NOVEL SUBSTITUTED PYRIDINO ARYLPIPERAZINES USEFUL IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

FIELD OF THE INVENTION

This invention relates to a series of pyridino arylpiperazine derivatives, pharmaceutical compositions containing them as well as methods of their use. The compounds of the invention selectively inhibit binding to the $\alpha 1_a$ adrenergic receptor, receptor which has been implicated in benign prostatic hyperplasia. In addition, compounds of the invention reduce intraurethral pressure in an in vivo model. As such the compounds are potentially useful in the treatment of this disease.

BACKGROUND

Benign prostatic hyperplasia (BPH), a nonmalignant enlargement of the prostate, is the most common benign tumor in men. Approximately 50% of all men older than 65 years have some degree of BPH and a third of these men have clinical symptoms consistent with bladder outlet obstruction (Hieble and Caine, 1986). In the U.S., benign and malignant diseases of the prostate are responsible for more surgery than diseases of any other organ in men over the age of fifty.

There are two components of BPH, a static and a dynamic component. The static component is due to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of urine from the bladder. The dynamic component is due to increased smooth muscle tone of the bladder neck and the prostate itself (which interferes with emptying of the bladder) and is regulated by alpha 1 adrenergic receptors ($\alpha 1$-ARs). The medical treatments available for BPH address these components to varying degrees, and the therapeutic choices are expanding.

Surgical treatment options address the static component of BPH and include transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), open prostatectomy, balloon dilatation, hyperthermia, stents and laser ablation. TURP is the preferred treatment for patients with BPH and approximately 320,000 TURPs were performed in the U.S. in 1990

at an estimated cost of $2.2 billion (Weis et al., 1993). Although an effective treatment for most men with symptomatic BPH, approximately 20 - 25% of patients do not have a satisfactory long-term outcome (Lepor and Rigaud, 1990). Complications include retrograde ejaculation (70-75% of patients), impotence (5-10%), postoperative urinary tract infection (5-10%), and some degree of urinary incontinence (2-4%) (Mebust et al., 1989). Furthermore, the rate of reoperation is approximately 15-20% in men evaluated for 10 years or longer (Wennberg et al., 1987).

Apart from surgical approaches, there are some drug therapies which address the static component of this condition. Finasteride (Proscar®, Merck), is one such therapy which is indicated for the treatment of symptomatic BPH. This drug is a competitive inhibitor of the enzyme 5α-reductase which is responsible for the conversion of testosterone to dihydrotestosterone in the prostate gland (Gormley et al., 1992). Dihydrotestosterone appears to be the major mitogen for prostate growth, and agents which inhibit 5α-reductase reduce the size of the prostate and improve urine flow through the prostatic urethra. Although finasteride is a potent 5α-reductase inhibitor and causes a marked decrease in serum and tissue concentrations of dihydrotestosterone, it is only moderately effective in treating symptomatic BPH (Oesterling, 1995). The effects of finasteride take 6-12 months to become evident and for many men the clinical improvement is minimal (Barry, 1997).

The dynamic component of BPH has been addressed by the use of adrenergic receptor blocking agents (α1-AR blockers) which act by decreasing the smooth muscle tone within the prostate gland itself. A variety of α1-AR blockers (terazosin, prazosin, and doxazosin) have been investigated for the treatment of symptomatic bladder outlet obstruction due to BPH, with terazosin (Hytrin™, Abbott) being the most extensively studied. Although the α1-AR blockers are well-tolerated, approximately 10-15% of patients develop a clinically adverse event (Lepor, 1995). The undesirable effects of all members of this class are similar, with postural hypotension

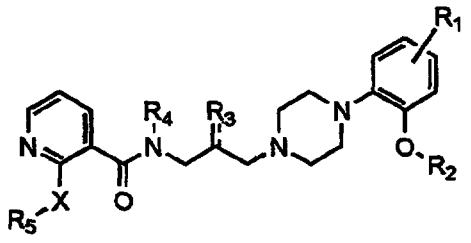
being the most commonly experienced side effect (Lepor et al., 1992). In comparison to the 5α-reductase inhibitors, the α1-AR blocking agents have a more rapid onset of action (Steers, 1995). However, their therapeutic effect, as measured by improvement in the symptom score and the peak urinary flow rate, is moderate. (Oesterling, 1995)

The use of α1-AR antagonists in the treatment of BPH is related to their ability to decrease the tone of prostatic smooth muscle, leading to relief of the obstructive symptoms. Adrenergic receptors are found throughout the body play a dominant role in the control of blood pressure, nasal congestion, prostrate function and other processes (Harrison et al., 1991). However, there are a number of cloned α1-AR receptor subtypes: $\alpha1_a$-AR, $\alpha1_b$-AR and $\alpha1_d$-AR (Bruno et al., 1991; Forray et al., 1994; Hirasawa et al., 1993; Ramarao et al., 1992; Schwinn et al., 1995; Weinberg et al., 1994). A number of labs have characterized the α1-ARs in human prostate by functional, radioligand binding, and molecular biological techniques (Forray et al., 1994; Hatano et al., 1994; Marshall et al., 1992; Marshall et al., 1995; Yamada et al., 1994). These studies provide evidence in support of the concept that the $\alpha1_a$-AR subtype comprises the majority of α1-ARs in human prostatic smooth muscle and mediates contraction in this tissue. These findings suggest that the development of a subtype-selective α1a-AR antagonist might result in a therapeutically effective agent with reduced side effects for the treatment of BPH.

SUMMARY OF THE INVENTION

The compounds of this invention selectively bind to the $\alpha1_a$-AR receptor, antagonize the activity of said receptor and are selective for prostate tissue over aortic tissue. As such, these represent a viable treatment for BHP without the side effects associated with known α1-AR antagonists.

The invention includes compounds of Formula I



I

wherein:

R_1 is hydrogen, halogen, C_{1-5}alkoxy, hydroxyl, or C_{1-5}alkyl;

R_2 is C_{1-6}alkyl, substituted C_{1-6}alkyl
where the alkyl substituents are independently selected from
one or more halogens,
phenyl,
substituted phenyl
where the phenyl substituents are independently selected from
one or more members of the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl,
phenylC_{1-5}alkyl,
or substituted phenylC_{1-5}alkyl
where the phenyl substituents are independently selected from
one or more members of the group consisting of C_{1-5}alkyl, halogen, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl;

R_3 is hydrogen, hydroxy or C_{1-5}alkoxy if the hashed line is absent or is oxygen if the hashed line is present;

R_4 is hydrogen, C_{1-5}alkyl, phenylC_{1-5}alkyl or substituted phenylC_{1-5}alkyl
where the phenyl substitutents are independently selected from
one or more members of the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl;

R_5 is C_{1-6}alkyl,
substituted C_{1-6}alkyl
where the alkyl substitutents are independently selected from
one or more halogens,
phenyl,
substituted phenyl
where the phenyl substitutents are independently selected from
one or more members of the group consisting of C_{1-6}alkyl,
hydrogen, halogen, hydroxy, C_{1-6}alkyl,
substituted C_{1-6}alkyl
where the alkyl substitutents are independently
selected from one or more halogens,
C_{1-5}alkoxy, amino, C_{1-5}alkylamino, diC_{1-5}alkylamino,
C_{1-5}alkylcarbonyl, C_{1-5}alkoxycarbonyl, arylcarbonyl, nitrile,
aminosulfonyl, C_{1-5}alkylsulfonyl, phenylsulfonyl, and
substituted phenylsulfonyl
where the phenyl substitutents are independently
selected from one or more members of the
group consisting of C_{1-6}alkyl hydrogen,
halogen, hydroxy and nitro;
phenylC_{1-5}alkyl,
substituted phenylC_{1-5}alkyl
where the phenyl substitutents are independently selected from
one or more members of the group consisting of C_{1-6}alkyl
hydrogen, halogen, hydroxy, C_{1-6}alkyl, substituted
C_{1-6}alkyl
where the alkyl substitutents are independently
selected from one or more halogens,
C_{1-5}alkoxy, amino, C_{1-5}alkylamino, diC_{1-5}alkylamino,
C_{1-5}alkylcarbonyl, C_{1-5}alkoxycarbonyl, and nitro;

X is oxygen, sulfur or NH;

pharmaceutically acceptable salts thereof;

and stereoisomers, racemic mixtures, as well as enantiomers thereof.

In addition this invention contemplates pharmaceutical compositions containing an effective dose of compounds of Formula I. Still further this invention contemplates methods of treating diseases associated with the α-1_a adrenergic receptor consisting of administering an effective dose of a compound of Formula I to a mammal. This invention also contemplates a method of treating benign prostatic hyperplasia consisting of administering an effective dose of a compound of Formula I to a mammal.

DETAILED DESCRIPTION OF THE INVENTION

The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are defined. "HBSS" refers to Hank's Balanced Salt Solution. "Independently" means that when there are more than one substituent, the substitutents may be different. The term "alkyl" refers to straight, cyclic and branched-chain alkyl groups and "alkoxy" refers O-alkyl where alkyl is as defined supra. "DMAP" refers to dimethylaminopyridine, "HOBT" refers to hydroxybenzotriazole hydrate, and "EDCI" refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The term "HATU" refers to O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetrametyluronium hexafluorophosphate and the symbol "Ph" refers to phenyl, and "aryl" includes mono and fused aromatic rings such as phenyl and naphthyl. The symbol "ES" refers to electrospray and the symbol "MS" refers to mass spectrum. Some of the compounds of Formula I include a chiral carbon atom. Therefore those compounds may be prepared as stereoisomers, racemic mixtures or pure enantiomers. All stereoisomers, pure enantiomers and racemic mixtures are considered to be within the scope of this invention.

