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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/010504 A2

(51) International Patent Classification:
C07D 209/48 (2006.01) *A61P 13/00* (2006.01)
A61K 31/496 (2006.01) *A61P 13/08* (2006.01)

(21) International Application Number:
PCT/IB2006/052516

(22) International Filing Date: 21 July 2006 (21.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1940/Del/2005 22 July 2005 (22.07.2005) IN

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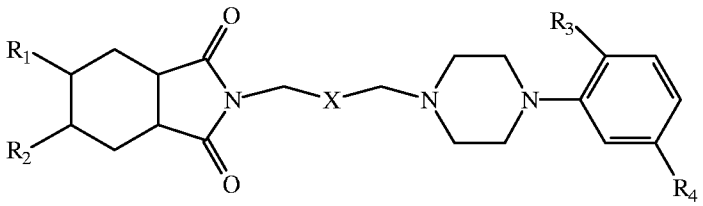
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

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

Published:
— *without international search report and to be republished upon receipt of that report*

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

(54) Title: ACID ADDITION SALTS OF ADRENERGIC RECEPTOR ANTAGONISTS



(I)

(57) Abstract: Provided herein are acid addition salts of compounds of Formula (I). The acid addition salts of Formula I described herein can be used to treat benign prostatic hyperplasia (BPH) and the related symptoms thereof. Further, these compounds can be used to treat lower urinary tract symptoms (LUTS) that may or may not be associated with BPH. Process for preparing the compounds described herein, pharmaceutical compositions thereof, and the methods of treating BPH or related symptoms thereof and LUTS that may or may not be associated with BPH are also provided.

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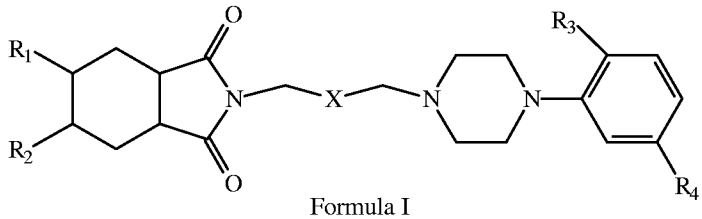
ACID ADDITION SALTS OF ADRENERGIC RECEPTOR ANTAGONISTS

Field of the Invention

Provided herein are acid addition salts of compounds of Formula I.



Formula I

The acid addition salts of Formula I described herein can be used to treat benign prostatic hyperplasia (BPH) and the related symptoms thereof. Further, these compounds can be used to treat lower urinary tract symptoms (LUTS) that may or may not be associated with BPH. Process for preparing the compounds described herein, pharmaceutical compositions thereof, and the methods of treating BPH or related symptoms thereof and LUTS that may or may not be associated with BPH are also provided.

Background of the Invention

Benign prostatic hyperplasia (BPH) is a condition, which develops in elderly males and refers to the benign overgrowth of the stromal and epithelial elements of the prostate with aging. The symptoms of BPH vary, but the most common ones involve changes or problems with urination, such as hesitant, interrupted, weak stream or urgency and leaking or dribbling or more frequent urination, especially at night. Consequences of BPH can involve hypertrophy of bladder smooth muscle, a decompensated bladder and an increased incidence of urinary.

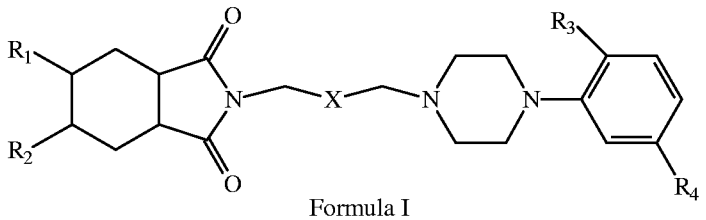
There are two components of BPH, static and a dynamic component. The static component is due to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of the urine from the bladder. The dynamic component is due to increased smooth muscle tone of the bladder neck and prostate itself

and is regulated by α-1 adrenergic receptors. There are several reports that an antagonist with high affinity for α_{1a} or α_{1a}/α_{1d} can cause some degree of vasodilatation but that it is much smaller than with non-subtype-selective α_{1a} adrenoceptor antagonist. Further, there is increased vascular α_{1b} adrenoceptor expression in elderly patients and thus α_{1a}/α_{1d} selective agents with selectivity over α_{1b} adrenoceptor subtype would be of particular importance in benign prostatic hyperplasia. Antagonism of both α_{1a} adrenoceptor and α_{1d} adrenoceptor is important to relieve lower urinary tract symptoms especially associated (suggestive of) with BPH. Targeting α_{1a} adrenoceptor with antagonists is important in relaxing prostate smooth muscle and relieving bladder outlet obstruction whereas α_{1d} adrenoceptor antagonism is important to target irritative symptoms.tract infection.

