ARYLPIPERAZINE DERIVATIVES USEFUL AS UROSELECTIVE ALPHA1-ADRENOCEPTOR BLOCKERS

1. Field of the Invention

The present invention relates to certain novel piperazine derivatives having protracted uro-selective α_1-adrenoceptor antagonistic activity exceeding those of previously described compounds. The compounds of the present invention hold promise for treating benign prostatic hyperplasia (BPH). This invention also relates to methods for making the novel compounds, pharmaceutical compositions containing the compounds, and methods of treating benign prostatic hyperplasia using the compounds.

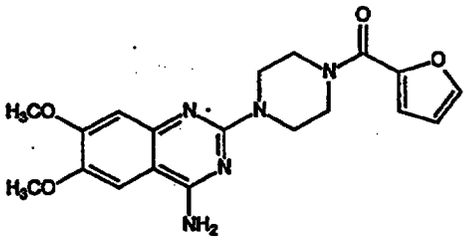
2. Description of the Related Art

A review in J.Med.Chem., 1997, V.40, No.9, pp.1292-1315, describes the most important pharmacological options available at present in the treatment of benign prostatic hyperplasia. The two most successful therapies are based on α-adrenergic receptor antagonism and androgen levels modulation by 5α-reductase inhibitors. 5α-reductase inhibitors are of limited effectiveness in terms of immediate symptomatic and urodynamic relief. α_1-antagonists appear to be much more effective and provide immediate subjective symptomatic improvements and are therefore the preferred modalities of treatment in the control of benign prostrate hypertrophy. α_1-adrenoceptors are also present in blood vessels and play an important role in the regulation of blood pressure.

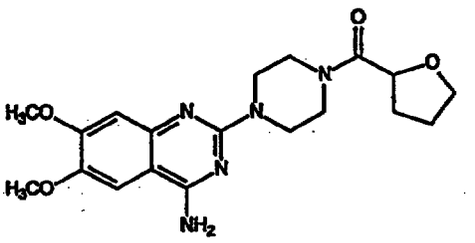
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Thus, α_1-adrenoceptor antagonists are of particular importance as they were originally developed as antihypertensive agents and are likely also to have a beneficial effect on lipid dysfunction and insulin resistance, which are commonly associated with essential hypertension.

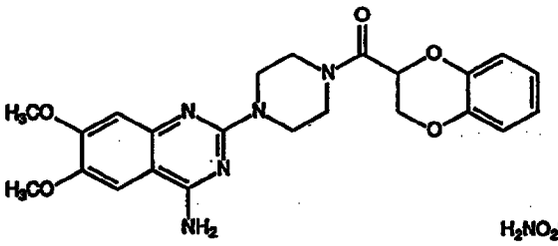
The more important of the α_1-adrenoceptor antagonists which are currently used in the management of BPH are shown below.



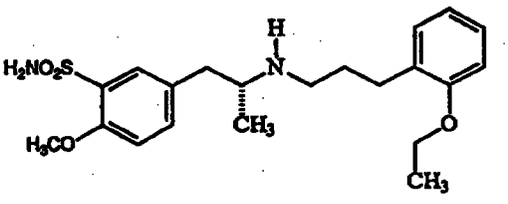
PRAZOSIN



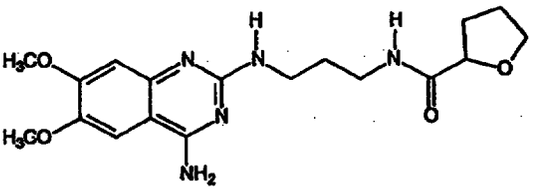
TERAZOSIN



DOXAZOSIN



(R)-(-)-TAMSULOSIN

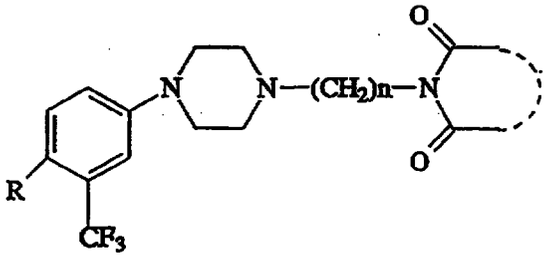


ALFUZOSIN

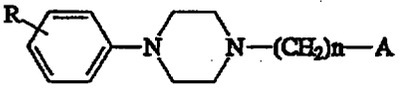
However, most of these known drugs are associated with vascular side effects (e.g., postural hypertension, syncope, dizziness, headaches, etc.) due to lack of selectivity of action between prostatic and vascular α_1-adrenoceptors. Clearly, α_1-adrenoceptor antagonists which have inherently greater selectivity for prostatic α_1-adrenoceptors offer the potential of increased urodynamic benefits. This underscores the importance of the discovery of prostate-selective α_1-adrenoceptor antagonists which will confer urodynamic improvement without the side effects associated with existing drugs.

Recently, it has been demonstrated that the prostate tissue of higher species like man and dog is overvalued by low affinity α_{1A}-adrenoceptor subtype. This makes it possible to develop agents with selective action against these pathological urodynamic states. The present invention is directed to the development of novel α_1-antagonists, namely, a new class of piperazine compounds, with greater selectivity of action against α_{1A} adrenoceptors and which would thus offer selective relief for prostate hypertrophy as well as essential hypertension.

There are many descriptions in the literature of the pharmacological activities associated with phenyl piperazines. Eur. J. Med. Chem.-Chimica Therapeutica , 1977, V. 12, No. 2, pp. 173-176, describes substituted trifluoromethyl phenyl piperazines having cyclo-imido alkyl side chains shown below as anorectic agents with no CNS side effects.

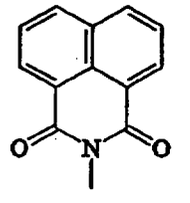


The synthesis and pharmacology of some 2-[3-(4-aryl-1-piperazinyl)propyl]-1*H*-benz[de]isoquinolin-1,3-(2*H*)-diones/2,5-pyrrolidinediones (J. Indian Chem. Soc., 1986, V. LXIII, pp. 529-530), of N-(N^4-aryl-N^1-piperozinylmethyl)-4-(4'-methoxyphenyl)piperidine-2,6-diones (J. Indian Chem. Soc., 1978, v. LV, pp.819-821), and of N-(N^4-arylpiperazinylalkyl)- phthalimides (J. Indian Chem. Soc., 1979, V. LVI, pp. 1002-1005), as shown below, have been reported. The compounds were shown to exhibit antihypertensive and CNS depressant activity in experimental animals.

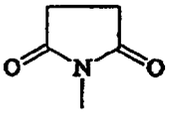


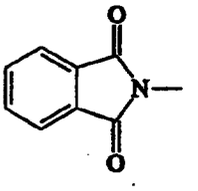
n = 1-3

A=

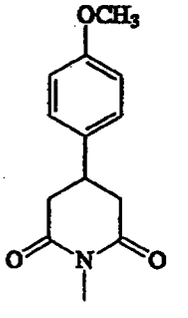


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However, in those papers there is no mention of the adrenoceptor blocking activity of these compounds, and thus their usefulness in the treatment of benign prostate hyperplasia did not arise.