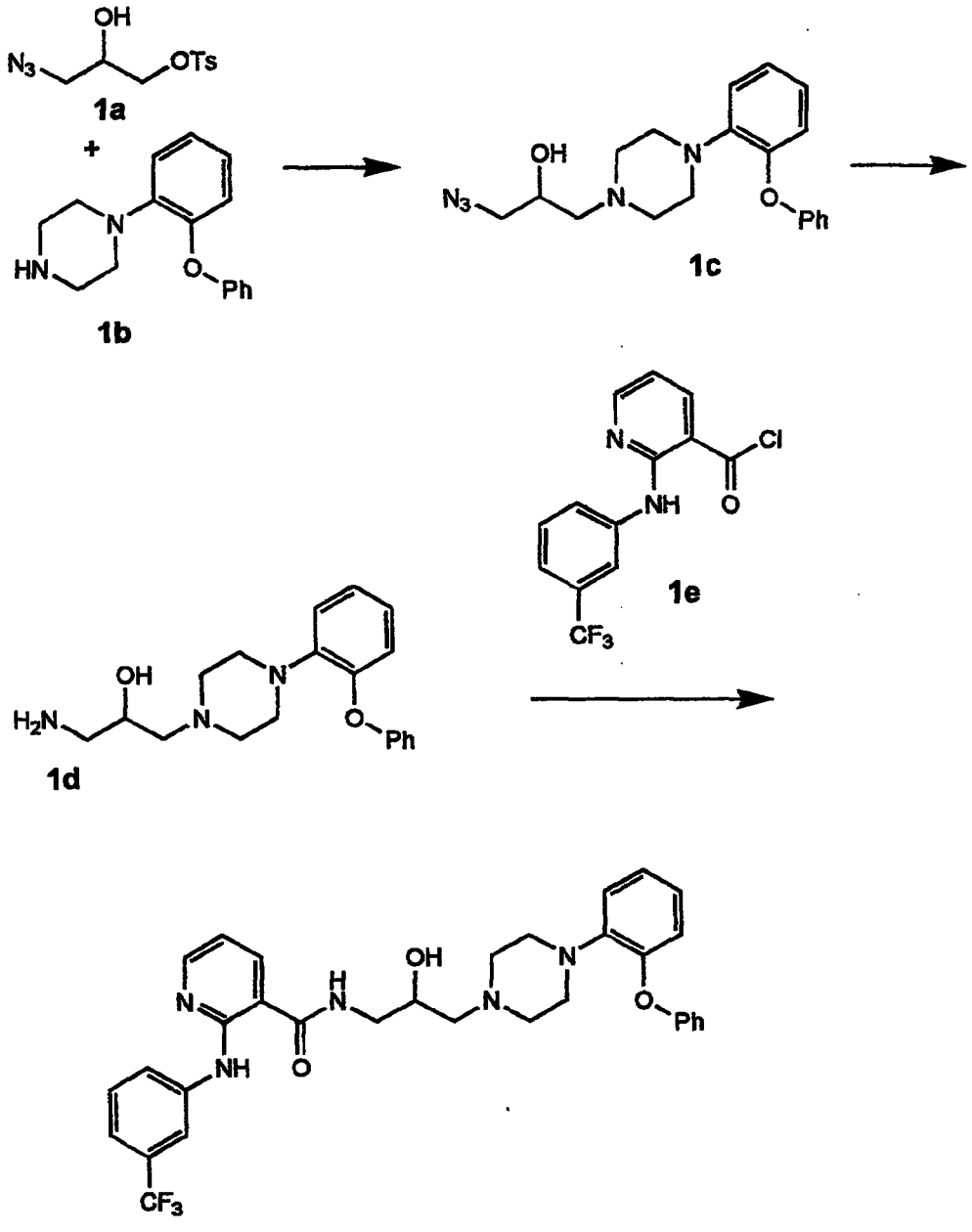
The compounds of the invention may be prepared by the following schemes, where some schemes produce more than one embodiment of the invention. In those cases, the choice of scheme is a matter of discretion which is within the capabilities of chemists.

A compound of Formula I where X is NH, R_1 is hydrogen, R_2 is phenyl, R_3 is hydroxy, R_4 is hydrogen, and R_5 is 3-trifluoromethylphenyl may be prepared using Scheme 1. 1-Azido-3-(p-toluenesulfonyloxy)propan-2-ol 1a, is heated at about 100 °C with an appropriately substituted piperazine derivative, 1b for about 2-5 days to give the azide 1c. This azide is treated with Pd/C and H_2 (50 psi) in an inert solvent over 16 h to give the free amine 1d. This amine is treated with a 3-acyl-2-substituted pyridine derivative, such as 2-[(3-trifluoromethylphenyl)amino]-3-pyridinecarbonyl chloride, 1e, DMAP and N,N-diisopropylethylamine in methylene chloride at about room temperature for 2-16 h to give the desired compound of Formula I. This scheme may be used to prepare a number of compounds of Formula I. For example, to prepare compounds where R_1 and R_2 vary, simply replace the illustrated 1b with any known substituted piperazines. Although the illustrated product was prepared from the racemic azide 1a, the pure enantiomers of this azide are known and can be used in this scheme. To prepare compounds where R_5 is other than substituted phenyl, replace the acyl pyridine derivative 1e with another acyl pyridine. For example to prepare a compound where R_5 is phenylmethyl, replace the illustrated 1e with 2-[(phenylmethyl)amino]-3-pyridinecarbonyl chloride. To prepare compounds where X is other than NH, replace the amino substituted acylpyridine with a thio or an oxy substituted pyridine. For example to prepare a compound where X is sulfur, R_1 is hydrogen, R_2 is phenyl, R_3 is hydroxy, R_4 is hydrogen, and R_5 is phenyl, replace the illustrated 1e with 2-(phenylthio)pyridine -3-carboxylic acid chloride.

To prepare compounds where R_3 is $C_{1\text{-}5}$alkoxy replace starting material 1c with 1-[1-azido-2-methoxypropan-1-yl]-4-[2-isopropoxyphenyl]piperazine and carry out the remaining steps of the scheme.

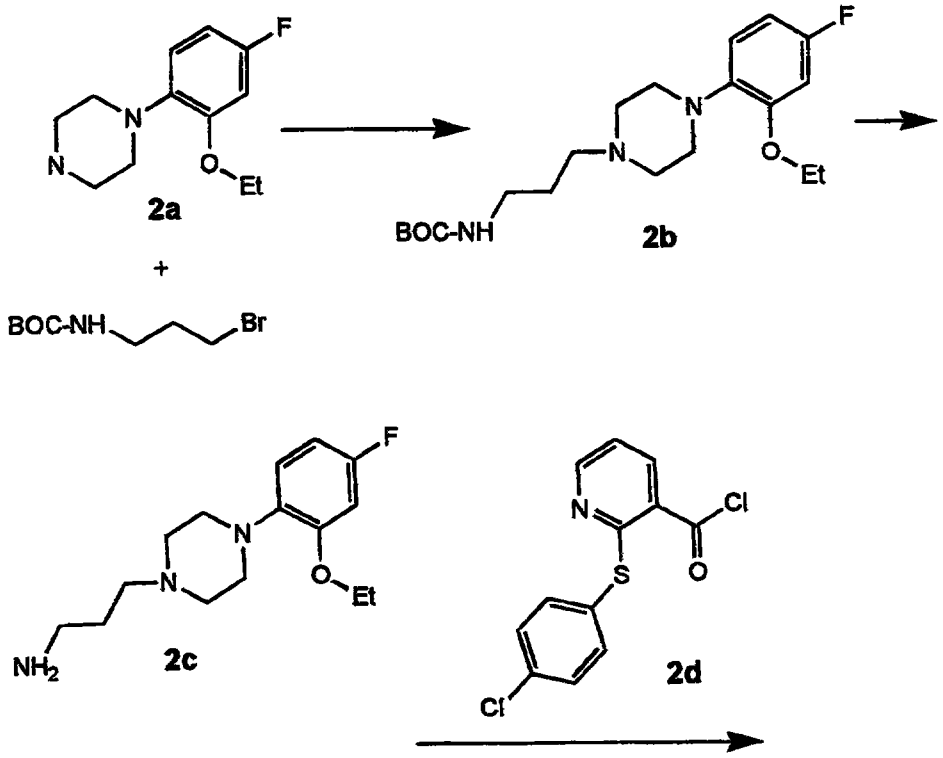
Compounds where R_3 is carbonyl may be prepared by treating the products of Scheme 1 with an oxidizing agent such as the Swern's reagent (formed from oxalyl chloride and DMSO) at -78 °C to room temperature over 30 min to 1h.

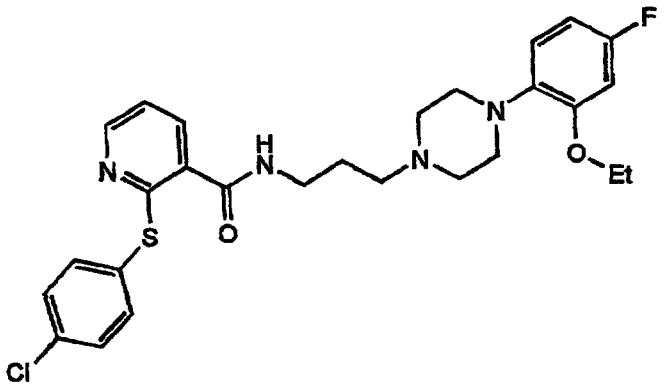
Scheme 1



Scheme 2 may be used to prepare compounds of Formula I where X is sulfur, R_1 is fluoro, R_2 is ethyl, R_3 is hydrogen, R_4 is hydrogen, and R_5 is 4-chlorophenyl. An appropriately substituted piperazine derivative 2a is treated with N-BOC protected 3-bromopropylamine and cesium carbonate in acetonitrile at reflux for 16 h to give the substituted piperazine derivative 2b. This derivative is converted to the free amine, 2c, by treatment with TFA and methylene chloride at room temperature over 2-6 h. Derivative 2c is coupled with a substituted acyl pyridine derivative 2d using DMAP, and N,N-diisopropylethylamine in methylene chloride at about room temperature for 2-6 h to give the desired compound of Formula I. As described in Scheme 1, Scheme 2 may be modified to give many compounds of Formula I.