Compounds of Formula I, described in International Patent Application No. WO 2005/118537, are adrenergic receptor antagonists. Compounds described therein exhibit substantial affinity towards α_{1a} and α_{1d} adrenoceptor subtypes and good selectivity for α_{1a} vs. α_{1b} adrenoceptor subtypes. The relatively lower affinity at α_{1b} adrenoceptors limits cardiovascular side effects such as orthostatic hypotension.

Summary of the Invention

Provided herein are the acid addition salts of compounds of Formula I,



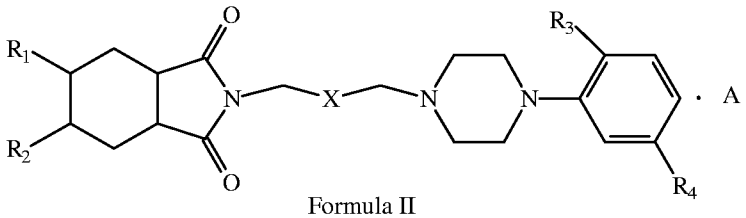
Formula I

which can be used to treat benign prostatic hyperplasia or related symptoms thereof, lower urinary tract symptoms associated with or without BPH, and process for preparing these compounds (salts). Pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites of compounds described herein are also within the scope of this invention. The pharmaceutical compositions comprising the compounds described herein, their prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates alone or in combination with pharmaceutically acceptable

carriers, optionally included excipients and diluents that are useful for the treatment of benign prostatic hyperplasia or related symptoms thereof, lower urinary tract symptoms associated with or without BPH are included in this invention.

The acid addition salts described herein exhibit better solubility, stability, excellent storage and handling stabilities, and are less susceptible to degradation at lower temperatures.

Also provided herein are compounds having the structure of Formula II:



Formula II

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein,

A can be an organic acid such as acetic, succinic, maleic, trifluoroacetic, oxalic, citric, malonic, tartaric, adipic, ascorbic, camphor sulfonic, nicotinic, butyric, lactic or glucuronic acids, or an inorganic acid such as hydrobromic, phosphoric, sulfuric, nitric, boric or perchloric acids; R_1 and R_2 can be independently hydrogen, hydroxy or halogen; X can be CO, CHOH or CH_2; R_3 and R_4 can be independently hydrogen, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_5-C_6 cycloalkoxy. In particular embodiments, A can be tartaric, succinic, maleic or phosphoric acid.

Also provided herein are illustrative compounds including:

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione citrate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

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2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate, and

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof.

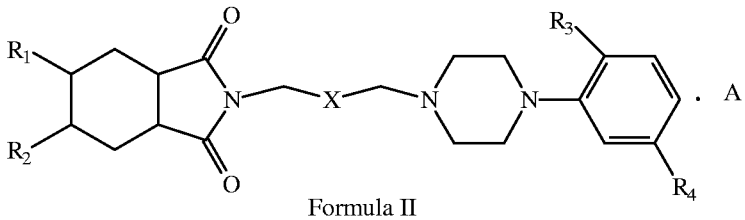
Also provided herein are methods for treating diseases or disorders mediated through α_{1a} and/or α_{1d} adrenergic receptors, comprising administering to patient in need thereof a therapeutically effective amount of a compound described herein and optionally one or more pharmaceutically acceptable carriers, excipients or diluents.

These methods can encompass one or more of the following features. For example, the disease or disorder can be benign prostatic hyperplasia. In another example,

the compound causes minimal decrease or no decrease in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

Also provided herein are methods for treating lower urinary tract symptoms associated with or without benign prostatic hyperplasia, comprising administering to a patient in need thereof a therapeutically effective amount of a compound described herein and optionally one or more pharmaceutically acceptable carriers, excipients or diluents.