The earlier synthesis of various 1-(4-aryl-piperazin-1-yl)-3-(2-oxo-pyrrolidin-1-yl/piperidin-1-yl) alkanes and their usefulness as hypotensive and antischemic agents is disclosed in unpublished Indian patent applications DEL 496/95 (March 3, 1995), DEL/500/95 (March 21, 1995) and DEL/96/96 (March 29, 1996) by the inventors herein. These compounds had low α_1-adrenergic blocking activity (pKi ~ 6 as compared to >8 of the known α_1-antagonists such as prazosin), and practically no adrenoceptor sub-class selectivity for α_{1A} vs. α_{1B} or α_{1D} adrenoceptors. It has now been discovered that structural modification of these compounds from lactam to dioxo compounds, i.e., from 2-oxopyrrolidin to 2,5- dioxopyrrolidin and 2,6-dioxopiperidine, enhances the adrenoceptor blocking activity, and also greatly increases the selectivity for α_{1A} in comparison to α_{1B}-adrenoceptor blocking activity, an essential requirement for compounds to be good candidates for treatment of BPH.

3. Objects of the Invention

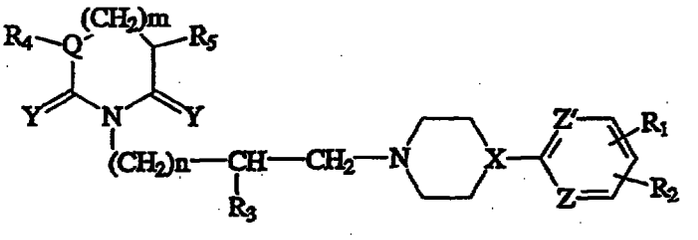
An object of the present invention, therefore, is to provide novel arylpiperazine derivatives that exhibit significantly greater α_{1A}- adrenergic blocking potency than available with the known compounds in order to provide specific treatment for benign prostatic hyperplasia.

It is also an object of the invention to provide a method for synthesis of the novel compounds.

It is a further object of the invention to provide compositions containing the novel compounds which are useful in the treatment of benign prostatic hyperplasia.

4. Summary of the Invention

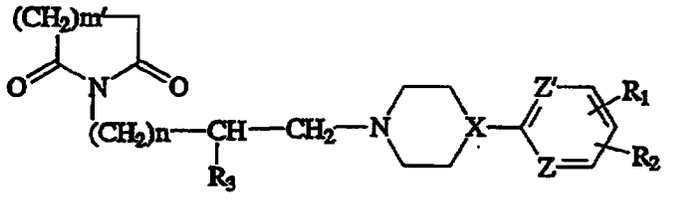
The above-mentioned objectives are achieved by a novel class of piperazine derivatives of general Formula I below



(I)

wherein Y is O or S; Q, X, Z and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring. Preferably, R_1 is H, R_2 is H, Cl or CF_3, R_3, R_4, and R_5 = H, Y = O and Q = CH when m=0 and n=1; or R_1 is H, R_2 is OCH_3, R_3, R_4 and R_5 = H, Y = O and Q = CH when m = 0 and n = 2.

Compounds within the scope of Formula I but having the structure of Formula II below



(II)

wherein n, X, Z, Z', R'$_1$, R$_2$ and R$_3$ are as defined for Formula I and wherein m' = 1-4, are preferred as selective and potent α_{1A}-adrenoceptor antagonistic activity over the α_{1B}- and α_{1D}-adrenoceptors. In Formula II, preferably R$_1$ is H, R$_2$ is H, Cl or CF_3, and R$_3$ is H when m' = 1 and n = 1; or R$_1$ is H, R$_2$ is OCH_3, and R$_3$ is H when m' = 1 and n = 2.

The present invention also provides pharmaceutical compositions for the treatment of benign prostatic hyperplasia. These compositions comprise an effective amount of at least one of the above compounds of Formula I, or preferably of Formula II, and/or an effective amount of at least one physiologically acceptable acid addition salt thereof, with a pharmaceutically acceptable carrier.

An illustrative list of particular compounds of the invention is given below:

Compound No.	Chemical Name
1.	**1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
2.	**1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
3.	**1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
4.	**1-[4-(2-Pyridyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
5.	**1-[4-(3-Chlorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
6.	**1-[4-(2-Pyrimidyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
7.	**1-[4-(3,4-Dimethylphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**
8.	**1-[4-(Phenylpiperazin)-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane**

9. 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane

10. 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-2-(2,5-dioxopyrrolidin-1-yl)ethane

11. 1-[4-(3-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane

12. 1-[4-(4-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane

13. 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

14. 1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

15. 1-[4-(4-Chlorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

16. 1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

17. 1-[4-(2-Fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

18. 1-[4-(2-Methylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

19. 1-[4-(2-Pyridyl)piperazin-1-yl)-3-(2,6-dioxopiperidin-1-yl)propane

20. 1-[4- (3-Chlorophenyl)piperazin -1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

21. 1-[4-(3,4-Dimethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

22. 1-[4-(2-Pyrimidyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

23. 1-[4-(3-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

24. 1-[4-(4-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane

25. 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-4-(2,6-dioxopiperidin-1-yl)butane

26. 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-[2,5-dioxo-3-phenyl-pyrolidin-1-yl]propane

27. 1-[4-(Phenyl)piperidin-1-yl]-3-[2,5-dioxopyrolidin-1-yl]propane

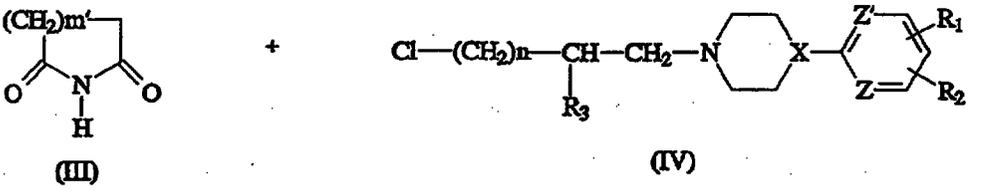
5. Detailed Description of the Invention

5a. Synthesis of the compounds of the invention

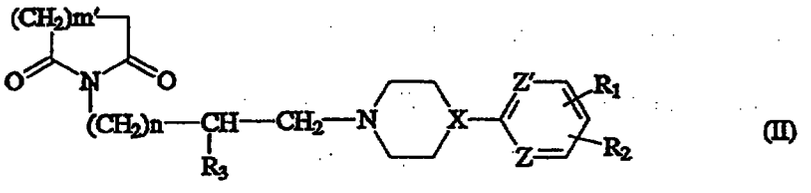
The compounds of the present invention may be prepared by one of the reaction sequences (Schemes I, II & III) shown below to yield compounds of Formula II with the R_1, R_2, R_3, R_4, R_5, R_6, m, n, Z, Z', Q and Y groups as defined above. The starting materials for Schemes I, II and III may be suitably adapted to produce the more general compounds of Formula I.

