted against the logarithm of the compound concentrations (Schild plot) to evaluate the affinity constant K_b . When only one or two concentrations of the tested compounds were utilized, the apparent K_b value was calculated using the formula: $K_b = [B]/(\text{DOSE RATIO}-1)$, where B is the antagonist concentration.

The tested compounds showed selectivity for the α_{1b} -adrenoceptor *versus* the α_{1L} -adrenoceptor. Their functional affinity for this receptor proved, in fact, at least 10-fold lower than that for the α_{1b} -subtype (Table 2).

TABLE 2

<i>Functional affinity of the tested compounds for α_{1L}-adrenoceptor subtype</i>	
	K_b , nM
Compound A - Example 1	631.0
Compound B - Example 2	741.0
Compound C - Example 3	3715.0
Prazosin	20.9
Phentolamine	251.0

Example 10

Intracavernous and blood pressure recording in rats

The evaluation of the erectile properties of the different compounds tested in rats was performed according to the method of Giuliano et al. (Giuliano et al., *J. Urol.* **150**: 519-524, 1993).

Rats were anaesthetised by an intraperitoneal injection of urethane (1.5 g/kg in sterile saline) and placed on an homeothermic blanket. Their temperature was maintained at 37°C. Rats were tracheotomized to facilitate spontaneous breathing and to prevent aspiration of saliva. A catheter filled with heparinized saline (25 IU/ml) was placed into the carotid to record mean blood pressure (BP, mmHg). The penis was desheathed and the corpora cavernosa were exposed. A 25-gauge stainless-steel needle was inserted into one corpus cavernosum to record intracavernous pressure (ICP in mmHg). The needle was attached to a catheter filled with heparinized saline (25 IU/ml). Pressure catheters were connected to pressure transducers (Model 750, Elcomatic Ltd, Glasgow, UK).

Following a resting period of 10 minutes, the compound solvent was delivered intracavernously (50 µl/injection). Then, increasing doses of one compound were injected every ten minutes by the same route. Five injections (one solvent plus four cumulative doses) were performed in each rat, and five rats were used for the study of one compound. For each injection and for each compound, mean BP averaged over the ten minutes following the injection was measured. The maximal ICP value reached during the ten-minute period following an injection was also recorded. In these experiments, all the compounds tested were dissolved and diluted in propylene glycol-Sorensen solvent. The ICP and BP values were reported as mean $\pm$ s.e. of the mean, or percent variation ($\pm$ s.e.) of the basal values. The ratios (ICP/BP)*100, which correspond to the percentage of BP reached by ICP, were calculated by using the peak effect value on ICP on the mean blood pressure observed for 10 min after injection of the compounds, and reported as mean $\pm$ s.e. of the mean.

The effects of Compound A, prazosin and phentolamine are summarized in Tables 3 to 5. Compound A dose-dependently increased ICP (from 33.9 mmHg after injection of

vehicle to 50.6 mmHg) and slightly decreased BP (about 30%). The ICP increase lasted several minutes, but never overlapped the ten-minute period of screening (data not shown). Prazosin was unable to elicit any ICP increase and decreased blood pressure by 41% between solvent injection and after injection of 1000 $\mu\text{g/kg}$. Phentolamine did not modify ICP up to 300 $\mu\text{g/kg}$. After injection of 1000 $\mu\text{g/kg}$ it elicited a sustained intracavernous pressure increase that lasted several minutes (not exceeding 10 minutes); at this dose phentolamine decreased BP by 30%.

Figure 1 shows the effects of vehicle and different doses of the compounds tested on the ICP/BP ratios, corresponding to the percentage of blood pressure (BP) reached by intracavernous pressure (ICP), after intracavernous injection in rats. Data represent the mean values of the ratio. Basal: first bar; vehicle: 2nd bar; different tested doses: other bars (Compound A: 10, 30, 100 and 300 μg ; prazosin and phentolamine: 10, 30, 100, 300 and 1000 μg). The percent decreases of mean BP evaluated *versus* the basal values reported in Tables 3-5 are also shown. Compound A increased the ICP/BP ratio in a dose-dependent manner. Increases higher than 40% were obtained in presence of decreases of blood pressure not exceeding 20%. On the contrary, the increases of ICP/BP induced by prazosin and phentolamine were poorly dose-dependent and both compounds induced, at the same doses, marked hypotension, being the decrease of blood pressure equal to or higher than 40%.

Compound A increased the ratio from 31.8 following injection of the solvent to 66.4 following injection of 300 $\mu\text{g/kg}$ of the compound. The increase obtained with the highest dose of prazosin reflects only the decrease in blood pressure, since ICP did not increase at all. Phentolamine induced a slight increase only at the highest dose.