Also provided herein are methods for preparing compounds of Formula II,

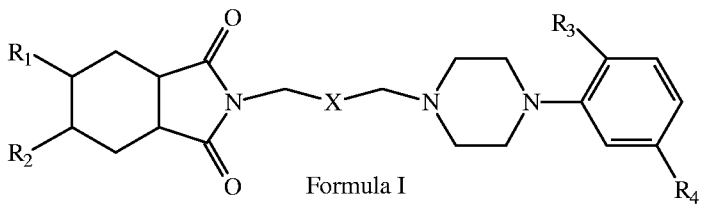


Formula II

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein,

A can be an organic acid such as acetic, succinic, maleic, trifluoroacetic, oxalic, citric, malonic, adipic, ascorbic, camphor sulfonic, nicotinic, butyric, lactic or glucuronic acid; or an inorganic acid such as hydrobromic, phosphoric, sulfuric, nitric, boric or perchloric acid. R_1 and R_2 can be independently hydrogen, hydroxy or halogen; X can be CO, CHOH or CH_2; R_3 and R_4 can be independently hydrogen, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_5-C_6 cycloalkoxy. The method can comprise:

reacting a compound of Formula I,

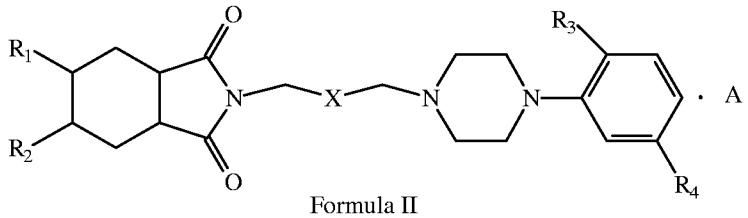


Formula I

with an organic or inorganic acid to form a compound of Formula II.

Detailed Description of the Invention

In one aspect, provided herein are compounds having the structure of Formula II:



Formula II

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein,

A can be organic acid such as acetic, succinic, maleic, trifluoroacetic, oxalic, citric, malonic, tartaric, adipic, ascorbic, camphor sulfonic, nicotinic, butyric, lactic or glucuronic acid, or an inorganic acid such as hydrobromic, phosphoric, sulfuric, nitric, boric or perchloric acid. R_1 and R_2 can be independently hydrogen, hydroxy or halogen; X can be CO, CHOH or CH_2; R_3 and R_4 can be independently hydrogen, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_5-C_6 cycloalkoxy.

In an embodiment, provided herein are the acid addition salts of compounds having the structure of Formula II, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein, A can be tartaric, succinic, maleic or phosphoric acid.

In another aspect, provided herein are illustrative compounds including:

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 1),

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate (Compound No. 2),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 3),

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate (Compound No. 4),

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate(Compound No. 5),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate (Compound No. 6),

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione succinate (Compound No. 7),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 8),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 9),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 10),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione succinate (Compound No. 11),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate (Compound No. 12),

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 13),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 14),

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 15),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 16),

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 17),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 18),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 19),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 20),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 21),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 22),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate (Compound No. 23),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 24),

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate (Compound No. 25),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 26),

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate (Compound No. 27),

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate (Compound No. 28),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate (Compound No. 29),

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione maleate (Compound No. 30),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 31),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 32),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 33),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione maleate (Compound No. 34),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate (Compound No. 35),

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 36),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 37),

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 38),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 39),

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 40),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 41),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 42),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 43),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 44),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 45),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 46),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 47),

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate (Compound No. 48),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 49),

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate (Compound No. 50),

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate (Compound No. 51),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate (Compound No. 52),

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione tartarate (Compound No. 53),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 54),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 55),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 56),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione tartarate (Compound No. 57),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate (Compound No. 58),

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 59),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 60),

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 61),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 62),

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 63),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 64),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 65),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 66),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 67),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 68),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate (Compound No. 69),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione citrate (Compound No. 70),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 71),

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate (Compound No. 72),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 73),

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate (Compound No. 74),

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate (Compound No. 75),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate (Compound No. 76),

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione phosphate (Compound No. 77),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 78),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 79),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 80),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione phosphate (Compound No. 81),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate (Compound No. 82),

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 83),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 84),

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 85),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 86),

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 87),

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 88),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 89),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 90),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 91),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 92),

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 93),

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 94), and

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof.