Scheme - I

Scheme-I shows the synthesis of compounds of the Formula II in which R_1, R_2, R_3, R_4, R_5, R_6, m', n, Z, Z', Q, X, and Y are as defined earlier. The preparation comprises condensing α,ω-dicarboximides of Formula III with 1-(4-arylpiperazin-1-yl)-ω-chloroalkanes of Formula IV, in the presence of a base and an organic solvent at a temperature ranging from 80-150°C for a period varying between 8-24 hours to produce the corresponding 1-(4-arylpiperazin-1-yl)-ω-[N-(α,ω-dicarboximido)]alkanes of the Formula II where R_1 and R_2 have the meanings given above. Phase transfer catalysts, preferably tetrabutylammonium bromide, are particularly useful in catalysing the reaction.



(III) (IV)

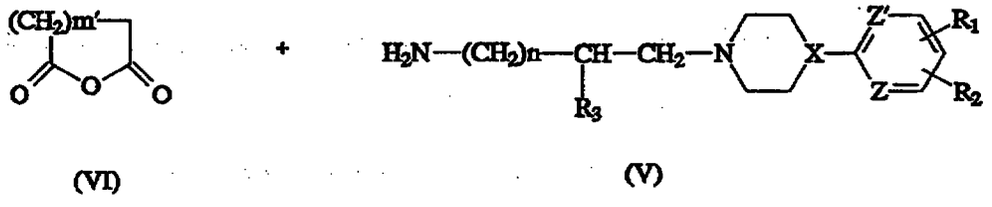


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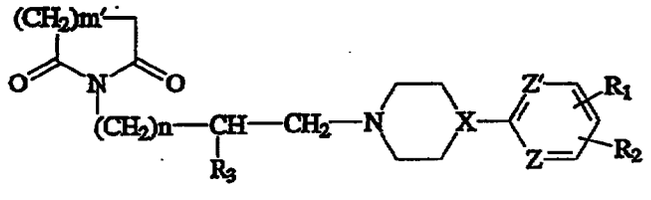
Scheme-I

Scheme - II

The compounds of Formula II can also be prepared by condensation of the piperazines of the Formula V with the anhydrides of Formula VI wherein R_1, R_2, R_3, Y, Z, Z', X, and m' are as defined above.



(VI) (V)

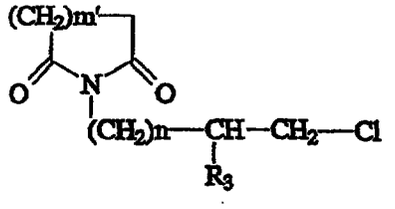


(II)

Scheme-II

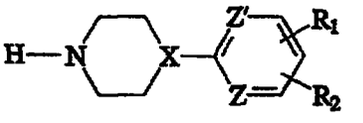
Scheme-III

The compounds of Formula II can also be prepared by alkylation of the α,ω-dicarboximide moiety with α,ω-dihaloalkanes followed by condensation of 1-(ω-haloalkyl)dicarboximide thus obtained (Formula VII) with 1-arylpiperazines (Formula VIII) as shown below, wherein R_1, R_2, R_3, Y, Z, Z', X, m' and n are as defined above. The reaction is preferably carried out in the presence of a base and an organic solvent at a temperature ranging from 60-100°C for a period varying between 10-24 hours to produce the corresponding 1-(4-arylpiperazin-1-yl)-ω-[N-(α,ω-dicarboximido)]alkanes of Formula II. Phase transfer catalysts, more preferably tetrabutylammonium bromide and potassium iodide, are useful in catalysing the reaction.

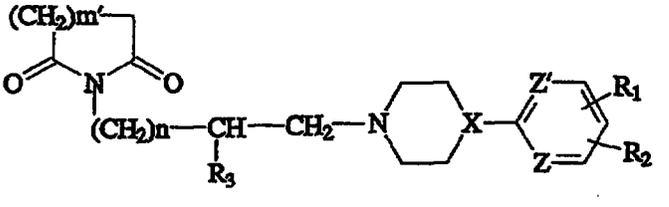


(VII)

+



(VIII)



(II)

Scheme-III

In the above Schemes, where specific bases, acids, solvents, phase transfer catalysts, etc., are mentioned, it is to be understood that other acids, bases, solvents, phase transfer catalysts, etc., known to those skilled in the art may also be used. Similarly, the reaction temperature and duration of the reactions may be adjusted according to the desired needs.

The starting piperazines of the Formulas IV, V and VIII are known in the art and may be synthesized by the procedures described in Kiritzy, J.A., et al., J. Med. Chem., 1978, V. 21, p. 1301 ; U.S. Patent No. 3,637,705 (Abbott, 1972); FR 2,179,491 (1973); Aggarwal S.K., et al., Ind. J. Chem., 1982, V.21B; pp. 435-439; and U.S. Patent No. 2,922,788 (Parcell, 1960).

5b. Pharmacological Testing Results

The affinity of the compounds of the invention for each subtype of α-adrenoceptor can be assessed by receptor binding assays (RBA's) described in the examples given below. It should be noted that the identification and characterization of the foregoing receptors is still in progress and that their types and subtypes are subject to review and refinement.

Receptor binding and in vitro functional assay studies described below indicated that the compounds of the present invention possess selective and potent α_{1A} adrenoceptor antagonistic activity over the α_{1B} and α_{1D} adrenoceptors. The present invention also provides a method to demonstrate the selective affinity of the compounds for prostatic tissues over vascular tissues. Further, the examples presented below describe a method to treat BPH in mammals wherein the test compounds alleviated pressure at dosages which did not result in significant change in blood

pressure. Several of the compounds of present invention demonstrated manifest selectivity for prostatic tissues in comparison to known compounds, such as terazosin, doxazosin, etc. The compounds of the present invention also lowered the blood pressure with prolonged duration of action. The compounds of the present invention have been demonstrated to be useful for treating warm blooded animals and mammals. These compounds can be administered orally or parenterally in suitable pharmaceutical compositions.

Preferred compounds of the invention are 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane (Compound No. 2), 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane (Compound No. 9), and 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane (Compound No. 13).

Pharmaceutically acceptable, non-toxic, acid addition salts of the compounds of the present invention having the utility of the free bases of Formulas I and II may be formed with inorganic or organic acids, by methods well known in the art and may be used in place of the free bases. Representative examples of suitable acids for formation of such acid addition salts are malic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene salicylic, methanesulfonic, ethane disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfamic, phosphoric, hydrobromic, sulfuric, cyclohexylsulfamic, hydrochloric and nitric acids.

The present invention also includes within its scope prodrugs of the compounds of Formulas I and II. In general, such prodrugs will be functional derivatives of these compounds which are readily converted in vivo into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

The invention also includes the enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts of these compounds, as well as metabolites having the same type of activity. The invention further includes pharmaceutical compositions comprising the molecules of Formula I and II, or prodrugs, metabolites, enantiomers, diastereomers, N-oxides, or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

In yet another aspect, the invention is directed to methods for selectively blocking α_{1A} receptors by delivering in the environment of said receptors, e.g., to the extracellular medium (or by administering to a mammal possessing said receptors), an effective amount of the compounds of the invention.

The invention will now be illustrated by the following non-limiting examples.