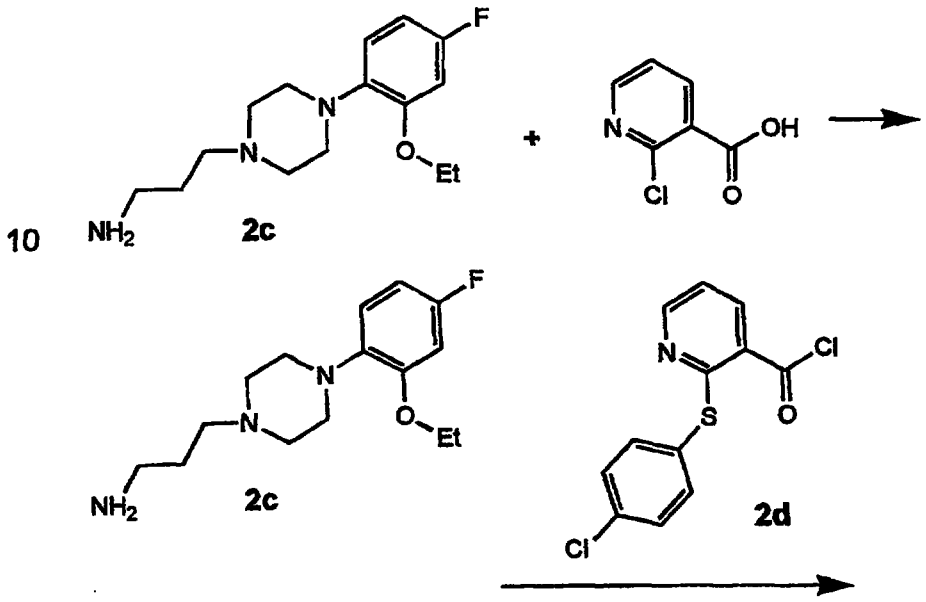
Scheme 2

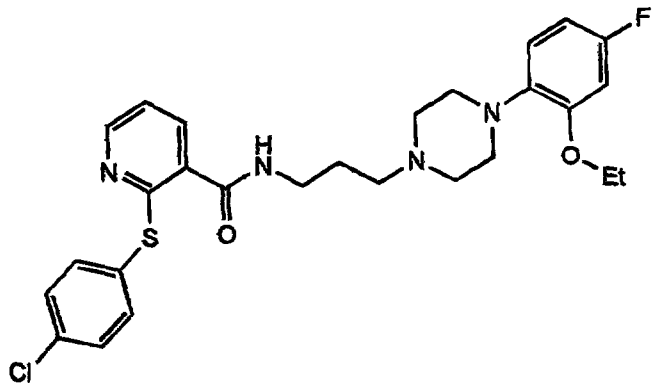




Another method of preparing compounds of the invention is illustrated by Scheme 3. Treatment of derivative 2c and 2-chloronicotinic acid with HOBT, DMAP, EDCI and N,N-diisopropylethylamine in methylene chloride at about room temperature for 2-6 h gives the chloropyridine 3a. Treatment of this derivative with an aromatic alcohol such as 3b gives a compound of the invention where X is oxygen, R_1 is fluoro, R_2 is ethyl, R_3 is hydrogen, R_4 is hydrogen, and R_5 is 4-methylphenyl.

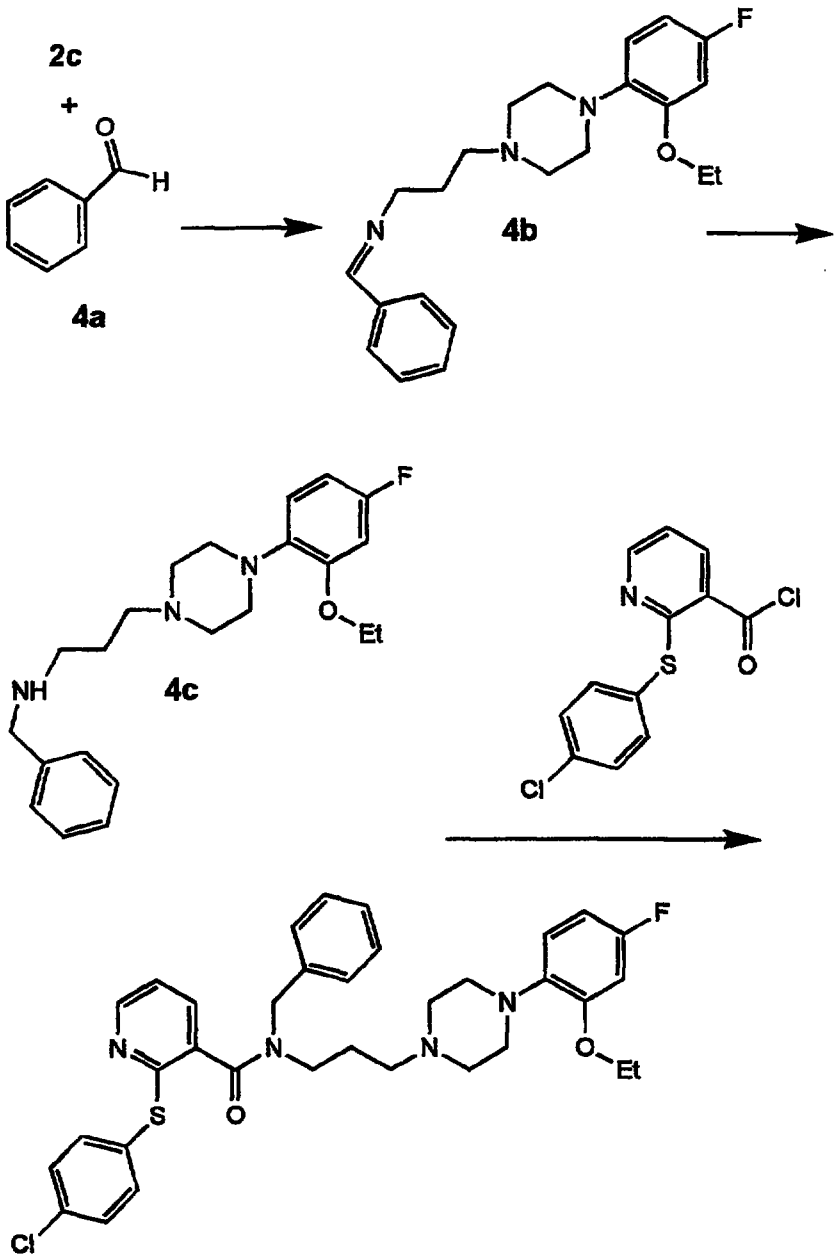
Scheme 3





To produce compounds of the invention where R_4 is other than hydrogen, Scheme 4 may be used. The amino group of intermediates 2c may be treated with an aldehyde 4a such as benzaldehyde to give the imine 4b. This intermediate may be reduced with $NaBH_4$ at room temperature to give the monoamine 4c. This amine is coupled with a substituted acyl pyridine derivative, using DMAP and N,N-diisopropylethylamine in methylene chloride at about room temperature for 2-6 h to give the desired compound of Formula I. As described in previous schemes, Scheme 4 may be modified to give a number of compounds of Formula I. For example, to produce a compound where R_3 is hydroxy, replace 2c with intermediate 1d and follow the remaining steps of Scheme 4.