In another aspect, provided herein are methods for treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors, comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds or pharmaceutical composition described herein.

In an embodiment, provided herein are methods for treating benign prostatic hyperplasia (BPH) and related symptoms, comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds or pharmaceutical composition described herein.

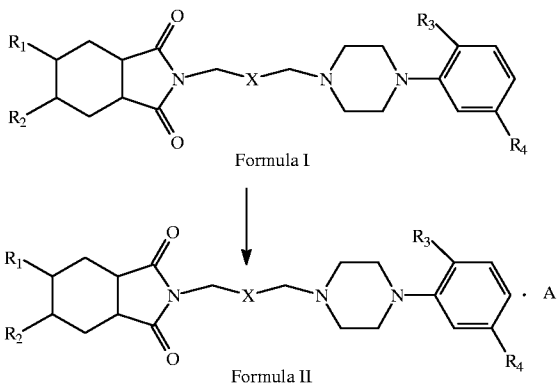
In another aspect, provided herein is a method for the treatment of a patient suffering from lower urinary tract symptoms (LUTS) with or without BPH, comprising administering to a patient, a therapeutically effective amount of a compound or pharmaceutical composition described herein. LUTS may include, for example, irritative symptoms (*e.g.* frequent urination, urgent urination, nocturia or unstable bladder contractions), or obstructive symptoms (*e.g.* hesitancy, poor stream, prolong urination or feelings of incomplete emptying).

In another aspect, provided herein is a method for the treatment of a patient suffering from BPH or LUTS with or without BPH, comprising administering to a patient, a therapeutically effective amount of one or more compounds (or compositions) described herein in combination with one or more bladder selective muscarinic receptor antagonists and/or testosterone 5α-reductase inhibitors.

In yet another aspect, provided herein is a process for preparing the acid addition salts as described above.

The compounds of the present invention may be prepared by techniques known in the art. For example, the compounds of the present invention may be prepared by the following reaction sequence:

Scheme I



The compounds of Formula II can be prepared by following Scheme I. Thus, compounds of Formula I can be reacted with an organic or inorganic acid to give

compounds of Formula II (wherein A, R_1-R_4 and X are the same as defined earlier). Using the methods known to those in the art, the compounds of Formula II are isolated.

The reaction of compounds of Formula I with an organic or inorganic acid can be carried out in one or more solvents. Acids used may also be contacted with one or more solvents. "Solvents" as used herein include, but are not limited to, aliphatic hydrocarbons (*e.g.*, hexane, cyclohexane or heptane), aromatic hydrocarbons (*e.g.*, benzene, toluene or xylene), halogenated hydrocarbons (*e.g.*, dichloromethane, dichloroethane, chloroform or carbon tetrachloride), ethers (*e.g.*, diethyl ether, tetrahydrofuran or dioxane), ketones (*e.g.*, acetone or diethyl ketone), esters (*e.g.*, ethyl acetate or propyl acetate), nitriles (*e.g.*, acetonitrile or propionitrile), or alcoholic solvents (*e.g.*, methanol, ethanol or isopropanol). The solvents described herein are used provided they have no adverse effect on the reaction and they can dissolve the starting material and the acid to some extent.

The solvent used to react compounds of Formula I can be the same as or different from the solvent employed to solublize the acid, provided that the choice of the acid solvent does not adversely affect the solubility of compounds of Formula I when the two solutions are conacted together during the treatment step.

Acid can be added to the compound in any proportion with respect to compounds of Formula I which results in the formation of at least some of the desired acid addition salt.

The solution of compounds of Formula I (free base) can be treated with an organic or inorganic acid directly, for example, by bubbling gaseous acid into the solution or acid can first be dissolved in a solvent and then added as a solution of acid. The acid solution can be added all at once or can be added in two or more portions, or can be added incrementally.

The reaction of compounds of Formula I can be conducted at any temperature at which compound of Formula I is soluble in the chosen solvent.