Preparation of 1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-[2,5-dioxopyrrolidin-1-yl]propane (Compound No. 1)

Scheme-I: A mixture of 2,5-dioxopyrrolidine (0.500 g, 5 mmol), 1-[4-(4-fluorophenyl)-piperazin-1-yl]-3-chloropropane (1.28 g, 5 mmol), potassium carbonate (0.502 g, 3.75 mmol) and tetrabutylammonium bromide (0.322 g, 1 mmol) in acetone (25 ml) was refluxed for 16 hours at 80°C with stirring. The solvent was evaporated off in vacuo and the residue was suspended in water (80 ml). The aqueous solution was extracted with chloroform (3x50 ml), and the

organic layers combined, washed with water (2x50 ml), dried over Na_2SO_4 and evaporated in vacuo to give the title compound. The product was purified by column chromatography over flash silica gel using chloroform-methanol (98:2) as eluent; yield 1.00 g (65%), oil.

Scheme-II: 1-amino-3-[4-(4-fluorophenyl)piperazin-1-yl]propane (0.700 g, 2.95 mmol) and succinic anhydride (0.295 g, 2.95 mmol) were refluxed in pyridine (10 ml) for 10 hours. Acetic anhydride (2 ml, excess) was added and the mixture was further refluxed for 5 hours. Solvent was removed in vacuo and the residue was suspended in water and extracted with chloroform (2x25 ml). Organic layers were combined, washed with water (2x25 ml), dried over Na_2SO_4 and concentrated. The compound was purified by column chromatography over flash silica gel using chloroform-methanol (98:2) as eluent; yield 0.436 g (46%), oil.

Scheme-III: A mixture of 1-chloro-3-(2,5-dioxopyrrolidin-1-yl) propane (1.54 g, 8.80 mmol), 1-(4-fluorophenyl)piperazine (1.58 g, 8.80 mmol), potassium carbonate (1.21 g, 8.80 mmol) and potassium iodide (0.146g, 0.88 mmol) in N,N-dimethylformamide (25 ml) was heated at 100°C for 18 hours. Solvent was evaporated under reduced pressure. Residue was shaken with water (25 ml), extracted with chloroform (2x25 ml), and the organic layers combined, washed with water (2x20 ml), dried over Na_2SO_4 and concentrated to give an oil which was purified by column chromatography over flash silica gel using chloroform-methanol (98:2) as eluent; yield 2.00g (71%), oil.

The hydrochloride salt of 1-[4-(4-fluorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)-propane (Compound No. 1) was formed in quantitative yield by the addition of ethereal hydrogen chloride solution to a methanolic solution of the free base and the resultant precipitate was collected by filtration, m.p 246-247°C.

Preparation of 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-[2,5-dioxopyrrolidin-1-yl]propane (Compound No. 2)

Scheme-I: A mixture of 2,5-dioxopyrrolidine (3.68 g, 37.24 mmol), 1-[4-(2-methoxyphenyl)-piperazin-1-yl]-3-chloropropane (10.0 g, 37.24 mmol), potassium carbonate (7.70 g, 55.8 mmol) and tetrabutylammonium bromide (2.38 g, 7.4 mmol) in acetone (100 ml) was refluxed for 12 hours at 80°C with stirring. The solvent was evaporated off in vacuo and the residue was taken up in water (80 ml). The aqueous solution was extracted with chloroform (3 x 50 ml) and the organic layers combined, washed with water (2 x 50 ml), dried over Na_2SO_4 and evaporated in vacuo to give the title compound. The product was purified by column chromatography over flash silica gel using chloroform-methanol (99:1) as eluent; yield 8.00 g (65%) in oil. The hydrochloride salt was prepared by the method described above; mp 199-202°C.

Scheme-II: A mixture of 1-chloro-3-(2,5-dioxopyrrolidin-1-yl) propane (28.00 gm, 159.5 mmol), 1-(2-methoxyphenyl)piperazin hydrochloride (36.45 g, 159.5 mmol), potassium carbonate (44.03 g, 319.0 mmol) and potassium iodide (1.58 g, 9.57 mmol) in N,N-dimethylformamide (115 ml) was heated at 80°C for 17 hours and the solvent was evaporated under reduced pressure. Residue was suspended in ethyl acetate (600 ml), washed with water (5 x 100 ml.) and dried over Na_2SO_4 and concentrated to give an oil which was purified by column chromatography over silica gel (100-200 mesh) using chloroform-methanol (99:2) as eluent; yield 55.1 g, (80%), oil. The hydrochloride salt of this product was formed in the manner described above; mp 199-202°C.

1-Chloro-3-(2,5-dioxopyrrolidin-1-yl)propane can be prepared by the reaction of 2,5-dioxopyrrolidine and 1-bromo-3-chloropropane in the presence of potassium carbonate and tetrabutylammonium bromide in acetone.

Preparation of 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-[2,5-dioxopyrrolidin-1-yl]butane (Compound No. 9)

Scheme-III: A mixture of 1-chloro-4-(2,5-dioxopyrrolidin-1-yl)butane (11.0 g, 58.04 mmol), 1-(2-methoxyphenyl)piperazine hydrochloride (12.99 g, 56.85 mmol), potassium carbonate (16.02 g, 116.09 mmol) and potassium iodide (0.577 g, 3.48 mmol) in N,N-dimethylformamide (45 ml) was stirred at 100°C for 18 hours. N,N-dimethylformamide was evaporated at reduced pressure and the residue was taken up in water (100 ml) and extracted with chloroform (2x100 ml). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 1-

[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane as an oil which was purified by column chromatography over silica gel (230-400 mesh) using chloroform-methanol (98:2) as eluent; yield 18.00 g, (92%), oil. Hydrochloride salt was prepared by the method described above; mp 218-220°C.

1-Chloro-4-(2,5-dioxopyrrolidin-1-yl)butane can be prepared by the reaction of 2,5-dioxopyrrolidine and 1-bromo-3-chlorobutane in the presence of potassium carbonate and tetrabutylammonium bromide in acetone.

Preparation of 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-[2,6-dioxopiperidin-1-yl)propane (Compound No. 13)

Scheme-I: A mixture of 2,6-dioxopiperidine (2.60 g, 23.02 mmol), 1-[4-(2-methoxyphenyl)-piperazin-1-yl]-3-chloropropane (6.18 g, 23.02 mmol), potassium carbonate (2.38 g, 17.27 mmol) and tetrabutylammonium bromide (1.48 g, 4.60 mmol) in acetone (80 ml) was refluxed for 16 hours at 80°C with stirring. The solvent was evaporated off in vacuo and the residue suspended in water (60 ml), extracted with chloroform (3x40 mmol) and the organic layers combined, washed with water (2.40 ml), dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the title compound. The product was purified by column chromatography over flash silica gel (230-400 mesh) using chloroform-methanol (98:1) as eluent; yield 3.58 g (45%), oil.

The hydrochloride salt was prepared in the quantitative yield by the method described above; m.p. 206-210°C.