TABLE 3

<i>Effects on intracavernous pressure and blood pressure after intracavernous injection of Compound A in anaesthetised rats (n=5)</i>			
Dose ($\mu\text{g/kg}$)	ICP (mmHg)	BP (mmHg)	ICP/BP Ratio
BASAL	14.5 $\pm$ 1.6	92.6 $\pm$ 5.9	15.8 $\pm$ 1.9
Vehicle	33.9 $\pm$ 6.6	105.7 $\pm$ 10.1	31.8 $\pm$ 5.5
10	36.8 $\pm$ 8.7	91.3 $\pm$ 9.4	38.3 $\pm$ 5.8
30	37.6 $\pm$ 10.1	82.7 $\pm$ 11.0	43.0 $\pm$ 7.0
100	38.7 $\pm$ 12.3	74.8 $\pm$ 9.3	47.9 $\pm$ 9.2
300	50.6 $\pm$ 13.7	72.5 $\pm$ 5.6	66.4 $\pm$ 15.6
<i>ICP = intracavernous pressure, BP = blood pressure</i>			

TABLE 4

<i>Effects on intracavernous pressure and blood pressure after intracavernous injection of prazosin in anaesthetised rats (n=5)</i>			
Dose ($\mu\text{g/kg}$)	ICP (mmHg)	BP (mmHg)	ICP/BP Ratio
BASAL	11.5 $\pm$ 2.9	87.5 $\pm$ 11.0	13.2 $\pm$ 1.3
Vehicle	26.5 $\pm$ 17.3	73.1 $\pm$ 9.2	38.0 $\pm$ 24.7
10	20.1 $\pm$ 6.4	54.9 $\pm$ 7.7	31.3 $\pm$ 6.2
30	14.9 $\pm$ 3.3	60.0 $\pm$ 7.4	24.8 $\pm$ 5.7
100	19.0 $\pm$ 6.6	56.8 $\pm$ 7.9	31.5 $\pm$ 8.1
300	18.9 $\pm$ 6.8	41.3 $\pm$ 3.0	43.0 $\pm$ 12.6
1000	26.9 $\pm$ 3.5	43.7 $\pm$ 4.1	62.5 $\pm$ 16.3
<i>ICP = intracavernous pressure, BP = blood pressure</i>			

TABLE 5

<i>Effects on intracavernous pressure and blood pressure after intracavernous injection of phentolamine in anaesthetised rat (n=5)</i>			
Dose ($\mu\text{g/kg}$)	ICP (mmHg)	BP (mmHg)	ICP/BP Ratio
BASAL	12.9 $\pm$ 1.5	119.6 $\pm$ 4.2	10.8 $\pm$ 1.1
Vehicle	12.4 $\pm$ 1.5	84.6 $\pm$ 4.1	15.1 $\pm$ 2.5
10	12.6 $\pm$ 1.7	79.8 $\pm$ 7.3	16.6 $\pm$ 3.0
30	10.1 $\pm$ 1.4	72.2 $\pm$ 4.3	14.3 $\pm$ 2.3
100	10.5 $\pm$ 1.4	61.1 $\pm$ 7.0	17.9 $\pm$ 3.3
300	12.5 $\pm$ 2.3	63.0 $\pm$ 2.2	20.4 $\pm$ 4.4
1000	20.6 $\pm$ 2.1	59.8 $\pm$ 3.6	34.3 $\pm$ 2.7
<i>ICP = intracavernous pressure, BP = blood pressure</i>			

Example 11

Intracavernous and blood pressure recording in dogs

The evaluation of the erectile properties in dogs was performed according to the method of Carati (Carati et al., *J. Physiol.* **384**: 525-538, 1987), with some modifications.

Male *beagle* dogs were anaesthetised with pentobarbital sodium (i.v. Nembutal, 35 mg/kg for induction and 4 mg/kg/h for maintenance) and intubated with an endotracheal cuffed tube to facilitate free ventilation. A collateral of the left femoral vein was cannulated with a PE catheter for infusion of the anaesthetic. Systemic BP was monitored via a Mikro-tip 6F (Millar Instruments) pressure transducer introduced into the aortic arch through the right common carotid artery. ICP was measured by means of a 20-gauge needle placed into the left or right corpus cavernosum and the same needle was used for intracavernous injection of the drugs. The needle was attached to a catheter filled with heparinized saline (25 iu / ml). Pressure signal was triggered by BM 614/2 amplifiers on a multichannel polygraph. The compounds to be tested were injected intracavernously in a volume of 0.5 ml and, after each injection, the needle was flushed with 0.5 ml of saline. The vehicles for drug dissolution were tested before the first dose of each drug. The compounds were administered in a cumulative way, with a 30-minute interval between doses. ICP (mmHg) was measured at the peak effect after the administration of the compounds. The duration of tumescence (DT, min) was measured from the beginning of the rise of ICP over its basal value up to the return to baseline. The systolic blood pressure and diastolic blood pressure (mmHg) were measured at the peak effect after the administration of drugs, in order to evaluate the effects of the compounds on BP independently from the effects on ICP. Moreover, the systolic blood pressure was measured at the time of maximal ICP value after intracavernous injection, to evaluate the ICP/BP ratios.