Following the addition of acid, the solution can be aged for a period of time to permit intimate mixing of acid and compounds of Formula I.

The reaction temperature and duration of reaction will depend on the selection of reagents, solvents and the like.

As used, herein, the term 'aging' means allowing the reactants to allow remaining in contact for a time under the conditions effective for the completion of the reaction. The present invention also includes within its scope prodrugs of these agents. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedure for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs", Ed. H Bundgaard, Elsevier, 1985. The present invention also includes metabolites, which become active upon introduction into the biological system. The compounds of the invention possess two chiral centers, they may, therefore, exist as enantiomers and diastereomers. All such stereo isomers and racemic mixtures therefore are encompassed within the scope of the present invention.

The crystalline or amorphous forms of compounds described herein may exist as polymorphs, hydrates or solvates, such are included in the present invention.

Compounds described herein can be administered to a patient (*e.g.*, human or animal) orally, parenterally, topically, rectally, internasally, subcutaneously or transdermally. Pharmaceutical compositions of the present invention can comprise pharmaceutically effective amounts of one or more compounds of the present invention formulated together with one or more pharmaceutically acceptable carriers.

The term "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filter, diluent, encapsulating material or formulation auxiliary of any type.

Solid form preparations for oral administration includes capsules, tablets, pills, powder, granules, cachets or suppositories. For solid form preparations, one or more active compounds can be mixed with one or more inert, pharmaceutically acceptable excipients or carriers, for example, sodium citrate, dicalcium phosphate and/or one or more fillers or extenders, for example, starch, lactose, sucrose, glucose, mannitol, silicic acid or mixtures thereof; one or more binders, for example, carboxymethylcellulose,

alginates, gelatins, polyvinylpyrolidinone, sucrose, acacia or mixtures thereof; disintegrating agents, for example, agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates, sodium carbonate or mixtures thereof; absorption accelators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol, glycerol, monostearate or mixtures thereof; adsorbents, for example, kaolin; lubricants, for example, talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulfate or mixtures thereof.

For capsules, tablets or pills, dosage forms can also comprise one or more buffering agents.

Solid preparations of tablets, capsules, pills or granules can also be prepared with one or more coatings and/or shells, for example, enteric coating and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or elixirs. For liquid form preparations, one or more active compounds can be mixed with water and/or other solvent(s), one or more solubilizing agents or emulsifiers, for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor or sesame oil), glycerol, fatty acid esters of sorbitan or mixtures thereof. In addition to inert diluents, oral compositions can also include one or more adjuvants, for example, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents or mixtures thereof.

Injectable preparations (*e.g.*, sterile injections, aqueous or oleaginous suspensions) may be formulated according to methods known to one of ordinary skill in the art, for example, using one or more suitable dispersing agents, wetting agents, suspending agents or mixtures thereof. Acceptable carriers or solvents that may be employed include, for example, water, Ringer's solution, U.S.P., isotonic sodium chloride or mixtures thereof.

Dosage forms for topical or transdermal administration includes ointments, pastes, creams, lotions, gel, powders, solutions, spray, inhalants or patches. Active compound can

be admixed under sterile conditions with one or more pharmaceutically acceptable carriers, as well as any preservatives or buffers as may be required. Ophthalmic formulations, eardrops, eye ointments, powders and solutions are also encompassed within the scope of this invention.

Pharmaceutical preparations may be in unit dosage form. In particular, preparations may be subdivided into unit dosage forms containing appropriate and therapeutically effective quantities of one or more active ingredients. Unit dosage forms can be packaged preparations containing discrete capsules, powders, in vials or ampoules, ointments, capsules, cachets, tablets, gels, creams, or any combination thereof and in appropriate numbers of unit dosages.

Formulations of the present invention may be formulated by methods known to one of ordinary skill in the art to provide immediate release, as well as sustained- or delayed-release of active ingredients after administration to a patient.