Scheme-III: A mixture of 1-chloro-3-(2,6-dioxopiperidin-1-yl)propane (22.06 gm, 116.40 mmol), 1-(2-methoxyphenyl)piperazine (21.90 g, 114.06 mmol), potassium carbonate (16.06g, 116.40 mmol) and potassium iodide (1.16g, 6.98 mmol) in N,N-dimethylformamide (90 ml), was heated at 80°C for 17 hrs. and the solvent was evaporated under reduced pressure. Residue was dissolved in ethyl acetate (400 ml), washed with water (5 x 100 ml) and dried over Na_2SO_4 and concentrated to given an oil which was purified by column chromatography over silica gel (100-200 mesh) using chloroform-methanol (99:1) as eluent; yield 33.8 g, (86%), oil. The hydrochloride salt was prepared in the quantitative yield by the addition of excess ethereal hydrogen chloride solution to a methanolic solution of the free base and collected by filtration of the resultant precipitate; m.p. 206-210°C.

An illustrative list of the compounds of the invention which were synthesized by one or more of the above described methods is now given.

1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 246-247°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 199-202°C.

1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 218-220°C.

1-[4-(2-Pyridyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 261-262°C.

1-[4-(3-Chlorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 230-231°C.

1-[4-(2-Pyrimidyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 196-198°C.

1-[4-(3,4-Dimethylphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl) propane hydrochloride; m.p. 244-246°C.

1-[4-(Phenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 258-259°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane hydrochloride; m.p. 218-220°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-2-(2,5-dioxopyrrolidin-1-yl)ethane hydrochloride; m.p. 232-234°C.

1-[4-(3-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 199-201°C.

1-[4-(4-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane hydrochloride; m.p. 240-242°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)-propane hydrochloride; m.p. 206-210°C.

1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane; m.p. 200-202°C.

1-[4-(4-Chlorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 206-208°C.

1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 228-229°C.

1-[4-(2-Fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 215-216°C.

1-[4-(2-Methylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 206-207°C.

1-[4-(2-Pyridyl)piperazin-1-yl)-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 244-245°C.

1-[4-(3-Chlorophenyl)piperazin -1-yl]-3 -(2, 6-dioxopiperidin -1-yl)propane hydrochloride; m.p. 214-215°C.

1-[4-(3,4-Dimethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; low melting hygroscopic.

1-[4-(2-Pyrimidyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 195-196°C.

1-[4-(3-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 196-197°C.

1-[4-(4-Methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 218-220°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-4-(2,6-dioxopiperidin-1-yl)butane hydrochloride; m.p. 190-192°C.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxo-3-phenylpyrrolidin-1-yl]propane hydrochloride; m.p. 171-172°C.

1-[4-(Phenyl)piperadin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl]propane hydrochloride; m.p. 208-209°C.

All the melting points reported above are uncorrected and measured by an open capillary method using Buchi 535.

Receptor Binding Assay

In vitro receptor binding

Receptor binding assays (RBA's) were performed for native α_1-adrenoceptors. Rat submaxillary and rat liver membrane preparations were used to assess the affinity for α_{1A} and α_{1B} subtypes, respectively. Aliquots of membrane protein (100 - 200 mg) were incubated in a final volume of 250 ml assay buffer (50 mM Tris, 0.5 mM EDTA at pH 7.4) with 0.5 nM [^{3}H] prazosin for 60 mins at 28°C. Reaction was stopped by rapid filtration on Millipore filters. Filters were dried and bound radioactivity counted. Non-specific binding was determined in the presence

of 0.3 mM prazosin. Protein was assayed according to the method of protein estimation by Lowry, O.H. et al., J. Biol. Chem., V. 193, pp. 265-275 (1951). Results are listed in Table 1.

Table 1

Compound No.	RBA (Ki nM)		In Vitro Functional Assay (pK_B)			In Vivo BP	
	α_{1A}	α_{1B}	α_{1A}	α_{1B}	α_{1D}	Fall in mmHg	Duration in min.
Compound 1	>2500	1000	7.1	7.0	6.8	5.0	15.0
Compound 2	19	244	8.7	7.6	7.3	25	120.0
Compound 3	1500	1000	-	7.2	5.0	-	-
Compound 4	1660	2100	-	-	5.6	-	-
Compound 5	106	175	5.3	5.3	7.0	-	-
Compound 6	1140	>2500	4.7	5.3	6.5	-	-
Compound 7	450	282	6.4	6.7	6.5	-	-
Compound 8	57	590	7.5	-	6.6	-	-
Compound 9	1	35	9.0	8.0	8.3	46	>180
Compound 10	1600	2350	6.9	6.7	6.9	-	-
Compound 11	>2500	>2500	-	-	-	-	-

Compound 12	>2500	>2500	-	-	-	-	-
Compound 13	3	168	8.6	8.0	7.9	50.0	>180
Compound 14	67	192	8.4	7.4	7.1	20.0	60.0
Compound 15	520	201	6.7	6.0	6.2	-	-
Compound 16	345	765	6.5	-	6.9	-	-
Compound 17	21	396	8.0	7.1	7.9	50.0	120.0
Compound 18	9	267	8.2	5.5	8. 5	40.0	>150
Compound 19	164	>2500	6.4	-	6.7	-	-
Compound 20	22	113	7.5	-	7.6	-	-
Compound 21	2130	176	6.5	6.7	6.5	-	-
Compound 22	>2500	>2500	6.4	-	7.0	-	-
Compound 23	2170	940	-	-	-	-	-
Compound 24	<2500	>2500	-	-	-	-	-
Compound 25	1.6	7.5	-	-	-	-	-
Compound 26	30	600	-	-	-	-	-
Compound 27	1300	2000	-	-	-	-	-

In vitro Functional Studies

In vitro α_1-Adrenoceptor selectivity

In order to study selectivity of action of the present compounds towards different α-adrenoceptor subtypes, the ability of these compounds to antagonize α_1-adrenoceptor agonist induced contractile response of aorta (α_{1D}), prostate (α_{1A}) and spleen (α_{1B}) was studied. Aorta, prostate and spleen tissues were isolated from urethane anaesthetized (1.5 gm/kg) male wistar rats. Isolated tissues were mounted in organ bath containing Krebs Henseleit buffer of the following composition (mM): NaCl 118; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4 \cdot 7H_2O$ 1.2; $NaHCO_3$ 25; KH_2PO_4 1.2; glucose 11.5. Buffer was maintained at 37°C and aerated with a mixture of 95% O_2 and 5% CO^2. A resting tension of 2g (aorta) or 1 g (spleen and prostate) was applied to tissues. Contractile response was monitored using a force displacement transducer and recorded on chart recorders. Tissues were allowed to equilibrate for 2 hours. At the end of equilibration period, concentration response curves to norepinephrine (aorta) and phenylephrine (spleen and prostate) were obtained in the absence and presence of the tested compound (at concentrations of 0.1, 1 and 10 μM). Antagonist affinity was calculated and expressed as pK_B values in Table 1.

In vitro Receptor Selectivity

Selectivity of action of the present componds was tested against a range of different receptors, e.g., $ß_1$- and α_2-adrenergic, muscarinic cholinergic, serotoninergic (5-HT_{2A}), histaminergic (H_1), angiotensin II, endothelin (ET_A and $_B$,), as well as calcium and potassium channels. Rat aorta was used to study the effect of the compounds on 5-HT_{2A},-ET_A, calcium

and potassium channels. Angiotensin II receptor antagonistic activity was studied in rabbit aorta. Muscarinic cholinergic receptor and ET_B receptor antagonistic activity was studied in rat trachea, while guinea pig trachea was used to study H_1 receptor antagonistic activity. Electrically stimulated rat vas deferens was used to investigate the effect of α_2-adrenoceptors, while β_1-adrenoceptor antagonistic activity was studied using electrically stimulated rat ventricular strips. Results of this selectivity study is shown in (Table 2).