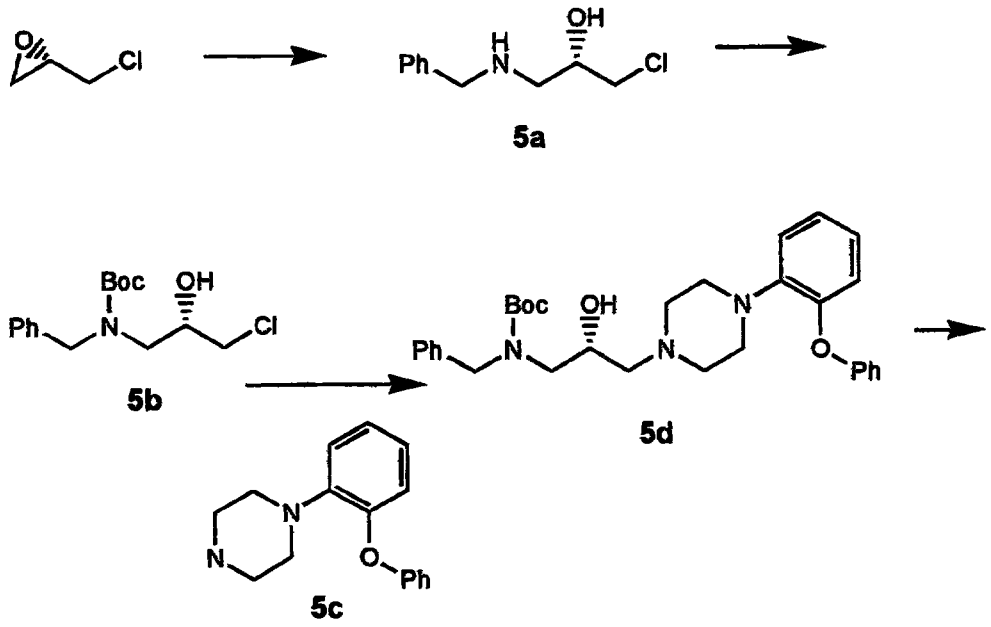
Scheme 4

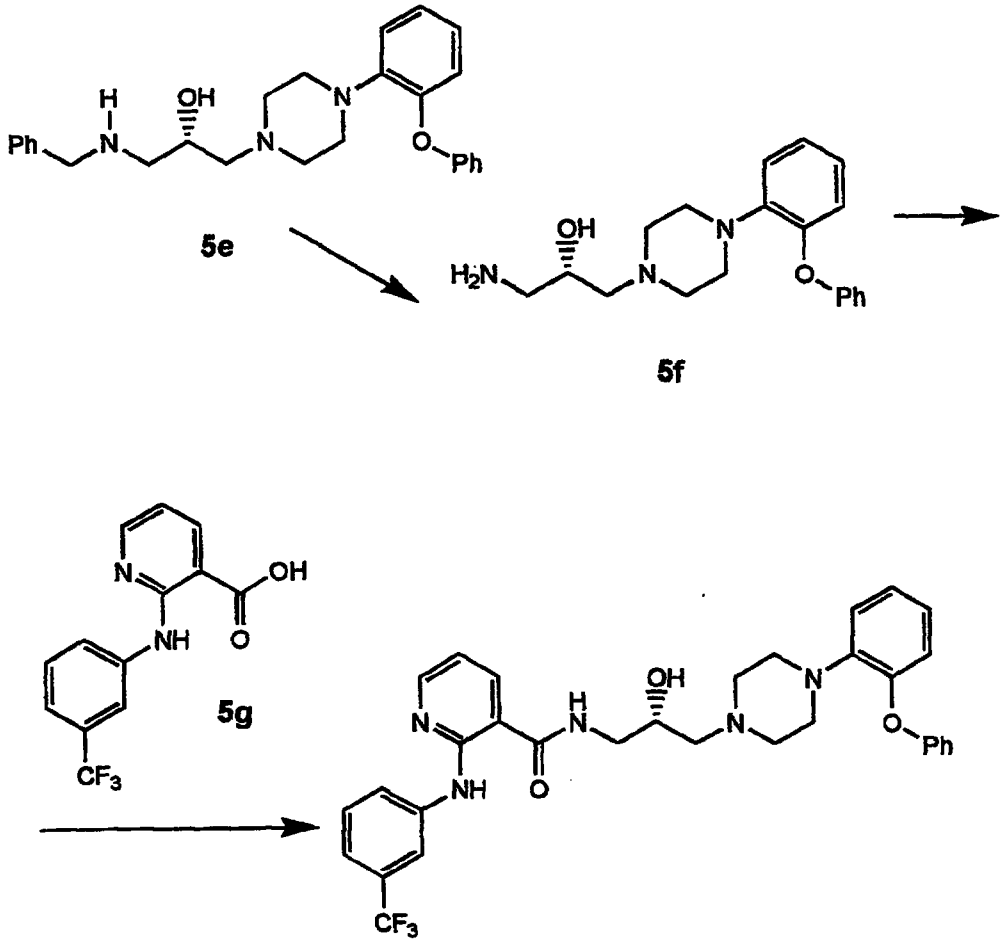


To produce pure enantiomers of compounds of Formula I where R_3 is hydroxy, Scheme 5 may be used. (*S*)(+) epichlorohydrin (97% ee)may be treated with benzylamine in a suitable organic solvent such as hexane at about room temperature for about 48-72 hours to give hydroxy compound 5a. This intermediate may be treated with a BOC reagent agent such as di-tert-butyl dicarbonate, and an organic base such as triethylamine in an inert

solvent such as THF at about 0 °C to about room temperature over 10 to 24 h to give the N-protected derivative 5b. This intermediate may be treated with piperazine derivative, 5c, a base such as potassium hydroxide, in an alcoholic solvent such as methanol at about 0 °C to about room temperature over about 1 to about 3 days to give the coupled derivative 5d. This compound may be deprotected by treatment with an acid such as TFA at about room temperature over 18-24 h to give free amine 5e. This amine may be debenzylated with using a palladium catalyst and ammonium formate in an alcoholic solvent such as EtOH at about 45-60 °C over 20 h to give the primary amine 5f. This amine may be coupled to acids of type 5g using peptide coupling agents such as HATU to give a compound of Formula I. As described in Scheme I, Scheme 5 may be modified to give a number of compounds of Formula I.

Scheme 5





Although the claimed compounds are useful as antagonists of $\alpha 1_a$-AR, some compounds are more active than others and are either preferred or particularly preferred. The preferred compounds of the invention include compounds where:

R_1 is halogen or hydroxy,

R_2 is phenyl or hydrogen,

R_3 is C_{1-5}alkoxy,

R_4 is C_{1-5}alkyl,

R_5 is C_{1-5}alkyl, and

X is sulfur

The particularly preferred compounds of Formula I include compounds where:

R_1 is hydrogen,

R_2 is C_{1-6}alkyl

R_3 is hydroxy or hydrogen

R_4 is hydrogen,

R_5 is phenyl and C_{1-5}alkyl-substituted phenyl

X is oxygen

As indicated by the biological activity, the compounds of Formula I may be used in pharmaceutical compositions to treat patients (humans and other mammals) with disorders related to inhibiting the activity of the $\alpha 1_a$ adrenergic receptor. The preferred route is oral administration, however compounds Oral doses range from about 0.01 to about 100 mg/kg daily; where the optimal dose range is about 0.1 to about 25 mg/kg/per day. Infusion doses can range from about 0.001-1 mg/kg/min of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several daysmay be administered by intravenous infusion. .

The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms may be elixers, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium sterate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms. Parenteral dosage forms may be prepared using water or another sterile carrier.

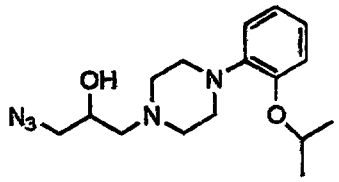
Typically the compounds of Formula I are isolated and used as free bases, however the compounds may be isolated and used as their pharmaceutically acceptable salts. Examples of such salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartatic, citric, benzoic, mandelic, methanesulfonic,

hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are meant only to suggest a method of practicing the invention. Those knowledgeable in the treatment of benign prostatic hyperplasia, chemical synthesis, pharmaceutical compounding as well as other specialties, may find other methods of practicing the invention. However those methods are deemed to be within the scope of this invention.

PREPARATIVE EXAMPLES

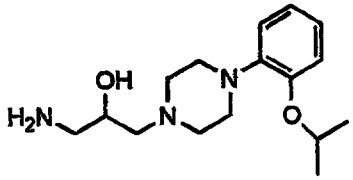
Example 1



Cpd. 1

The fumarate salt of 1-(2-isopropoxyphenyl)-piperazine (3.91 g, 12 mmol) was basified with 20% NaOH $_{(aq)}$ (100 mL) and extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated to give an oil (2.74 g). A mixture of the oil and 1-azido-3-(p-toluenesulfonyloxy)propan-2-ol (3.25 g, 12 mmol, Antonin Holy, *Collect. Czech. Chem. Comm.* 1989, *54*(2), 446) was stirred at 100 °C for 36 h. The cooled mixture was diluted with water and extracted with ether, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield compound 1 as (2.92 g, 76%) as a light-brown solid: MS (ES) m/z: 320 (MH^+); Anal. Calcd for $C_{16}H_{25}N_5O_2$:C, 60.17; H, 7.89; N, 21.93. Found: C, 60.45; H, 7.83; N, 22.01.

Example 2

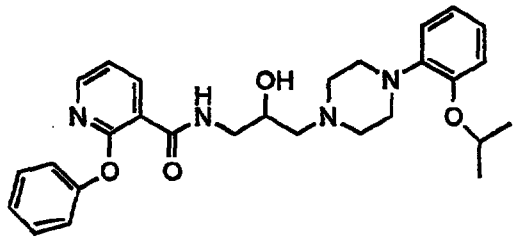


Cpd. 2

10% HCl (6 mL) was added to a mixture of compound 1 (2.43 g, 7.6 mmol) and 10% Pd/C (1.22 g) in MeOH (60 mL) and the mixture was hydrogenated under H_2 (50 psi) in a Parr shaker for 16 h at 20°C. The mixture was filtered through celite and the filtrate was concentrated. The residue was basified with 20% NaOH and extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and

concentrated to yield compound 2 as a yellowish oil (2.2 g, 95%): MS (ES) m/z: 294 (MH^+)

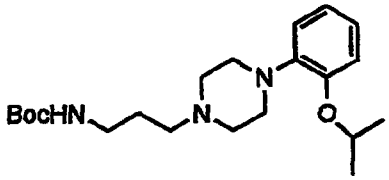
Example 3



Cpd. 3

A mixture of compound 2 (100 mg, 0.341 mmol), 2-phenoxypyridine-3-carbonyl chloride (81 mg, 0.341 mmol), DMAP (cat.) and N,N-diisopropylethylamine (0.23 mL) in methylene chloride (2 mL) was stirred at 20 °C for 16 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield 116 mg (69%) of compound 3 as a foam: ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.3 Hz, 1 H), 8.32 (brs, 1 H), 8.20 (d, J = 3.1 Hz, 1 H), 7.44 (m, 2 H), 7.21 (m, 4 H), 6.87 (m, 4 H), 4.57 (m, 1 H), 3.98 (m, 1 H), 3.75 (m, 1 H), 3.5 (m, 1 H), 3.06 (m, 4 H), 2.79 (m, 2 H), 2.48 (m, 4 H), 1.33 (d, J = 5.9 Hz, 6 H); MS (ES) m/z: 491(MH^+).