In these experiments, Compound A, Compound B and phentolamine (1 or 3 mg/ml) were dissolved in 10% (v/v) N,N-dimethylformamide and further diluted in deionized H₂O. Prazosin was dissolved in deionized H₂O. The data were reported as mean $\pm$ s.e. of the mean, or percent variation ($\pm$ s.e.) of the basal values.

The results of the intracavernous administration of the drugs in anaesthetised dogs are reported in Tables 6 to 9. The vehicles employed for drug dilution were tested before each dose of each compound and showed no effect on either intracavernous pressure or systemic blood pressure (data not shown).

All drugs tested induced an increase of intracavernous pressure (ICP). Compound A dose-dependently increased ICP (in comparison with basal ICP values) from 12 mmHg at 3 µg/kg to 96.5 mmHg with the highest dose (300 µg/kg). The duration of the increase of intracavernous pressure (DT), too, was dose-dependent and lasted at least 27 min at the highest dose. The compound induced a slight dose-dependent hypotension (computed on diastolic blood pressure) from -10 to -19 mmHg. Compound B increased ICP in a dose-dependent way from 13.7 mmHg (at 3 µg/kg) to 73.3 mmHg (1000 µg/kg) and induced hypotension only with the highest dose (-31 mmHg on diastolic blood pressure). DT lasted about 40 min at the highest dose. Prazosin and phentolamine increased ICP at doses that induced sustained hypotension. Furthermore the ICP increase observed after injection of these reference compounds was not dose-dependent. Prazosin, at 1000 µg, induced an ICP increase of 36 mmHg only, and decreased diastolic blood pressure by 71 mmHg. Similarly, phentolamine (at the same dose) increased ICP by 43 mmHg, but decreased diastolic blood pressure by 37 mmHg.

Figure 2 shows the effects of vehicle and different doses of the compounds tested on the ICP/BP ratios, corresponding to the percentage of blood pressure (BP) reached by intracavernous pressure (ICP) after intracavernous injection in dogs. Data represent the mean values of the ratio. Basal: first bar; different tested doses: other bars (Compound A: 3, 10, 30, 100 and 300 µg; Compound B: 3, 30, 100, 300 and 1000 µg; prazosin: 30, 100, 300 and 1000 µg; phentolamine: 10, 30, 100, 300 and 1000 µg). The percent decreases of DBP evaluated *versus* the basal values reported in Table 6-9 are also shown.

Compound A increased the ICP/BP ratio in a dose-dependent manner. Increases higher than 80% were obtained in presence of decreases of blood pressure not exceeding 20%. Similar results were obtained after administration of Compound B. On the contrary, the increases of ICP/BP induced by prazosin were lower than those obtained after Compounds A and B, and this reference compound induced a marked hypotension. Phentolamine increased the ICP/BP ratio only after the administration of the highest dose, which induced a relevant hypotension.

TABLE 6

DOSE ($\mu\text{g/kg}$)	ICP (mmHg)	DT (min)	SBP (mmHg)	DBP (mmHg)	SBP _{ICP} (mmHg)	ICP/BP RATIO
BASAL	14.5 $\pm$ 2.2	-	163.0 $\pm$ 5.4	126.5 $\pm$ 5.5	-	8.8 $\pm$ 1.2
3	26.7 $\pm$ 8.7	1.2 $\pm$ 0.2	155.3 $\pm$ 5.5	116.0 $\pm$ 5.9	156.7 $\pm$ 6.8	16.6 $\pm$ 4.7
10	75.0 $\pm$ 32.4	15.0 $\pm$ 8.4	157.5 $\pm$ 6.6	120.0 $\pm$ 5.9	158.5 $\pm$ 7.4	45.1 $\pm$ 18.6
30	91.5 $\pm$ 26.9	8.3 $\pm$ 3.2	154.0 $\pm$ 6.6	117.5 $\pm$ 6.5	156.5 $\pm$ 5.9	57.6 $\pm$ 16.0
100	95.0 $\pm$ 23.3	13.7 $\pm$ 5.6	147.5 $\pm$ 7.6	113.0 $\pm$ 7.3	148.5 $\pm$ 6.0	62.5 $\pm$ 13.3
300	111.0 $\pm$ 10.9	27.4 $\pm$ 7.8	140.0 $\pm$ 7.4	107.5 $\pm$ 7.4	142.0 $\pm$ 6.5	77.8 $\pm$ 4.8