Compounds described herein, bladder selective muscarinic receptor antagonists and/or 5α reductase inhibitors can be formulated in combination to achieve desired therapeutic effects, *i.e.*, combination therapies. As such, the dosage amounts of such active ingredients can be adjusted accordingly, without undue experimentation and well within the abilities of one of ordinary skill in the art. As one of ordinary skill in the art can appreciate, dosage amounts of compounds described herein, bladder selective muscarinic receptor antagonists and/or 5α reductase inhibitors may be independently optimized and combined to achieve a synergistic therapeutic result. In accordance with methods encompassed herein, individual components of any combination can be administered separately in any sequence at the same or different times during the course of therapy, or concurrently in divided or single combination forms.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided

to illustrate the particular aspect of the disclosure and do not limit the present invention as defined by the claims.

Examples

Example 1: General method for preparing compounds of Formula II (A=organic acid)

To a solution of compound of Formula I in alcoholic solvent corresponding acid (1 equiv.) was added and the solution was stirred for about 1 hour. The solvent was concentrated to 1/5th of the total volume. The salt was precipitated by addition of a non-polar solvent. The salt was filtered off, washed with ether and dried under vacuum.

Example 2: Preparation of 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate (Compound No. 24)

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione (10g, 0.02157 moles) was dissolved in absolute ethanol (200 mL) at about 40^0C. Maleic acid (2.5g, 0.02157 moles) dissolved in absolute ethanol (10mL) was added to the reaction mixture at about $25\text{-}35^0$C and stirred for about 2 hours at same temperature. The reaction mass was cooled to about $0\text{-}5^0$C for about 2 hours. Diethyl ether was added and stirred for about 4 hours. The solid thus formed was filtered, washed with diethyl ether, and dried *in vacuum* at about 40^0C for about 6 hours.

m.pt.: 131-133 °C; IR (KBr) in cm^{-1}: 3393, 1701 and 1118; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.33 (6H,d), 1.8-1.84 (2H,m), 2.06-2.07 (2H,t), 2.16-2.19 (2H,t), 3.07-3.11 (8H,m), 3.56-3.59 (6H,m), 3.78-3.79 (2H,m), 4.46-4.53 (1H,m), 6.27 (2H, s), 6.60-6.63 (1H,dd), 6.64-6.67 (1H,m), 6.7-6.8 (1H,m); Mass (m/z): 464 (M+1)

The following analogous compounds were prepared following the procedure described above:

Compound No. 1: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate, m.pt.: hygroscopic

Compound No. 47: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate, m.pt.: hygroscopic

Compound No. 70: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione citrate, m.pt.: hygroscopic

The following compounds can be prepared following the procedure described above:

Compound No. 2: 5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

Compound No. 3: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 4: 5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

Compound No. 5: 5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

Compound No. 6: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

Compound No. 7: 5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione succinate,

Compound No. 8: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 9: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 10: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 11: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione succinate,

Compound No. 12: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

Compound No. 13: 5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 14: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 15: 5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 16: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 17: 2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 18: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 19: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 20: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 21: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 22: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

Compound No. 23: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate

Compound No. 25: 5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

Compound No. 26: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 27: 5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

Compound No. 28: 5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

Compound No. 29: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

Compound No. 30: 5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione maleate,

Compound No. 31: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 32: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 33: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 34: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione maleate,

Compound No. 35: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

Compound No. 36: 5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 37: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 38: 5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 39: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 40: 2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 41: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

Compound No. 42: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate

Compound No. 43: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate

Compound No. 44: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate

Compound No. 45: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate

Compound No. 46: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate

Compound No. 48: 5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate

Compound No. 49: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 50: 5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 51: 5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 52: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 53: 5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione tartarate,

Compound No. 54: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 55: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 56: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 57: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione tartarate,

Compound No. 58: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 59: 5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 60: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 61: 5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 62: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 63: 2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 64: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 65: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 66: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 67: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 68: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

Compound No. 69: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate.

Example 3: General method for preparing compounds of Formula II (A=inorganic acid)

An equimolar quantity of compound of Formula I can be added in dichloromethane. The solid, which precipitates, is then filtered, washed with non-polar solvent to obtain the inorganic salt of the respective compound.