Example 4

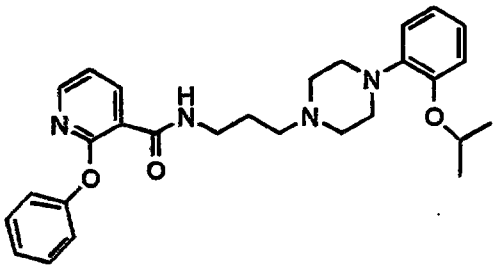


Cpd. 4

3-Bromopropylamine hydrobromide (5 g, 22.8 mmol) was dissolved in 10%NaOH (50 mL), extracted with methylene chloride and concentrated . To the free base in methylene chloride was added $(Boc)_2O$ (5.23 g, 23.9

mmol) and this mixture was stirred at 20 °C for 4h. The methylene chloride layer was washed with H_2O, diluted citric acid (6%), $NaHCO_3$ and sat NaCl solution, dried and concentrated. The product was purified by column chromatography (silica gel) to yield the protected amine (4.84g, 89%). The fumarate salt of 1-(2-isopropoxyphenyl)-piperazine (5.1g, 15 mmol) was basified with 20% $NaOH_{(aq)}$ (100 mL),extracted with methylene chloride, dried (Na_2SO_4) and concentrated to give a yellow oil (3.15 g). A mixture of the oil, the protected amine (3.42 g, 14.3 mmol), and Cs_2CO_3 (4.66 g, 14.3 mmol) in CH_3CN (50 mL) was heated at reflux overnight. The solid was filtered off and the filtrate was evaporated. The product was purified by column chromatography (silica gel) to yield compound 4(4.4 g, 81%): MS (ES) m/z: 378(MH^+)

Example 5

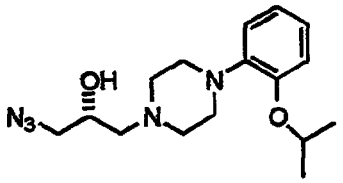


Cpd. 5

Compound 4 (0.185 g, 0.53 mmol), was dissolved in 25% TFA/methylene chloride (5 mL) and stirred for 1.5 h. The solvent was removed and the TFA salt was washed with toluene(3X) and then basified with 20% $NaOH_{(aq)}$ followed by extracted with methylene chloride (3X), dried (Na_2SO_4) and concentrated to give a oil. This oil was dissolved in methylene chloride (4 mL), diisopropylethyl amine (0.34 g, 2.64 mmol), catalytic amount of DMAP and 2-phenoxypyridine-3-carbonyl chloride (0.12 g, 0.53 mmol). The reaction was stirred at 20 °C under N_2 for 2 h and concentrated. The product was purified by column chromatography (silica gel) to yield compound 5 (0.2 g, 80%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J =7.5, 2.0 Hz, 1H), 8.20 (dd, J =4.9, 2.0 Hz, 1H), 8.05 (m, 1H), 7.46

(m, 2H), 7.29 (d, J =7.4 Hz, 1H), 7.15 (m, 3H), 6.88 (m, 4H), 4.56 (m, 1H), 3.59 (q, J =6.3 Hz, 2H), 3.03 (m, 4H), 2.56 (m, 4H), 2.49 (t, J =7.0 Hz, 2H), 1.87 (m, 2H), 1.32 (d, J =6.1 Hz, 6H); MS (ES) m/z: 475 (MH^+).

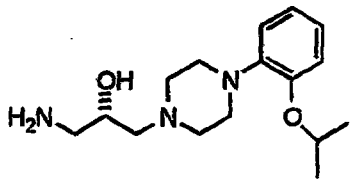
Example 6



Cpd. 6

The fumarate salt of 1-(2-isopropoxyphenyl)-piperazine (112.5 g, 345 mmol) was basified with 20% NaOH $_{(aq)}$ (500 mL),extracted with methylene chloride (3x), dried (Na_2SO_4), and concentrated to give about 70 g oil. A mixture of the oil and (2S)-3-azido-2-hydroxypropyl p-toluenesulfonate (91 g, 335 mmol, Kristina Juricova, *Collect. Czech. Chem. Comm.* **1995,** *60,* 237) was stirred at 100 °C in NMP with triethylamine (70 g, 690 mmol) for 30 h. The mixture was cooled, diluted with water and extracted with ether (3 x 500 mL). The combined extracts were back washed with NaCl (sat) (100 mL), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) and recrystallization (methylene chloride/hexanes) to yield 70.6 g (66%) of compound 6 (98.8% ee assay by chiralcel AD column) as a off-white: $[\alpha]^{25}_D$ -3.6° (c = 1, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4 H), 4.59 (m, 1 H), 3.93 (m, 1 H), 3.67 (brs,1 H), 3.42 (dd, J = 12.6, 3.8 Hz, 1 H), 3.23 (dd, J = 12.6, 5.4 Hz, 1 H), 3.12 (m, 4 H), 2.83 (m, 2 H), 2.53 (m, 3 H), 2.42 (dd, J = 12.2, 3.8 Hz, 1 H), 1.34 (d, J = 6.0 Hz, 6 H); MS (ES) m/z: 320 (MH^+)

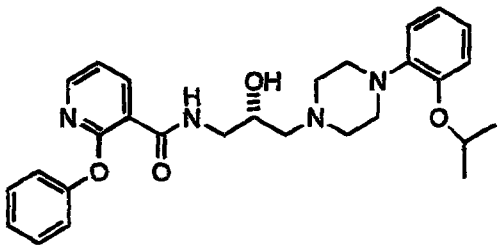
Example 7



Cpd. 7

10% HCl (6 mL), was added to a mixture of compound 6 (15 g, 47 mmol) and 10% Pd/C (4 g) in MeOH (100 mL). The mixture was hydrogenated under H_2 (50 psi) in a Parr shaker for 21 h at 20 °C. The mixture was filtered through celite and the filtrate was concentrated. The residue was basified with 20% $NaOH_{(aq)}$ (75 mL),extracted with methylene chloride (3x), dried (Na_2SO_4), and concentrated to yield compound 7 (14 g, ~100%) as a yellowish oil: $[\alpha]^{25}_D$ +23.6° (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4 H), 4.59 (m, 1 H), 3.76 (m, 1 H), 3.12 (m, 4 H), 2.83 (dd, J = 12.7, 3.7 Hz, 2 H), 2.82 (m, 1 H), 2.25-2.68 (m, 8 H), 1.34 (d, J = 6.1 Hz, 6 H); MS (ES) m/z: 294 (MH^+)

Example 8

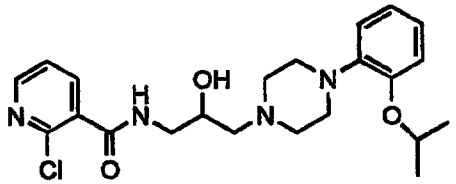


Cpd. 8

Piperazine 7 (8 g, 27.3 mmol) was dissolved in a mixture of diisopropylethylamine (14.1 g, 109.2 mmol) and methylene chloride (100 mL). The resulting light-yellowish solution was added slowly into a solution of methylene chloride (50 mL), 2-phenoxynicotinic acid (5.87 g, 27.3 mmol), EDCI (5.24 g, 27.3 mmol), HOBT (3.69 g, 27.3 mmol) and DMAP (50 mg, cat.) at 20 °C and stirred for 18 h. Water was added and the resulting

mixture was extracted with ether (3x). The combined organic extracts were washed with NaCl $_{(sat)}$, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (SiO_2, methylene chloride/acetone) to yield compound 8 (8.4 g, 62%) as a white foam: $[\alpha]^{25}_D$ +14.8° (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.5, 2 Hz, 1 H), 8.31 (brs, 1 H), 8.22 (dd, J = 4.7, 2 Hz, 1 H), 7.43 (brt, J = 7.7 Hz, 2 H), 7.14-7.30 (m, 4 H), 6.87 (m, 4 H), 4.58 (m, 1 H), 3.97 (m, 1 H), 3.75 (m, 1 H), 3.51 (m, 1 H), 3.06 (m, 4 H), 2.80 (m, 2 H), 2.49 (m, 4 H), 1.33 (d, J = 6.0 Hz, 6 H); MS (ES) m/z: 491 (MH^+).

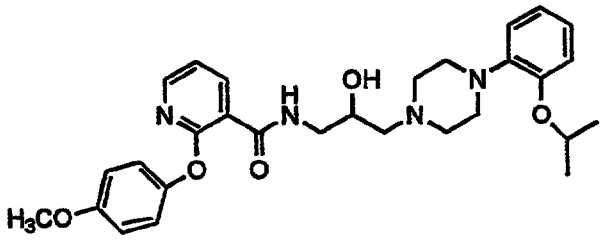
Example 9



Cpd. 9

A mixture of compound 2 (900 mg, 3.07 mmol), 2-chloronicotic acid (485 mg, 3.07 mmol), EDCI (589 mg, 3.07 mmol), HOBT (414 mg, 3.07 mmol), DMAP (cat.) and N,N-diisopropylethylamine (2 mL) in methylene chloride (20 mL) was stirred at 20 °C for 20 h. The mixture was concentrated, diluted with water and extracted with ether. The organic layer was dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield 580 mg (44%) of compound 9 as a white foam: MS (ES) m/z: 433 (MH^+)

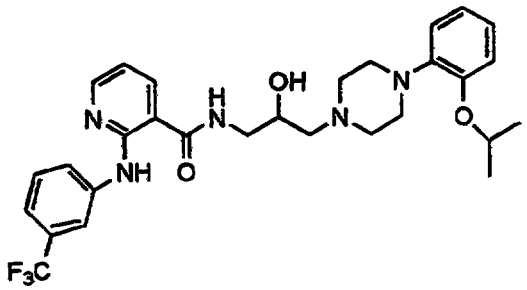
Example 10



Cpd. 10

A mixture of compound 9 (43 mg, 0.1 mmol), 4-methoxyphenol (124 mg, 1 mmol) and cesium carbonate (65 mg, 0.2 mmol) in NMP (1 mL) was stirred at 110 °C for 20 h. The resulting mixture was cooled, water was added and this mixture was extracted with ether. The extract was dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield compound 10 (36 mg, 69%) as a white foam: MS (ES) m/z: 521 (MH^+)

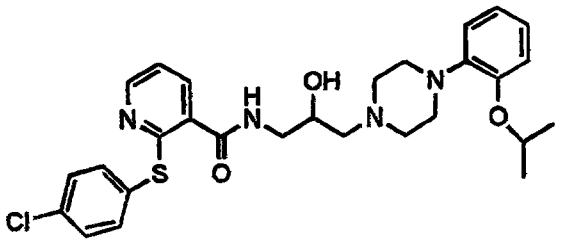
Example 11



Cpd. 11

A mixture of compound 2 (100 mg, 0.341 mmol), niflumic acid (96 mg, 0.341 mmol), EDCI (65 mg, 0.341 mmol), HOBT (46 mg, 0.34 mmol), DMAP (cat.) and N,N-diisopropylethylamine (0.23 mL) in methylene chloride (2 mL) was stirred at 20°C for 20 h. The mixture was concentrated. The product was purified by column chromatography (silica gel) to yield compound 11 (101 mg, 53%) as a foam: MS (ES) m/z: 558 (MH^+)