Table 2

Selectivity Study

Receptor Type pK_B	Compound 2	Compound 9	Compound 13
α_2-adrenergic	NE	NE	NE
ß-adrenergic	4.2	-	5.1
Muscarinic	5.0	5.0	5.5
H_1-Histaminergic	5.3	5.4	5.7
5-HT_{2A}	7.6	7.9	8.0
ET_A	-	4.3	4.3
ET_B	-	5.4	4.9
Angiotensin II	-	5.6	5.3
Calcium Channel	NE	NE	NE
Potassium Channel	NE	NE	5

NE : No effect
(-) : Not tested

In vivo Antihypertensive Effect

Antihypertensive effect of selected compounds according to the invention were studied for their ability to lower blood pressure in anaesthetized and conscious normotensive and spontaneously hypertensive rats via intravenous, oral and intraduodenal routes. Results are shown in Tables 1 and 3.

Anaesthetized Normotensive Rats

Intravenous Route

Male wistar rats were anaesthetized with urethane (2.5 g/kg). Femoral vein and carotid artery were cannulated. Blood pressure and heart rate were recorded using Statham pressure transducer. Data was recorded on Grass polygraph as well as using online data acquisition system (Buxco AT). Intravenously administered compounds of the invention were initially tested at 0.3 mg/kg over a period of 3 hours for their effect on blood pressure and the results are shown in Table 1. For a select few of the compounds, the blood pressure lowering effect upon intravenous administration was also studied at dosages of 0.03, 0.1, 0.3, and 1 mg/kg.

Intraduodenal Route

Male wistar rats were fasted for 18 hours. Rats were anaesthetized with urethane. Femoral vein and carotid artery were cannulated. A catheter was placed in the duodenum following lapratomy. The compounds of the present invention (at dosages of 0.3, 1, 3 and 10 mg/kg) were administered in the duodenum and blood pressure was monitored for 3 hours. Results are recorded in Table 3.

Table 3

Effect on mean arterial pressure in anaesthetized normotensive rats.

Compound No.	Dose (mg/kg)	Mean Arterial Pressure (% Change from basal)	Duration of Action
Compound 2	1	-19	> 2.5 hr
	3	-43	> 2.5 hr
	10	-42	> 2.5 hr
Compound 9	1	-19	> 3.0 hr
	3	-53	> 3.0 hr
	10	-57	> 3.0 hr
Compound 13	1	-32	< 3.0 hr
	3	-40	> 3.0 hr
	10	-42	> 3.0 hr

Conscious Normotensive Rats

Femoral artery of normotensive male wistar rats, maintained on an overnight light diet, were catheterized under pentobarbitone anaesthesia (35 mg/kg). Femoral artery catheter was exteriorized through the neck region for blood pressure recording. Compounds of the present invention (at dosages of 0.1, 0.3 and 1 mg/kg) were administered 24 hours following surgery through oral route in the form of gavage to overnight fasted rats. Blood pressure and heart rate were recorded with the help of Statham pressure transducer on a Grass polygraph and the results are shown in Table 4.

Table 4

Effect on systolic blood pressure in conscious spontaneously hypertensive rats

Compound No.	Dose (mg/kg)	Systolic Pressure (% Change from basal) (at 6 hours)
Compound 2	1	- 7.0
	3	- 12.0
	10	- 13.0
	30	- 17.0
Compound 9	1	- 0.4
	3	- 7.0
	10	-24.0
	30	-25.0
Compound 13	1	- 7.0
	3	- 18.0
	10	- 19.0
	30	- 14.0

Conscious Spontaneously Hypertensive Rats

Spontaneously hypertensive rats weighing between 250 - 300 g were used in this study. Rats were fasted overnight. Blood pressure was monitored from tail artery using semi-automatic noninvasive blood pressure monitoring apparatus. Compounds of the present invention (at dosages of 1, 3, 10, and 30 mg/kg) were administered orally. Blood pressure was monitored prior to and 1.5, 4, 6 and 24 hours after drug administration. Results are shown in Table 5.

Table 5

Effect on mean arterial blood pressure in conscious freely moving normotensive rats.

Compound No.	Dose (mg/kg)	Mean Arterial Pressure (% Change from basal)
Compound 2	3	-14
	10	-10
Compound 9	1	-4
	10	-11
Compound 13	1	-5
	3	-10

In Vivo Selectivity Study

Male mongrel dogs (12 - 20 Kg) were anaesthetized with pentobarbitone sodium (35 mg/kg, iv). Trachea was intubated for artificial respiration. Femoral artery and femoral vein were cannulated for recording blood pressure and for administration of drug solutions, respectively. Blood pressure was recorded on a polygraph through a pressure transducer. A paramedian incision was made lateral to the penis and the bladder was exposed. Urine was drained through a cannula put directly into the bladder and it was guided into the urethra gently and was placed at the prostatic urethra. Balloon was inflated with 2 cc air and its placement was confirmed by digital pressure. Intraurethral pressure was recorded on the polygraph through a pressure transducer. Graded dose response relationship of phenylephrine (1-16 μg/kg, iv) was obtained on prostatic pressure and blood pressure, prior to administration of the compounds of

the present invention. Compounds 2, 9, and 13 (at dosages of 0.01, 0.03, 0.1, and 0.3 mg/kg) were administered intravenously 10 min before obtaining phenylephrine dose response curves. Results were analyzed and pseudo pK_B values were calculated as described in Kenny et al (1996). Results are shown in Table 6.

Table 6

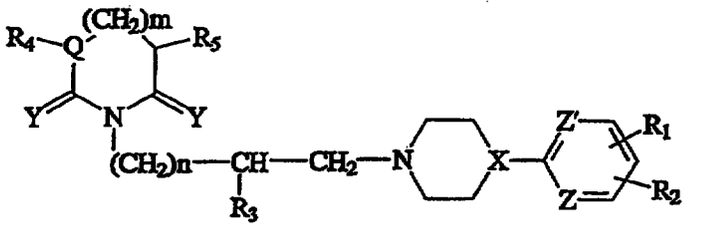
Effect on blood pressure and intraurethral pressure in anaesthetized dogs

	pseudo pK_B	
	Blood Pressure	Intraurethral Pressure
Compound 2	6.9	7.60
Compound 9	7.4	7.9
Compound 13	7.1	8.1

While the invention has been described by reference to specific embodiments, this was for purposes of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are deemed to be within the scope of the invention.