Example 4: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate (Compound No. 71)

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione (11g, 0.0237 moles) was dissolved in dichloromethane (250 mL) at about 25-35^{0}C. Ortho phosphoric acid (88%, 2.32gm) dissolved in dichloromethane was added to the reaction mixture at about 5-10^{0}C. The reaction was stirred at about 25-35^{0}C for about 2-3 hours. Hexane was added and stirred at about 25-35^{0}C for about 48 hours. The solid thus formed was filtered, washed with hexane, and dried at about 40^{0}C under vacuum for about 15 hours.

m.pt.: 106-108 °C; IR (KBr) in cm^{-1}: 1168, 1698 and 3400; Mass (m/z): 464 (M+1)

The following analogous compounds can also be prepared following the procedure given above:

Compound No. 72: 5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 73: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 74: 5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 75: 5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 76: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 77: 5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione phosphate,

Compound No. 78: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 79: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 80: 2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 81: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione phosphate,

Compound No. 82: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 83: 5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 84: 2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 85: 5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 86: 2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 87: 2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 88: {3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 89: {3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 90: {3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 91: {3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 92: {3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 93: {3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

Compound No. 94: {3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate.

Pharmacological Activity

Radioligand Binding Assays: Receptor binding assays are performed using native α-1 adrenoceptors. The affinity of different compounds for α_{1a} and α_{1b} adrenoceptor subtypes is evaluated by studing their ability to displace specific [^{3}H]prazosin binding from the membranes of rat submaxillary and liver respectively (*Michel et al, Br J Pharmacol, 98, 883-889 (1989)*). The binding assays are performed according to U'Prichard et al. (Eur J Pharmacol, 50:87-89 (1978) with minor modifications.

Submaxillary glands are isolated immediately after sacrifice. The liver is perfused with buffer (Tris hydrochloric acid 50 mM, sodium chloride100 mM, 10 mM ethylene diamine tetra acetic acid pH 7.4). The tissues are homogenized in 10 volumes of buffer (Tris HCl 50 mM, NaCl 100 mM, EDTA 10 mM, pH 7.4). The homogenate is filtered through two layers of wet guaze and filtrate is centrifuged at 500g for 10 min. The supernatant is subsequently centrifuged at 40, 000g for 45 min. The pellet thus obtained is resuspended in the same volume of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) and are stored at –70 ^{0}C until the time of assay.

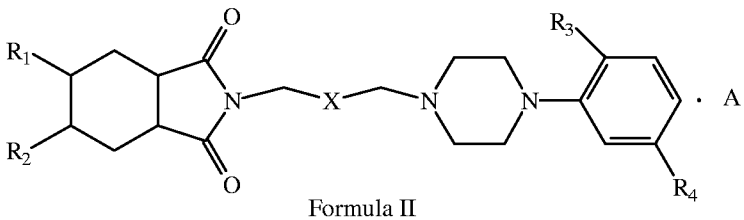
The membrane homogenates (150-250 μg protein) are incubated in 250 μl of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) at 24-25 ^{0}C for I hour. Non-specific binding is determined in the presence of 300 nM prazosin. The incubation is terminated by vaccum filtration over GF/B fibre filters. The filters are then washed with ice-cold 50 mM Tris HCl buffer (pH 7.4). The filtermats waere dried and bounded radioactivity retained on filters is counted. The IC_{50} and Kd are estimated by using the non-linear curve-fitting program using G pad prism software. The value of inhibition constant Ki is calculated from competitive binding studies by using Cheng and Prusoff equation (Cheng and Prusoff, Biochem Pharmacol, 1973, 22:3099-3108), $Ki = IC_{50}/(1+L/Kd)$ where L is the concentration of [^{3}H] prazosin used in the particular experiment.

In vitro functional studies (In vitro α_{1a} Adrenoceptor selectivity)