ICP = intracavernous pressure; DT = duration of tumescence; SBP, DBP = systolic and diastolic blood pressure, SBP_{ICP} = SBP measured at the time of maximal ICP value

TABLE 7

DOSE ($\mu\text{g/kg}$)	ICP (mmHg)	DT (min)	SBP (mmHg)	DBP (mmHg)	SBP _{ICP} (mmHg)	ICP/BP RATIO
BASAL	19.0 $\pm$ 1.6	-	152.3 $\pm$ 7.5	112.0 $\pm$ 5.3	-	12.8 $\pm$ 1.7
3	36.7 $\pm$ 2.2	2.5 $\pm$ 0.9	151.7 $\pm$ 7.3	110.7 $\pm$ 5.5	153.3 $\pm$ 7.0	24.2 $\pm$ 2.0
30	49.3 $\pm$ 14.2	4.3 $\pm$ 2.0	150.0 $\pm$ 5.9	107.3 $\pm$ 4.2	151.0 $\pm$ 5.7	32.3 $\pm$ 8.6
100	52.7 $\pm$ 13.0	4.4 $\pm$ 1.6	146.0 $\pm$ 4.8	104.3 $\pm$ 4.2	147.3 $\pm$ 5.0	36.0 $\pm$ 8.5
300	57.3 $\pm$ 11.4	3.5 $\pm$ 1.1	139.0 $\pm$ 6.6	98.0 $\pm$ 6.9	147.3 $\pm$ 5.7	39.4 $\pm$ 8.0
1000	93.3 $\pm$ 6.2	41.7 $\pm$ 11.6	121.7 $\pm$ 4.9	81.0 $\pm$ 4.3	135.7 $\pm$ 6.8	69.0 $\pm$ 4.3

ICP = intracavernous pressure; DT = duration of tumescence; SBP, DBP = systolic and diastolic blood pressure, SBP_{ICP} = SBP measured at the time of maximal ICP value

TABLE 8

<i>Effects on intracavernous pressure and blood pressure after intracavernous injection of prazosin in anaesthetised dogs (n=4)</i>						
DOSE ($\mu\text{g/kg}$)	ICP (mmHg)	DT (min)	SBP (mmHg)	DBP (mmHg)	SBP _{ICP} (mmHg)	ICP/BP RATIO
BASAL	16.0 $\pm$ 1.6	-	159.5 $\pm$ 3.7	130.5 $\pm$ 3.3	-	10.0 $\pm$ 0.8
30	25.5 $\pm$ 6.3	1.1 $\pm$ 1.1	140.0 $\pm$ 7.0	116.0 $\pm$ 2.9	142.5 $\pm$ 5.9	18.5 $\pm$ 5.5
100	27.0 $\pm$ 8.7	1.4 $\pm$ 1.1	122.0 $\pm$ 1.4	98.5 $\pm$ 1.9	130.0 $\pm$ 6.1	21.1 $\pm$ 7.2
300	37.5 $\pm$ 5.0	3.0 $\pm$ 1.5	102.0 $\pm$ 1.6	78.5 $\pm$ 3.5	117.0 $\pm$ 6.6	32.4 $\pm$ 4.9
1000	52.5 $\pm$ 5.0	17.7 $\pm$ 14.1	93.5 $\pm$ 1.9	59.0 $\pm$ 5.1	107.0 $\pm$ 8.9	49.8 $\pm$ 5.8
<i>ICP = intracavernous pressure; DT= duration of tumescence; SBP, DBP= systolic and diastolic blood pressure, SBP_{ICP} = SBP measured at the time of maximal ICP value</i>						

TABLE 9

<i>Effects on intracavernous pressure and blood pressure after intracavernous injection of phentolamine in anaesthetised dogs (n=3)</i>						
DOSE ($\mu\text{g/kg}$)	ICP (mmHg)	DT (min)	SBP (mmHg)	DBP (mmHg)	SBP _{ICP} (mmHg)	ICP/BP RATIO
BASAL	20.0 $\pm$ 2.3	-	166.7 $\pm$ 10.9	128.0 $\pm$ 8.0	-	11.9 $\pm$ 0.7
10	24.0 $\pm$ 0.0	-	166.7 $\pm$ 10.7	125.3 $\pm$ 9.4	166.7 $\pm$ 10.7	14.5 $\pm$ 0.9
30	20.0 $\pm$ 2.3	-	165.3 $\pm$ 7.3	125.3 $\pm$ 7.3	166.7 $\pm$ 9.7	11.9 $\pm$ 0.8
100	17.3 $\pm$ 1.3	-	159.3 $\pm$ 12.5	118.7 $\pm$ 11.2	165.3 $\pm$ 9.3	10.5 $\pm$ 0.2
300	16.0 $\pm$ 2.3	-	138.0 $\pm$ 16.3	108.7 $\pm$ 11.1	149.3 $\pm$ 9.3	10.6 $\pm$ 0.9
1000	62.7 $\pm$ 24.3	4.2 $\pm$ 2.1	126.0 $\pm$ 13.0	91.3 $\pm$ 14.7	141.3 $\pm$ 17.3	41.3 $\pm$ 12.5
<i>ICP = intracavernous pressure; DT = duration of tumescence; SBP, DBP= systolic and diastolic blood pressure, SBP_{ICP} = SBP measured at the time of maximal ICP value</i>						