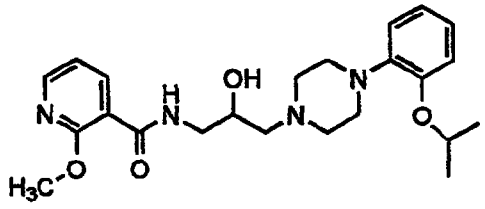
Example 12



Cpd. 12

A mixture of compound 2 (100 mg, 0.341 mmol), 2-(4-chlorophenylthio)pyridine-3-carboxylic acid (91 mg, 0.341 mmol), EDCI (65 mg, 0.341 mmol), HOBT (46 mg, 0.34 mmol), DMAP (cat.) and N,N-diisopropylethylamine (0.23 mL) in methylene chloride (2 mL) was stirred at 20°C for 20 h. The mixture was concentrated. The product was purified by column chromatography (silica gel) to yield compound 12 (128 mg, 70%) as a foam: MS (ES) m/z: 541 (MH^+)

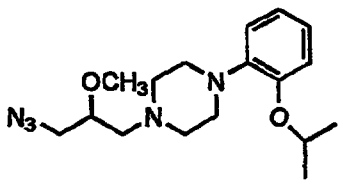
Example 13



Cpd. 13

A mixture of compound 2 (100 mg, 0.341 mmol), 2-methoxynicotinic acid (52 mg, 0.341 mmol), EDCI (65 mg, 0.341 mmol), HOBT (46 mg, 0.34 mmol), DMAP (cat.) and N,N-diisopropylethylamine (0.23 mL) in methylene chloride (2 mL) was stirred at 20°C for 20 h. The mixture was concentrated. 3% $K_2CO_{3(aq)}$ was added and extracted with ether, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield compound 13 (32 mg, 22%) as a foam: MS (ES) m/z: 429 (MH^+)

Example 14

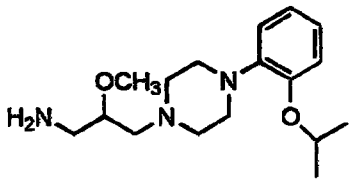


Cpd. 14

Compound 1 (0.8 g, 2.5 mmol) was dissolved in 50 mL of anhydrous THF. The solution was cooled to 0°C and 2 eq of 60% NaH (0.2 g, 5.0

mmol) was added. The solution was stirred for 10 min and 1.5 eq of CH_3I (0.53 g, 3.8 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h. NaH (0.1 g, 2.5 mmol) and 1eq of CH_3I (0.15 mL) were added and the mixture was stirred for another 2 h. The reaction was quenched with sat NH_4Cl, the solvent was evaporated, and the aqueous layer was washed with methylene chloride (3x), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel) to yield of compound A (0.69 g, 83%): MS (ES) m/z: 334 (MH^+).

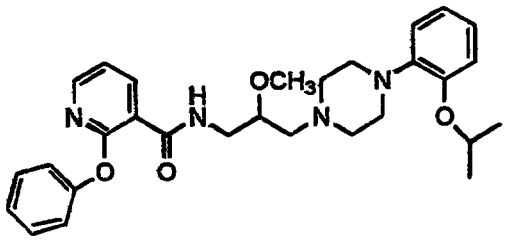
Example 15



Cpd. 15

10%HCl (0.3 mL) was added to a mixture of compound 14 (0.64 g, 1.9 mmol) and 10% Pd/C (0.13 g) in MeOH (5 mL) and the mixture was hydrogenated under H_2 (50 psi) in a Parr shaker overnight. The mixture was filtered through celite and the filtrate was concentrated. The residue was basified with 20% NaOH and extracted with methylene chloride (3x). The combined organic extract were dried (Na_2SO_4) and concentrated to give a yellow oil at quantitative yield. MS (ES) m/z: 308 (MH^+).

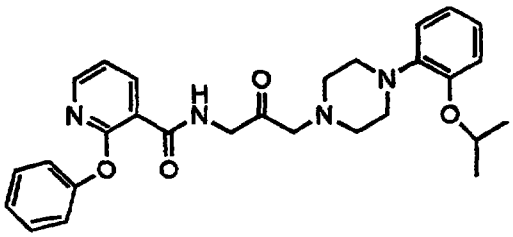
Example 16



Cpd. 16

Compound 15 (0.15 g, 0.49 mmol) was dissolved in methylene chloride (4 mL) and diisopropylethyl amine (0.25 g, 1.95 mmol) was added. To this solution was added a mixture of HATU (0.185 g, 0.49 mmol) and 2-phenoxynicotinic acid (0.11 g, 0.49mmol). The reaction was stirred under N_2 overnight at RT, the solvent was evaporated and the residue was dissolved in EtOAc. This solution was washed with 3% K_2CO_3, the organic layer was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography (SiO_2, methylene chloride/acetone = 10:1, 8:1, 6;1 4:1) to yield compound 16 (0.16 g, 64%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J =7.4 Hz, 1 H), 8.27 (brs, 1 H), 8.23 (m, 1 H), 7.44 (m, 2 H), 7.26 (m, 1 H), 7.17 (m, 3 H), 6.87 (m, 4 H), 4.58 (m, 1 H), 3.92 (m, 1 H), 3.55 (m, 2 H), 3.42 (s, 3 H), 3.03 (brs, 4 H), 2.54 (m, 6 H), 1.33 (d, J =6.0 Hz, 6 H); MS (ES) m/z: 308 (MH^+).

Example 17

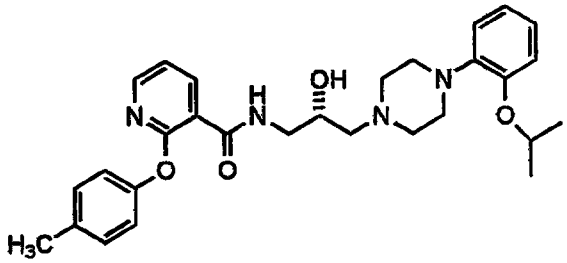


Cpd. 17

Oxalyl chloride (0.03 g, 0.22 mmol) was dissolved in 0.3 mL of methylene chloride. A mixture of DMSO (0.035 mL, 0.49 mmol) in methylene chloride (3.0 mL) was added dropwise to this solution at -78 °C. The mixture was stirred at -78 °C for 1h. A solution of compound 3 (68414, 0.1 g, 0.2 mmol) in methylene chloride (0.4 mL) was added slowly. The reaction mixture was stirred for 30 min and TEA (0.14 mL, 1.02 mmol) was added slowly. The mixture was allowed to warm up to room temperature, water was added and the resulting mixture was extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated to give compound 17 (13.2 mg, 13%): ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.69 (brs, 1 H), 8.61 (dd, J =7.6 Hz, 1 H), 8.23 (dd, J =4.6 Hz, 1H), 7.46 (m, 2 H), 7.28 (m, 3 H), 7.15 (m, 1 H), 6.89 (m, 4 H), 4.57 (m, 3H), 3.35 (s, 2 H), 3.15 (brs, 4 H), 2.70 (brs, 4 H), 1.33 (d, J = 5.97 Hz, 6 H); MS (ES) m/z: 489 (MH^+).

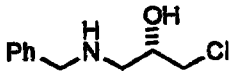
Example 18



Cpd.18

Piperazine 7 (150 mg, 0.51 mmol) was dissolved in a mixture of diisopropylethylamine (0.35 mL) and methylene chloride (2 mL). 2-(4-Methylphenoxy)pyridine-3-carbonyl chloride (126 mg, 0.51 mmol) and DMAP (cat.) were added into the above methylene chloride solution. The mixture was stirred at 20 °C for 16 h and concentrated. The product was purified by column chromatography (silica gel) to yield compound 18 (146 mg, 57%) as a foam: MS (ES) m/z: 505 (MH^+).

Example 19

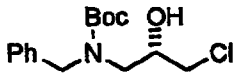


Cpd. 19

A mixture of (S)-(+)-epichlorohydrin (10 g, 108.1 mmol, Aldrich, 97% ee) and benzylamine (11.57 g, 108.1 mmol) in hexane (40 mL) were stirred at 20 °C for 62 h. White solid precipitated. More hexane (~ 350 mL) added, stirred for 20 min. and sonicated to break the big chunks of white solid. The white solid was collected by filtration and washed with hexane, dried under vacuum to give 19.8 g (92%) white solid. The white solid was recrystallized from EtOAc/hexane to give 17.76 g (82%) of 1 as a white crystallined solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 3.88 (m, 1 H), 3.79 (m, 2 H),

3.53 (d, J = 5.3 Hz, 2 H), 2.89 (m, 2 H), 2.81 (dd, J = 12.4, 4.1 Hz, 1 H), 2.69 (dd, J = 12.2, 7.9 Hz, 1 H); MS (ES): 200 (MH+); Anal. Calcd. for $C_{10}H_{14}NOCl$: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.10; H, 7.02; N, 6.92.