CLAIMS

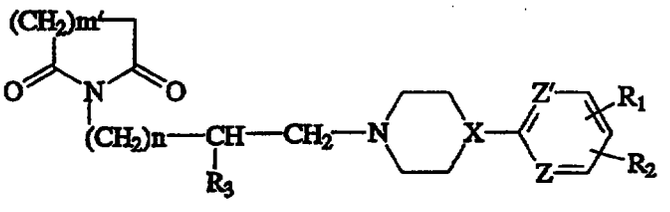
1. A compound having the structure of Formula I



(I)

its pharmaceutically acceptable salts, esters, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X, Z, and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring, except that R_1 is H, R_2 is H, Cl or CF_3, R_3, R_4 and R_5 = H, Y = O and Q = CH when m=0 and n=1; and also except that R_1 is H, R_2 is OCH_3, R_3, R_4 and R_5 = H, Y=O, Q=CH when m=0 and n=2.

2. The compound of claim 1 having the structure of Formula II



(II)



wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4, except that R_1 is H, R_2 is H, Cl or CF_3 and R_3 is H when m' = 1 and n = 1; and also except that R_1 is H, R_2 is OCH_3 and R_3 is H when m' = 1 and n = 2.

3. The compound of claim 1 which is 1-[4-(4-fluorophenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

4. The compound of claim 1 which is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

5. The compound of claim 1 which is 1-[4-(2-pyridyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl) propane or its hydrochloride salt.

6. The compound of claim 1 which is 1-[4-(2-pyrimidyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

7. The compound of claim 1 which is 1-[4-(3,4-dimethylphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

8. The compound of claim 1 which is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-2-(2,5-dioxopyrrolidin-1-yl)ethane or its hydrochloride salt.

9. The compound of claim 1 which is 1-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

10. The compound of claim 1 which is 1-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

11. The compound of claim 1 which is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.



12. The compound of claim 1 which is 1-[4-(4-fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

13. The compound of claim 1 which is 1-[4-(4-chlorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

14. The compound of claim 1 which is 1-[4-(3-trifluoromethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

15. The compound of claim 1 which is 1-[4-(2-fluorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

16. The compound of claim 1 which is 1-[4-(2-methylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

17. The compound of claim 1 which is 1-[4-(2-pyridyl)piperazin-1-yl)-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

18. The compound of claim 1 which is 1-[4-(3-chlorophenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

19. The compound of claim 1 which is 1-[4-(3,4-dimethylphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

20. The compound of claim 1 which is 1-[4-(2-pyrimidyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

21. The compound of claim 1 which is 1-[4-(3-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

22. The compound of claim 1 which is 1-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

* C L M S *

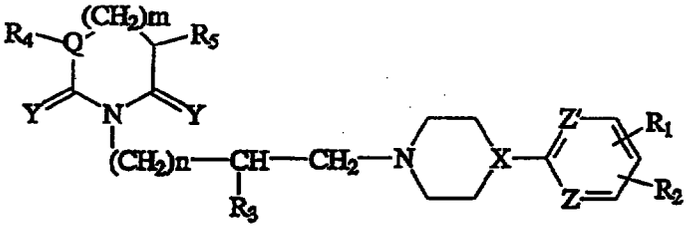
23. The compound of claim 1 which is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,6-dioxopiperidin-1-yl)butane or its hydrochloride salt.

24. The compound of claim 1 which is 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-[2,5-dioxo-3-phenyl-pyrolidin-1-yl]propane or its hydrochloride salt.

25. The compound of claim 1 which is 1-[4-(Phenyl)piperidin-1-yl]-3-[2,5-dioxopyrolidin-1-yl]propane or its hydrochloride salt.

26. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

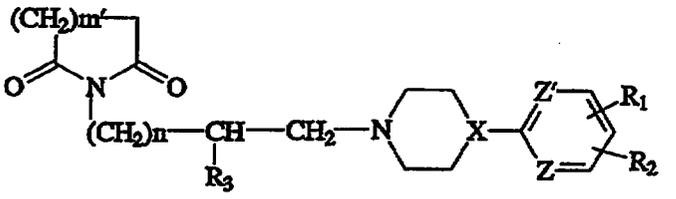
27. A method of selectively antagonizing α_1-adrenergic receptors in a mammal comprising administering to said mammal a compound having the structure of Formula I



(I)

its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X , Z, and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring.

28. The method of claim 27 wherein said compound has the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4.

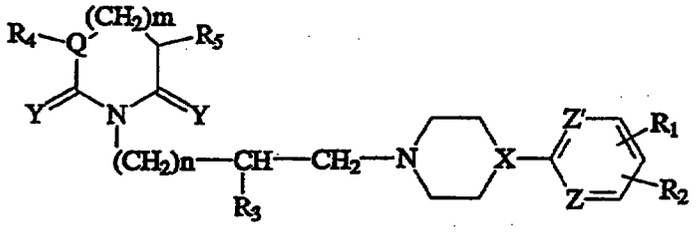
29. The method of claim 28 wherein said compound is 1-[4-(2-methoxy-phenyl)piperazin-1yl]-3-(2,5-dioxopyrrolidin-1-yl) propane or its hydrochloride salt.

30. The method of claim 28 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane or its hydrochloride salt.

31. The method of claim 28 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

* C L M S *

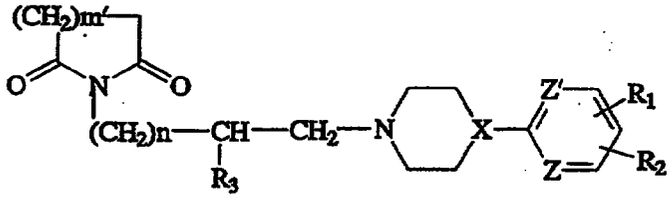
32. A method for treating benign prostatic hypertrophy in a mammal comprising administering to said mammal a compound of the structure of Formula I



(I)

its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X Z, and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring.

33. The method of claim 32 wherein said compound has the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4.

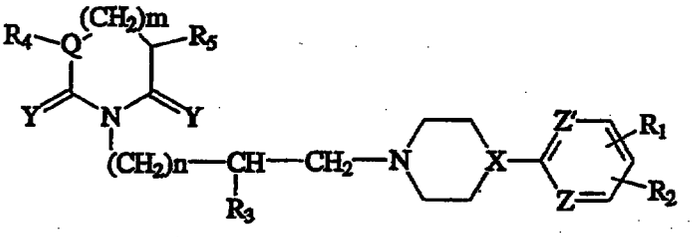


34. The method of claim 33 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

35. The method of claim 33 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane or its hydrochloride salt.

36. The method of claim 33 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

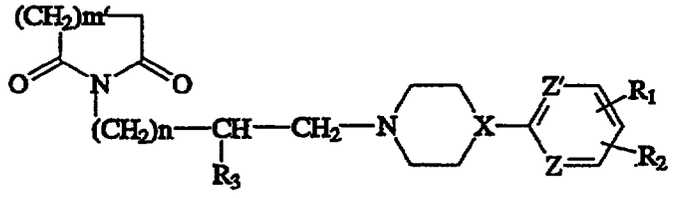
37. A method for treating vascular disease, congestive heart failure, or hypertension in a mammal comprising administering to said mammal a compound of the structure of Formula I



(I)

its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X, Z, and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring.