The results from Examples 10 and 11 show the usefulness of selective α_{1b} -antagonists for the treatment of erectile dysfunction.

Compound A, both in dogs and rats, and Compound B, in dogs, induced a dose-dependent increase in ICP with very low hypotensive effects. The proerectile activity of such compounds was obtained at doses lower than those of phentolamine and prazosin and the decrease in diastolic blood pressure was lower than that induced by the reference drugs.

Phentolamine increased ICP in dogs and rats at very high doses, and its proerectile activity was accompanied by sustained hypotension. In a similar way, prazosin in dogs induced an increase in ICP accompanied by strong hypotension. In rats, prazosin did not

increase intracavernous pressure when delivered intracavernously and, therefore, has no proerectile properties in this animal species.

Furthermore, the duration of action observed after injection of Compound A (and Compound B at the highest dose tested) in dogs was higher than that of the reference compounds tested.

Example 12

Evaluation of effect on vaginal and clitoral pressure in female rabbits

The method to evaluate the effects of the products of the invention on vaginal and clitoral pressure in females is that described by Park K et al., *Int. J. Impot. Res.* 9, 27-37 (1997), modified as appropriate.

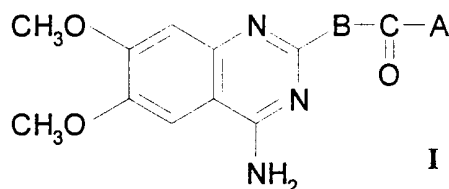
Female rabbits of the New Zealand strain were anaesthetised with phenobarbital and catheterised in the carotid artery to record blood pressure. The abdominal aortas and iliac arteries, on which electromagnetic flow sensors were placed to measure peripheral flow, and the branch of pelvic nerve which innervates the vagina and clitoris were exposed and isolated by median laparotomy. The pressure in the vaginal wall and clitoris was measured by inserting needles (gauge 21G), connected to a pressure transducer, in the vaginal corpus spongiosum and clitoral corpora cavernosa respectively. The test compounds were administered locally into the subepithelial layer of the vaginal spongy tissue or administered intravenously.

The effect on vaginal and clitoral pressure after local administration and the effect on pressure induced by electrical stimulation of the pelvic nerve (stimulation parameters: 10 V, 16 Hz, 8 msec) were measured.

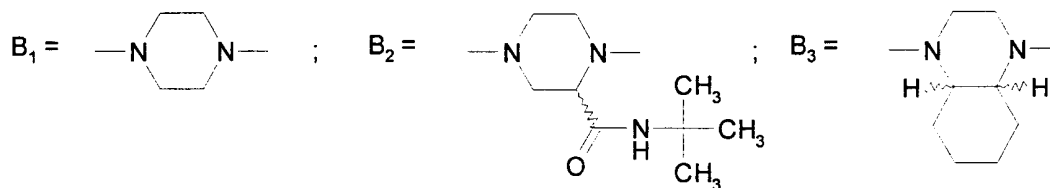
In the above experimental models, the results obtained with the compounds of the invention indicate effective use in the treatment of sexual dysfunction in the presence of very few side effects of a hypotensive origin.

CLAIMS

1. Use of a compound having the general formula I

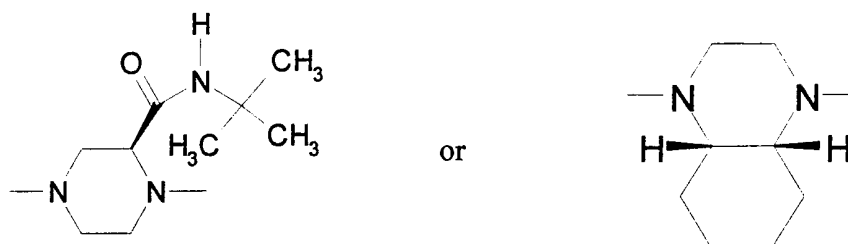


wherein A represents a 2-furyl, substituted 2-furyl, 2-tetrahydrofuryl, substituted alkoxy or substituted phenoxyalkyl group, and B represents one of the following groups of the formula B₁, B₂ or B₃:

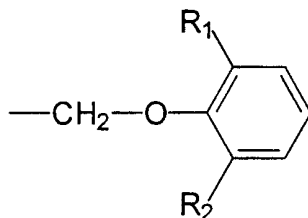


with the proviso that if B represents the group B₁ then A represents a substituted phenoxyalkyl group,
or of an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound,
for the preparation of a medicament for the treatment of sexual dysfunction.