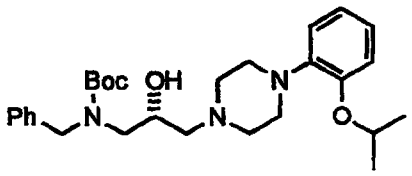
Example 20



Cpd. 20

Boc_2O (11 g, 50.1 mmol) and triethylamine (10.12 g, 100 mmol) were dissolved in THF (25 mL) and cooled to 0 °C . The amine 19 (10 g, 50.1 mmol) was added in portions and stirred for 20 h while the temperature was warm up to 20 °C overnight. The solvent was concentrated in vacuo and water added. The mixture was extracted with ether (3x), dried (Na_2SO_4) and concentrated. The crude residue was recrystallized from EtOAc/hexane to give 9.9 g (66%) of 20 as a white crystallined solid. The filtrate was concentrated (3.1 g as oil) and more product was purified by column chromatography (short column, 8 cm height of SiO_2, EtOAc/hexane as solvent). The oil was recrystallized from EtOAc/hexane to give another 2.78 g (18%) of 20 as a white crystalline solid; $[\alpha]_D^{25}$ = -10.20 (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.36 (m, 5 H), 4.52 (m, 2 H), 4.30 (brs, 0.5 H), 3.96 (m, 1 H), 3.36-3.97 (m, 4 H), 1.47 (s, 9 H); MS (ES): 322 (M+Na); Anal. Calcd. for $C_{15}H_{22}NO_3Cl$: C, 60.10; H, 7.40; N, 4.67. Found: C, 60.26, H, 7.42; N, 4.63

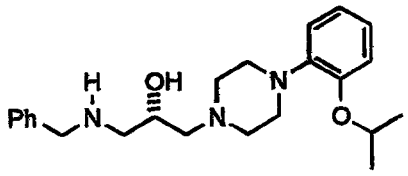
Example 21



Cpd. 21

KOH (11.23 g, 200.5 mmol) was dissolved in methanol (280 mL), and the fumarate salt of 1-(2-isopropoxyphenyl)-piperazine (10.9 g, 33.4 mmol) was added and stirred at 20 °C for 20 min then cooled to 0 °C . The Boc-protected amine 20 (10 g, 33.4 mmol) was added to the methanol solution at 0 °C and stirred for 20 h while the temperature was warm up to 20 °C overnight. The solvent was removed, water was added and the mixture was extracted with ether (3x), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (short column, 8 cm height SiO_2, EtOAc/hexane as solvent) to give 10.22 g (63%) of 3 (~100% ee, Chiralpak OD 4.6 x 250 mm. 1 mL/min, 254 nm, mobile phase: 90/10/0.1 of hexane/IPA/ 0.1% diethylamine) as a yellowish oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.35 (m, 5 H), 6.91 (m, 4 H), 4.68 (d, J = 15.6 Hz, 1 H), 4.59 (m, 3 H), 3.95 (m, 1 H), 3.35 (m, 2 H), 3.11 (m, 4 H), 2.75 (m, 2 H), 2.54 (m, 2 H), 2.38 (m, 2 H), 1.45 (m, 9 H), 1.34 (d, J = 6.1 Hz, 6 H); MS (ES): 484 (MH^+).

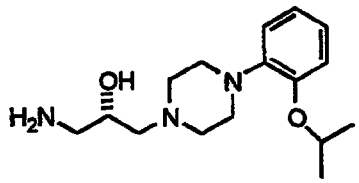
Example 22



Cpd. 22

A mixture of compound 21 (233 mg, 0.48 mmol) and 25% TFA/methylene chloride (3 mL) was stirred at 20 °C for 18 h. The solvent was concentrated in vacuo and the residue was basified with 20% NaOH (aq), extracted with methylene chloride (3x), dried (Na_2SO_4) and concentrated to give 174 mg (~95%) of 22 as an oil. Used directly without further purification; MS (ES): 384 (MH^+).

Example 23



Cpd. 23

To a mixture of 22 (~154 mg, 0.4 mmol) and 10% Pd/C (154 mg) in EtOH (3 mL) was added ammonium formate (151 mg, 2.4 mmol) and stirred at 55-60 °C for 20 h. The mixture was filtered thru celite and washed with methanol. The filtrate was concentrated. The product was purified by a short column (5 cm height of SiO_2) to give 63 mg (54%) of 23 as a oil; $[\alpha]_D^{25}$ +23.6° (c = 1, CHCl3);1H NMR (300 MHz, CDCl3) δ 6.91 (m, 4 H), 4.59 (m, 1 H), 3.76 (m, 1 H), 3.12 (m, 4 H), 2.83 (dd, J = 12.7, 3.7 Hz, 2 H), 2.82 (m, 1 H), 2.25-2.68 (m, 8 H), 1.34 (d, J = 6.1 Hz, 6 H); MS (ES): 294 (MH^+).

BIOLOGICAL EXAMPLES

The biological activity and selectivity of compounds of the invention was demonstrated by the following assays. The first assay tested the ability of compounds of Formula I to bind to membrane bound receptors $\alpha1_a$-AR, $\alpha1_b$-AR and $\alpha1_d$-AR.

Example 24

The DNA sequences of the three cloned human α1-AR subtypes have been published. Furthermore, the cloned cDNAs have been expressed both transiently in COS cells and stably in a variety of mammalian cell lines (HeLa, LM(tk-), CHO, rat -1 fibroblast) and have been shown to retain radioligand binding activity and the ability to couple to phosphoinositide hydrolysis. We used published DNA sequence information to design primers for use in RT-PCR amplification of each subtype to obtain cloned cDNAs. Human poly A+ RNA was obtained from commercially available sources and included hippocampus and prostate samples, sources which have been cited in the literature. For the primary screen a radio ligand binding assay was used

which employed membrane preparations from cells expressing the individual cloned receptor cDNAs. Radiolabeled ligands with binding activity on all three subtypes (non-selective) are commercially available ([125I]-HEAT, [3H]-prazosin).

Each α1 receptor subtype was cloned from poly A+ RNA by the standard method of reverse transcription-polymerase chain reaction (RT-PCR). The following sources of polyA+ RNA were used for the cloning of the α1 receptor subtypes: $\alpha1_a$-AR, human hippocampus and prostate, $\alpha1_b$-AR, human hippocampus, $\alpha1_d$-AR, human hippocampus. The resulting cDNAs were cloned into the pcDNA3 mammalian expression vector (Invitrogen Corp., San Diego CA). Each DNA was sequenced for verification and to detect any possible mutations introduced during the amplification process. Any deviation in sequence from the published consensus for each receptor subtype was corrected by site-directed mutagenesis.

The three α1-AR subtypes (a, b, d) were transfected into COS cells using a standard DEAE-dextran procedure with a chloroquine shock. In this procedure, each tissue culture dish (100mm) was inoculated with 3.5×10^6 cells and transfected with 10 μg of DNA. Approximately 72 hours post-transfection, the cells were harvested and COS membranes were prepared. Transfected COS cells from 25 plates (100mm) were scraped and suspended in 15mL of TE buffer (50mM Tris-HCl, 5mM EDTA, pH7.4). The suspension was disrupted with a homogenizer. It was then centrifuged at 1000xg for 10 minutes at 40 °C. The supernatant was centrifuged at 34,500xg for 20 minutes at 4 °C. The pellet was resuspended in 5mL TNE buffer (50mM Tris-HCl, 5mM EDTA, 150mM NaCl, pH7.4). The resulting membrane preparation was aliquoted and stored at -70°C. The protein concentration was determined following membrane solubilization with TritonX-100.

The ability of each compound to bind to each of the α1-AR subtypes was assessed in a receptor binding assay. [125I]-HEAT, a non-selective α1-AR ligand, was used as the radiolabeled ligand. Each well of a 96-well plate received: 140 μL TNE, 25 μL [125I]-HEAT diluted in TNE (50,000 cpm; final

concentration 50 pM), 10 µL test compound diluted in DMSO (final concentration 1 pM-10 µM), 25 mL COS cell membrane preparation expressing one of the three α1-AR subtypes (0.05-0.2 mg membrane protein). The plate was incubated for 1 hour at room temperature and the reaction mixtures were filtered through a Packard GF/C Unifilter filter plate. The filter plate was dried for 1 hour in a vacuum oven. Scintillation fluid (25 mL) was added to each well, and the filter plate was counted in a Packard Topcount scintillation counter. Data was analyzed using GraphPad Prism software.

Tables A lists IC_{50} values expressed in nanomolar concentration for select compounds of the invention in all receptor subtypes.

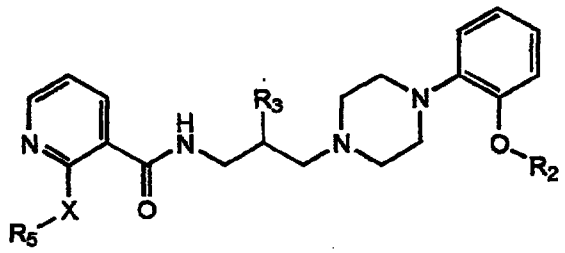


TABLE A

Cpd.	X	R_2	R_3	R_5	α1a	α1b	α1d
3	O	i-propyl	OH	Ph	1.5	909	211
5	O	i-propyl	H	Ph	0.64	151	40
8	O	i-propyl*	OH	Ph	0.76	668	81
35	O	i-propyl**	OH	Ph	10.2	889	314
10	O	i-propyl	OH	4-OCH_3-Ph	2.4	1910	131
36	O	i-propyl	OH	4-F-Ph	1.5	1162	148
37	O	i-propyl	OH	3-Cl-Ph	0.91	952	180
38	O	i-propyl	OH	3-$N(CH_3)_2$-Ph	2	972	56
39	O	i-propyl	OH	2-CH_3-Ph	1.1	730	1.7
40	O	i-propyl	OH	2-OCH_3-Ph	1.7	580	2.2
11	NH	i-propyl	OH	3-CF_3-Ph	25	1020	79
12	S	i-propyl	OH	4-Cl-Ph	2.6	806	299
41	O	i-propyl	OH	4-CH_3-Ph	0.52	928	21
42	O	i-propyl	OH	4-Cl-Ph	1	838	74
43	S	i-propyl	OH	Ph	2	1220	70
18	O	i-propyl*	OH	4-CH_3-Ph	0.51	290	50
27	O	i-propyl*	OH	4-Cl-Ph	0.86	791	57
28	O	i-propyl**	OH	4-CH_3-Ph	25	361	969
29	O	i-propyl	H	4-CH_3-Ph	0.27	>2000	43
30	O	i-propyl	OH	3,4-di-Cl-Ph	2	2251	56
31	NH	i-propyl	OH	Ph	25	736	25
32	O	CH_3	OH	Ph	30	1570	147
13	O	i-propyl	OH	CH_3	3.5	>2,000	191
33	O	i-propyl	OH	4-$(CH_3)_3C$-Ph	3.3	>2,000	78