38. The method of claim 37 wherein said compound has the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4.

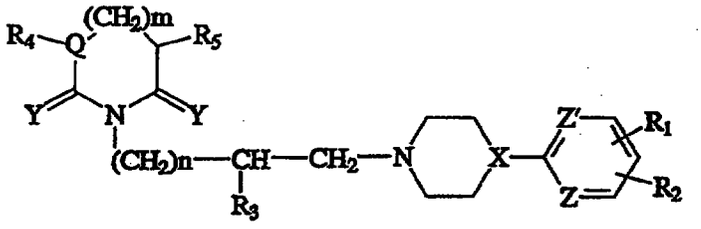
39. The method of claim 38 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,5-dioxopyrrolidin-1-yl)propane or its hydrochloride salt.

40. The method of claim 33 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-4-(2,5-dioxopyrrolidin-1-yl)butane or its hydrochloride salt.

41. The method of claim 33 wherein said compound is 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane or its hydrochloride salt.

* C L M S *

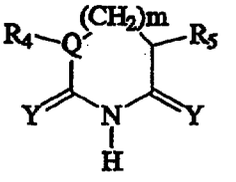
42. A method for making a compound having the structure of Formula I



(I)

its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X, Z and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring,

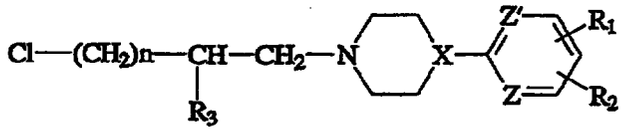
which comprises reacting a compound having the structure of Formula III'



(III')

* C L M S *

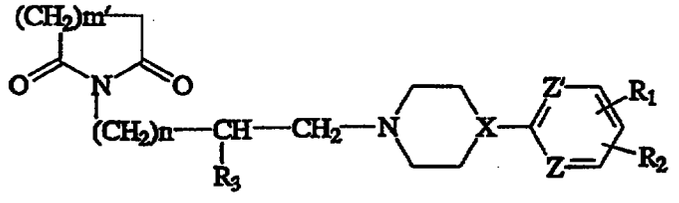
with a compound having the structure of Formula IV



(IV)

thereby to produce the compound of Formula I.

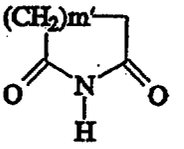
43. The method of claim 42 for producing a compound having the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4,

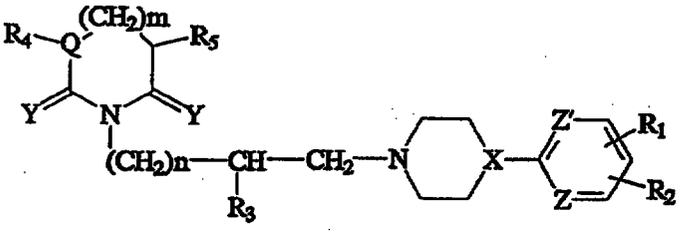
which comprises reacting a compound having the structure of Formula III



(III)

with said compound of Formula IV.

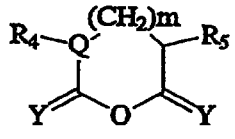
44. A method for making a compound having the structure of Formula I



(I)

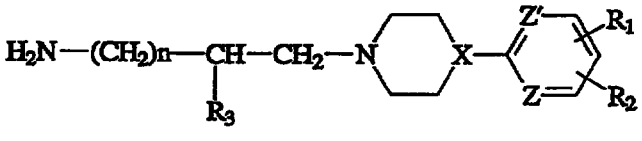
its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X, Z and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring,

which comprises reacting a compound having the structure of Formula VI'



(VI')

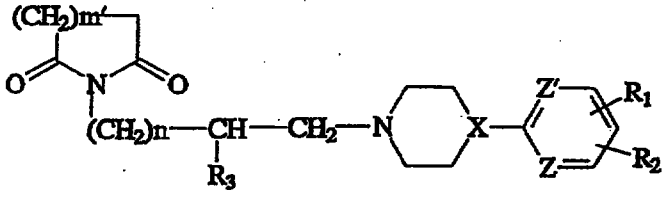
with a compound having the structure of Formula V



(V)

thereby to produce the compound of Formula I.

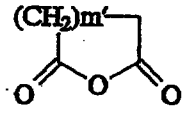
45. The method of claim 44 for producing a compound having the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4,

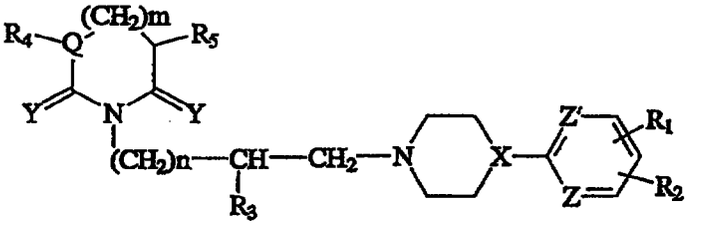
which comprises reacting a compound having the structure of Formula VI



(VI)

with said compound of Formula V.

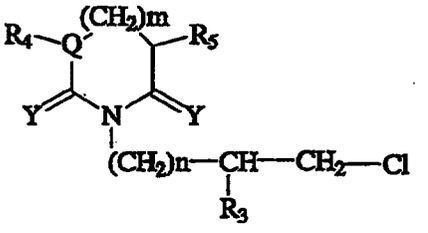
46. A method for making a compound having the structure of Formula I



(I)

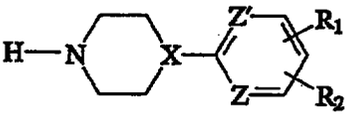
its pharmaceutically acceptable salts, esters, amides, enantiomers, diastereomers, N-oxides, amides, prodrugs, or metabolites, wherein Y is O or S; Q, X, Z and Z' are independently CH or N; m=0-3; n= 0-4; R_1, R_2 are independently selected from: H, F, Cl, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; R_3 is H, R_6, OH or OR_6; R_6 is a substituted or unsubstituted alkyl chain containing 1-6 carbon atoms; and R_4, R_5 are H, C_{1-3} alkyl, substituted or unsubstituted phenyl, or a 5-membered spiro ring,

which comprises reacting a compound having the structure of Formula VII'



(VII')

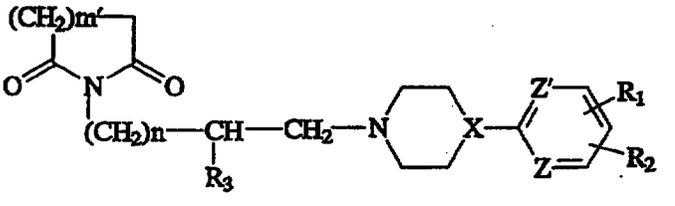
with a compound having the structure of Formula VIII



(VIII)

thereby to produce the compound of Formula I.

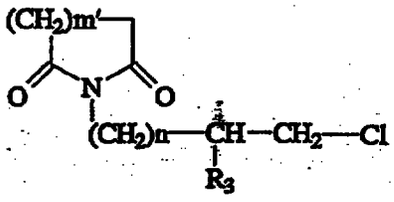
47. The method of claim 46 for producing a compound having the structure of Formula II



(II)

wherein n, X, Z, Z', R_1, R_2 and R_3 are as defined for Formula I and m' = 1-4,

which comprises reacting a compound having the structure of Formula VII.



(VII)

with said compound of Formula VIII.