2. Use according to claim 1 of a compound in which B represents one of the groups



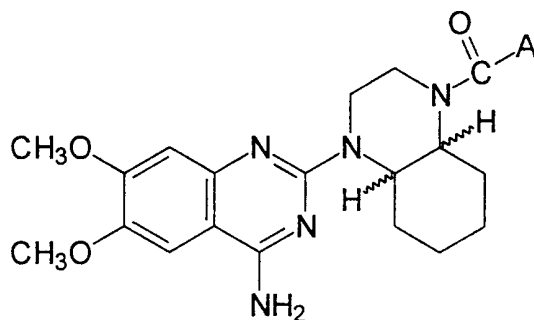
3. Use according to claim 1 or claim 2 of a compound in which A represents a group of the formula



wherein R_1 represents a linear or branched alkyl chain having from 1 to 5 carbon atoms and R_2 represents an alkoxy group having from 1 to 4 carbon atoms.

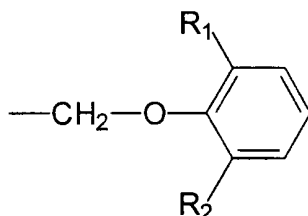
4. Use according to claim 1 or claim 2 of a compound in which A represents a 2-furyl or 6-isopropyl-2-methoxyphenoxyethyl group.
5. Use according to any preceding claim of any one of the following compounds:
- 4-amino-6,7-dimethoxy-2-[4-(2-methoxy-6-isopropylphenoxyacetyl)-1-piperazinyl]-quinazoline,
 - 4-amino-6,7-dimethoxy-2-[(4aR,8aS)-4-(2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline, and
 - 4-amino-6,7-dimethoxy-2[(3S)-3-(*t*-butyl-carbamoyl)-4-(2-furoyl)-1-piperazinyl]-quinazoline,
- or of an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound.
6. Use according to any preceding claim for the preparation of a medicament in unit dose form containing from 0.1 to 10.0 mg of the compound, enantiomer, diastereoisomer or salt.
7. Use according to any preceding claim for the preparation of a medicament formulated for administration by intracavernous injection.

8. Use according to any of claims 1 to 6 for the preparation of a medicament formulated for administration on an intraurethral catheter.
9. Use according to any of claims 1 to 6 for the preparation of a medicament formulated for transdermal administration.
10. Use according to any of claims 1 to 6 for the preparation of a medicament formulated for administration in a vaginal douche.
11. Use according to any of claims 1 to 6 for the preparation of a medicament formulated for administration in a vaginal cream.
12. Use according to any of claims 1 to 6 for the preparation of a medicament formulated for administration in vaginal ovules.
13. Use according to any of claims 1 to 6 for the preparation of a medicament additionally containing a prostaglandin, a direct vasodilator or a 5 cGMP phosphodiesterase inhibitor.
14. Use according to claim 13 for the preparation of a medicament containing sildenafil.
15. Use according to claim 13 or claim 14 for the preparation of a medicament formulated for oral administration.
16. Use according to claim 13 or claim 14 for the preparation of a medicament formulated for intravenous administration.
17. A compound having the general formula



wherein A represents a 2-tetrahydrofuryl, substituted 2-furyl, substituted alkoxy or substituted phenoxyalkyl group,
or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound.

18. A compound according to claim 17 in which the octahydroquinazoline ring has the (4aR, 8aS) configuration.
19. A compound according to claim 17 or claim 18 in which A represents a group of the formula



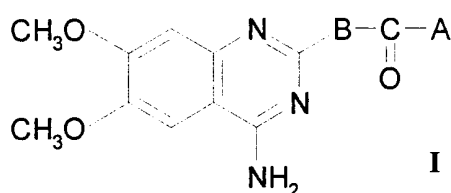
wherein R₁ represents a linear or branched alkyl chain having from 1 to 5 carbon atoms and R₂ represents an alkoxy group having from 1 to 4 carbon atoms.