34	O	CH_3CH_2	OH	Ph	9.1	132	206
16	O	i-propyl	OCH_3	Ph	2.4	1356	21
17	O	i-propyl	O	4-$(CH_3)_3C$-Ph	63	887	546

* indicates "S" stereochemistry
** indicates "R" stereochemistry

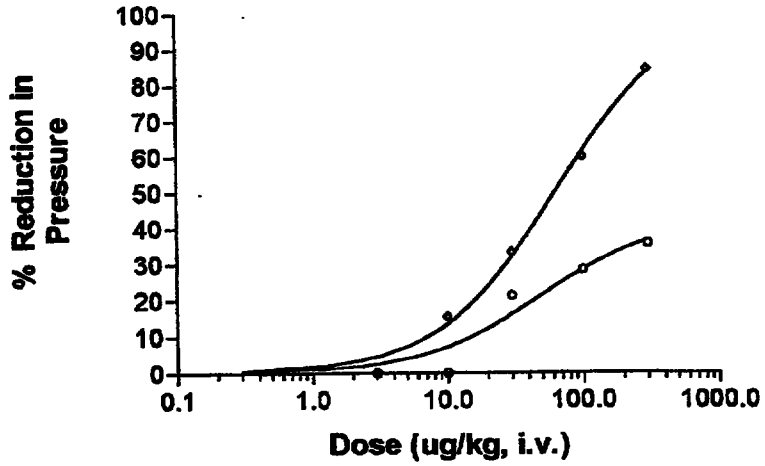
Example 25

The antagonist activity and the selectivity of compounds of the invention for prostate tissues over aortic tissues as well as their antagonists was demonstrated as follows. The contractile responses of rat prostatic tissue and rat aorta tissues were examined in the presence and absence of antagonist compounds. As an indication of the selectivity of antagonism, test compound effects on vascular smooth muscle contractility ($\alpha 1_b$-AR and $\alpha 1_d$-AR) were compared to the effects on prostatic smooth muscle ($\alpha 1_a$-AR). Strips of prostatic tissue and aortic rings were obtained from Long Evans derived male rats weighing 275 grams and sacrificed by cervical dislocation. The prostate tissue was placed under 1 gram tension in a 10 ml bath containing phosphate buffered saline pH 7.4 at 32 ° C. and isometric tension was measured with force transducers. The aortic tissue was placed under 2 grams tension in a 10 ml bath containing phosphate buffered saline pH 7.4 at 37 °C. The ability of test compound to reduce the norepinephrine-induced contractile response by 50 % (IC_{50}) was determined. Compound 3 inhibited the contractile response in aortic tissue with an IC_{50} of 4.74 μM and in prostate tissue with an IC_{50} of 0.143 μM. Compound 35 inhibited the contractile response in aortic tissue with an IC_{50} of 8.5 μM and in prostate tissue with an IC_{50} of 0.18 μM.

Example 26

Select compounds of the invention were tested for their ability to antagonize phenylephrine (PE) induced increases in intraurethral pressure in dogs. The selectivity of these compounds was demonstrated by comparing their effect upon PE induced increases in mean arterial pressure (MAP) in the dog.

Male beagle dogs were anesthetized and catheterized to measure intraurethral pressure (IUP) in the prostatic urethra. Mean arterial pressure (MAP) was measured using a catheter placed in the femoral artery. Dogs were initially administered six i.v. bolus doses (1 to ≤ 32mg/kg) of phenylephrine (PE) to establish a control agonist dose-response curve. IUP and MAP were recorded following each dose until the IUP returned to baseline. The dogs then were given an i.v. bolus dose of the antagonist compound, followed by i.v. PE challenges of ascending doses, as in the control agonist dose-response curve. IUP and MAP measurements following each PE challenge were recorded. The antagonist compound was tested over a dose range of 3 to 300 ug/kg in half-log increments. The interval between antagonist doses was at least 45 min and three experiments were performed for each test compound. The graph below illustrates the mean percentage reductions in IUP and MAP for Compound 8.



Effects of Compound 8 upon IUP and MAP at 3 μg/kg PE in dogs

■ **IUP**

● **MAP**

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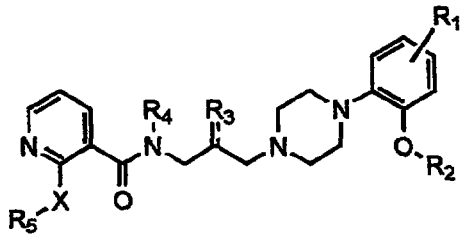
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What is claimed is:

1. A compound of Formula I



I

R_1 is hydrogen, halogen, C_{1-5}alkoxy, hydroxyl, or C_{1-5}alkyl;

R_2 is C_{1-6}alkyl, substituted C_{1-6}alkyl
where the alkyl substituents are independently selected from one or more halogens,
phenyl,
substituted phenyl
where the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl,
phenylC_{1-5}alkyl,
or substituted phenylC_{1-5}alkyl
where the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5}alkyl, halogen, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl;

R_3 is hydrogen, hydroxy or C_{1-5}alkoxy if the hashed line is absent or is oxygen if the hashed line is present;

R_4 is hydrogen, C_{1-5}alkyl, phenylC_{1-5}alkyl or substituted phenylC_{1-5}alkyl
where the phenyl substitutents are independently selected from one or more members of the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, and trihaloC_{1-5}alkyl;

R_5 is C_{1-6}alkyl,

substituted C_{1-6}alkyl

where the alkyl substitutents are independently selected from one or more halogens,

phenyl,

substituted phenyl

where the phenyl substitutents are independently selected from one or more members of the group consisting of C_{1-8}alkyl, hydrogen, halogen, hydroxy, C_{1-8}alkyl, substituted C_{1-8}alkyl

where the alkyl substitutents are independently selected from one or more halogens, C_{1-5}alkoxy, amino, C_{1-5}alkylamino, diC_{1-5}alkylamino, C_{1-5}alkylcarbonyl, C_{1-5}alkoxycarbonyl, arylcarbonyl, nitrile, aminosulfonyl, C_{1-5}alkylsulfonyl, phenylsulfonyl, and substituted phenylsulfonyl

where the phenyl substitutents are independently selected from one or more members the group consisting of C_{1-8}alkyl hydrogen, halogen, hydroxy and nitro;

phenylC_{1-5}alkyl,

substituted phenylC_{1-5}alkyl

where the phenyl substitutents are independently selected from one or more members of the group consisting of C_{1-8}alkyl hydrogen, halogen, hydroxy, C_{1-8}alkyl, substituted C_{1-8}alkyl

where the alkyl substitutents are independently selected from one or more halogens, C_{1-5}alkoxy, amino, C_{1-5}alkylamino, diC_{1-5}alkylamino, C_{1-5}alkylcarbonyl, C_{1-5}alkoxycarbonyl, and nitro;

X is oxygen, sulfur or NH;

pharmaceutically acceptable salts thereof;

and stereoisomers, racemic mixtures, as well as enantiomers thereof.

2. The compound of claim 1 wherein R_3 is oxygen.

3. The compound of claim 1 wherein R_3 is hydrogen or hydroxy.

4. The compound of claim 3 wherein R_1 is hydrogen, halogen, or hydroxy, R_2 phenyl, hydrogen or C_{1-6}alkyl, R_4 is C_{1-5}alkyl or hydrogen, and R_5 is C_{1-5}alkyl, phenyl or substituted phenyl and X is sulfur or oxygen.

5. The compound of claim 4 wherein R_1 is hydrogen, R_2 is C_{1-5}alkyl, R_3 is hydroxy, R_4 is hydrogen, R_5 is substituted phenyl and X is oxygen.

6. The compound of claim 1 wherein R_1 is hydrogen, R_2 is i-propyl, R_3 is hydroxy or hydrogen, R_4 is hydrogen, R_5 is phenyl or substituted phenyl where the phenyl substitutents are independently selected from one or more members of the group consisting of C_{1-5}alkoxy, halogen, diC_{1-5}alkylamino C_{1-5}alkyl, and halogen substituted C_{1-5}alkyl, and X is oxygen.

7. The compound of claim 1 where R_1 is hydrogen, R_2 is i-propyl, R_3 is hydroxy, R_4 is hydrogen, R_5 is phenyl, X is oxygen and the stereochemistry of the chiral carbon is *S*.

8. A method of treating benign prostatic hyperplasia consisting of administering an effective dose of a compound of Formula I to a mammal.

9. The method of claim 8 where the effective dose is about 0.1 to about 25.0 mg/kg.

10. A method of treating diseases associated with the α-1_a adrenergic receptor consisting of administering an effective dose of a compound of Formula I to a mammal.

11. The method of claim 10 where the effective dose is about 0.1 to about 25.0 mg/kg.

12. A pharmaceutical composition containing an effective dose of a compound of Formula I.

13. A pharmaceutical composition of claim 12 where the effective dose of a compound of Formula I is about 0.1 to about 25.0 mg/kg.

14. A pharmaceutical composition of claim 12 where the effective dose of a compound of Formula I is about 0.01 to about 1.0 mg/kg.

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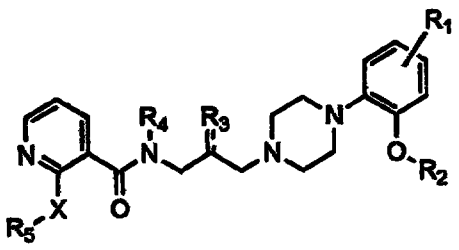
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(I)

(57) Abstract

This invention relates to a series of heterocyclic substituted piperazines of Formula (I), methods of treatment, pharmaceutical compositions containing them, and intermediates used in their manufacture. The compounds of the invention selectively inhibit binding to the α-1_a adrenergic receptor, a receptor which has been implicated in benign prostatic hyperplasia. As such the compounds are potentially useful in the treatment of this disease.