In order to study selectivity of action of the present compounds towards different α_{1a} adrenoreceptor subtypes, the ability of these compounds to antagonize α_{1a} adrenoreceptor agonist induced contractile response of aorta (α_{1d}), prostate (α_{1a}) and spleen (α_{1b}) is studied. Aorta, prostate and spleen tissue are isolated from thipentane anaesthetized (≈ 300 mg/Kg) male wistar rats. Isolated tissues are mounted in organ bath containing Krebs Henseleit buffer of the following composition (mM): sodium chloride (NaCl) 118; potassium chloride (KCl) 4.7; calcium chloride ($CaCl_2$) 2.5; magnesium sulphate hepta hydrate ($MgSO_4$. $7H_2O$) 1.2; sodium bicarbonate ($NaHCO_3$) 25; potassium dihydrogen phosphate (KH_2PO_4) 1.2; glucose 11.1. Buffer was maintained at 37 ^{0}C and aerated with a mixture of 95% oxygen (O_2) and 5% carbon dioxide (CO_2). A resting tension of 2 g (aorta and spleen) or 1 g (prostate) is applied to tissues. Contractile response is monitored using a force displacement transducer and recorded on chart recorders. Tissues are allowed to equilibrate for 1 and 1/2 hour. At the end of equilibration period, concentration response curves to nor epinephrine (aorta) and phenyl epinephrine (spleen and prostate) are obtained in the absence and presence of the tested compound (at concentration of 0.1, 1 and 10 μM).

We Claim:

1. Acid addition salts of compounds having the structure of Formula II:



Formula II

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein:

A is an organic acid selected from acetic, succinic, maleic, trifluoroacetic, oxalic, citric, malonic, adipic, ascorbic, camphor sulfonic, nicotinic, butyric, lactic and glucuronic acid; an inorganic acid selected from hydrochloric, hydrobromic, phosphoric, sulfuric, nitric, boric and perchloric; R_1 and R_2 are independently hydrogen, hydroxy or halogen; X is CO, CHOH or CH_2; and R_3 and R_4 are independently hydrogen, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_5-C_6 cycloalkoxy.

2. Acid addition salts of claim 1, wherein A is selected from tartaric, succinic, maleic and phosphoric acid.

3. A compound which is selected from:

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione succinate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione succinate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione maleate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione maleate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione tartarate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione citrate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

5,6-Dihydroxy-2-{3-[4-(2-methoxy-5-methylphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-6-hydroxy-2-{2-hydroxy-3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-6-hydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Hydroxy-2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-hexahydro-isioindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-2-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

5-Fluoro-2-{3-[4-(5-fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-propyl}-5-fluoro-6-hydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate,

2-{3-[4-(2-Cyclopentyloxy-5-fluorophenyl)-piperazin-1-yl]-2-hydroxy-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate, and

2-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione phosphate.

4. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

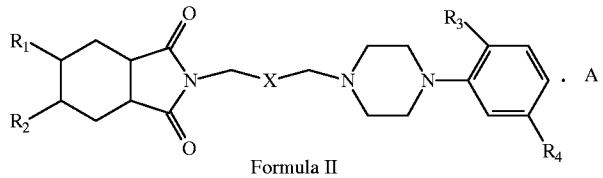
5. A method for treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors, comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds of claim 1 or pharmaceutical composition of claim 4.

6. A method for treating benign prostatic hyperplasia, comprising administering to a patient therapeutically effective amounts of one or more compounds of claim 1 or pharmaceutical composition of claim 4.

7. The method according to claim 5 wherein compound or composition causes minimal fall or no fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

8. A method for treating lower urinary tract symptoms associated with or without benign prostatic hyperplasia, comprising administering to patient therapeutically effective amounts of one or more compounds of claim 1 or a pharmaceutical composition of claim 4.

9. A method for preparing compounds having the structure of Formula II,

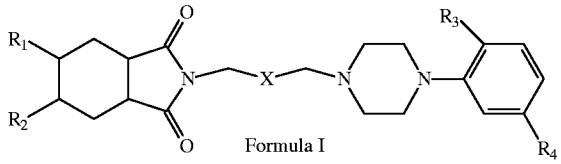


Formula II

pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein,

A is an organic acid selected from acetic, succinic, maleic, trifluoroacetic, oxalic, citric, malonic, adipic, ascorbic, camphor sulfonic, nicotinic, butyric, lactic and glucuronic; an inorganic acid selected from hydrobromic, phosphoric, sulfuric, nitric, boric and perchloric acid; R_1 and R_2 are independently hydrogen, hydroxy or halogen; X is CO, CHOH or CH_2; R_3 and R_4 are independently hydrogen, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_5-C_6 cycloalkoxy, which method comprises:

reacting a compound of Formula I,



Formula I

with an organic or inorganic acid to form a compound of Formula I.