20. Any one of the following compounds:
 - 4-amino-6,7-dimethoxy-2-[(±)-4-(2-methoxy-6-isopropylphenoxyacetyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline,
 - 4-amino-6,7-dimethoxy-2-[(±)-4-(5-methyl-2-furoyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline,

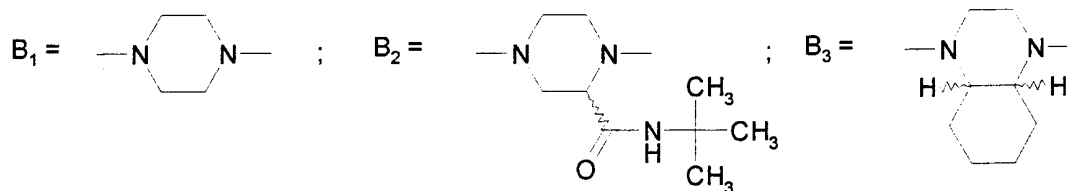
- 4-amino-6,7-dimethoxy-2-[(±)-4-(2-tetrahydrofuroyl)-*cis*-octahydro-1-quinoxaliny]-quinazoline,
- 4-amino-6,7-dimethoxy-2-[(±)-4-benzyloxycarbonyl-*cis*-octahydro-1-quinoxaliny]-quinazoline,

or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound.

21. A pharmaceutical composition comprising a compound according to any of claims 17 to 20, or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound, in admixture with a pharmaceutically acceptable diluent or carrier.
22. A pharmaceutical composition comprising
(a) a compound having the general formula I



wherein A represents a 2-furyl, substituted 2-furyl, 2-tetrahydrofuryl, substituted alkoxy or substituted phenoxyalkyl group, and B represents one of the following groups of the formula B₁, B₂ or B₃:



with the proviso that if B represents the group B₁ then A represents a substituted phenoxyalkyl group,
or an enantiomer, diastereoisomer or pharmaceutically acceptable salt of such a compound,

- (b) a prostaglandin, a direct vasodilator or a 5 cGMP phosphodiesterase inhibitor,
and
 - (c) a pharmaceutically acceptable diluent or carrier.
23. A pharmaceutical composition according to claim 22, which contains a compound according to any of claims 17 to 20.
24. A pharmaceutical composition according to claim 22 or claim 23, which contains sildenafil.
25. A pharmaceutical composition according to any of claims 21 to 24, the composition being in unit dose form and containing from 0.1 to 10.0 mg of the compound, enantiomer, diastereoisomer or pharmaceutically acceptable salt.
26. A pharmaceutical composition according to any of claims 21 to 25 formulated for administration by intracavernous injection.
27. A pharmaceutical composition according to any of claims 21 to 25 formulated for administration on an intraurethral catheter.
28. A pharmaceutical composition according to any of claims 21 to 25 formulated for transdermal administration.
29. A pharmaceutical composition according to any of claims 21 to 25 formulated for intravaginal administration in a vaginal douche.
30. A pharmaceutical composition according to any of claims 21 to 25 formulated for intravaginal administration in a vaginal cream.
31. A pharmaceutical composition according to any of claims 21 to 25 formulated for intravaginal administration in vaginal ovules.

32. A pharmaceutical composition according to any of claims 22 to 24 formulated for oral administration.
33. A pharmaceutical composition according to any of claims 22 to 24 formulated for intravenous administration.
34. Use of a compound which
 - (a) binds to mammalian α_{1b} adrenergic receptors with an affinity of at least about 10^{-8} M and
 - (b) binds to mammalian α_{1b} adrenergic receptors with an affinity at least 10-fold higher than the affinity with which the compound binds to mammalian α_{1a} or α_{1d} or α_{1L} adrenergic receptorsfor the preparation of a medicament for the treatment of sexual dysfunction.
35. Use according to claim 34 for the preparation of a medicament in unit dose form containing from 0.1 to 10.0 mg of the compound, enantiomer, diastereoisomer or salt.
36. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for administration by intracavernous injection.
37. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for administration on an intraurethral catheter.
38. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for transdermal administration.
39. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for administration in a vaginal douche.

40. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for administration in a vaginal cream.
41. Use according to claim 34 or claim 35 for the preparation of a medicament formulated for administration in vaginal ovules.
42. Use according to claim 34 or claim 35 for the preparation of a medicament additionally containing a prostaglandin, a direct vasodilator or a 5 cGMP phosphodiesterase inhibitor.
43. Use according to claim 42 for the preparation of a medicament containing sildenafil.
44. Use according to claim 42 or claim 43 for the preparation of a medicament formulated for oral administration.
45. Use according to claim 42 or claim 43 for the preparation of a medicament formulated for intravenous administration.
46. A method for identifying a compound useful for the treatment of sexual dysfunction in patients suffering from this disorder, the method comprising the steps of
 - (a) individually measuring the binding affinity of test compounds for a mammalian α_{1b} adrenergic receptor and a mammalian α_{1a} or α_{1d} adrenergic receptor by radioreceptor binding techniques,
 - (b) measuring the affinity for a mammalian α_{1L} adrenergic receptor by antagonizing the contractile effect on α_1 adrenergic receptors on selected mammalian tissue, and
 - (c) identifying those compounds which
 - (1) bind to a α_{1b} adrenergic receptor with an affinity of at least 10^{-8} M, and

- (2) bind to a α_{1b} adrenergic receptor with an affinity at least 10-fold higher than the affinity with which the compound binds to mammalian α_{1a} or α_{1d} or α_{1L} adrenergic receptors.

Fig. 1

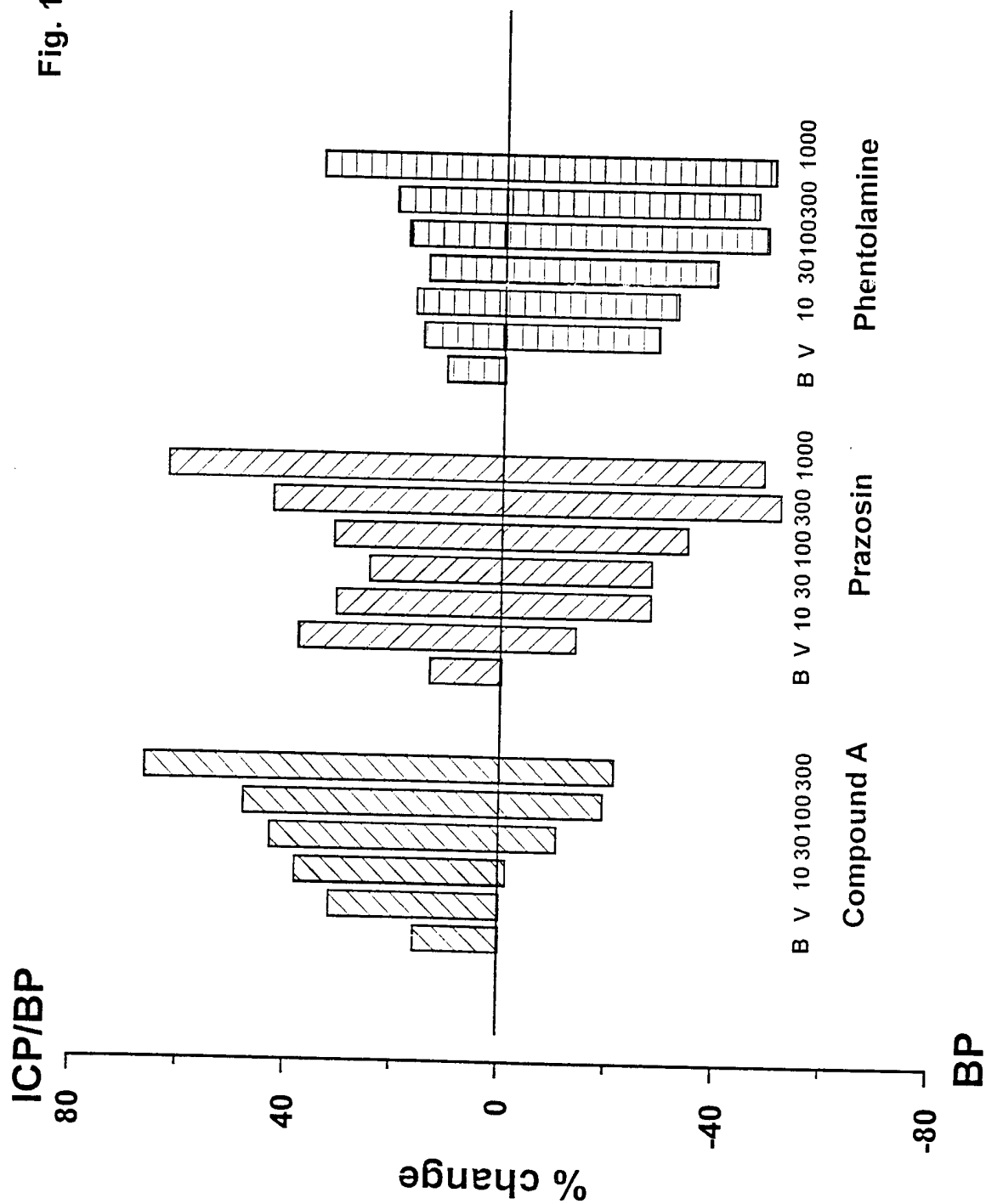


Fig. 2

