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(54) **Title:** SUCCINIMIDE AND GLUTARIMIDE DERIVATIVES AS ADRENERGIC RECEPTOR ANTAGONISTS

(57) **Abstract:** The present invention relates to succinimide and glutarimide derivatives, which can be used to treat a disease or disorder mediated through 1a and/or 1d adrenergic receptors. Compounds and pharmaceutical compositions disclosed herein can be used to treat benign prostatic hyperplasia (BPH) and related symptoms thereof. Further, such compounds can be used to treat lower urinary tract symptoms that may or may not be associated with BPH. The present invention also relates to processes to prepare the disclosed compounds, pharmaceutical compositions thereof, and methods of treating BPH or related symptoms thereof.

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SUCCINIMIDE AND GLUTARIMIDE DERIVATIVES AS ADRENERGIC RECEPTOR ANTAGONISTS

Field of the Invention

The present invention relates to succinimide and glutarimide derivatives, which can be used to treat a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors. Compounds and pharmaceutical compositions disclosed herein can be used to treat benign prostatic hyperplasia (BPH) and related symptoms thereof. Further, such compounds can be used to treat lower urinary tract symptoms that may or may not be associated with BPH. The present invention also relates to processes to prepare the disclosed compounds, pharmaceutical compositions thereof, and methods of treating BPH or related symptoms thereof.

Background of the Invention

Benign prostatic hyperplasia (BPH) is a condition that typically develops in elderly males. BPH causes benign overgrowth of the stromal and epithelial elements of the prostate with aging. Symptoms of BPH can vary and commonly involve changes or problems with urination, such as hesitation, interruption, weak stream, urgency, leaking, dribbling or increased frequency, particularly at night. BPH can consequently cause hypertrophy of bladder smooth muscle, a decompensated bladder or an increased incidence of urinary tract infection.

The symptoms of BPH are a result of two pathological components affecting the prostate gland: a static component and a dynamic component. The static component is related 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 related to increased smooth muscle tone of the bladder neck and prostate itself and is regulated by α_1 adrenergic receptor.

Currently, the most effective treatment for BPH is a surgical procedure known as transurethral resection of the prostate (TURP), which involves removing obstructing tissue (C. Chapple, *Br. Med. Journal*, **304**:1198-1199 (1992)). TURP is directed both to the static and dynamic components of the BPH. However, TURP is associated with mortality (1 %), adverse events, *e.g.*, incontinence (2-4 %), infection (5-10 %), and impotence (5-10 %). Therefore, noninvasive alternative treatments are highly desirable.

Some drug therapies address the static component of BPH. Administration of finasteride is one such therapy, which is indicated for the treatment of symptomatic BPH. This drug is a competitive inhibitor of the enzyme 5α- reductase that is responsible for the conversion of testosterone to dihydrotestosterone in the prostate gland. 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 that causes a marked decrease in serum and tissue concentrations of dihydrotestosterone, it is moderately effective in the treatment of symptomatic BPH. The effects of finasteride take 6-12 months to become evident and for many men the clinical development is minimal.

The dynamic component of BPH has been addressed by the use of adrenergic receptor blocking agents, which act by decreasing the smooth muscle tone within the prostate gland. A variety of α_{1a} AR antagonists, for example, terazosin, doxazosin, prazosin, alfuzosin and tamulosin, have been investigated for the treatment of symptomatic bladder outlet obstruction due to BPH. However, these drugs are associated with vascular side effects (*e.g.*, postural hypertension, syncope, dizziness, headache etc.) due to lack of selectivity of action between prostatic and vascular α_1 adrenoceptors. There are several lines of evidence suggesting that selectivity for α_{1a} adrenoceptor over α_{1b} adrenoceptor will result in relative lack of vascular side effects, thus lead to better tolerability. Mice deficient in α_{1b} adrenoreceptors show diminished blood pressure response to phenylephrine injection when compared to homozygous controls (decreased blood pressure response in mice deficient of α_{1b} adrenergic receptor. (*Proc. Nat'l Acad. Sci. USA*, **94**:1589-11594 (1997)). *In-vivo* studies in healthy subjects comparison of α_{1a}/α_{1d} selective antagonists (*e.g.*, tamsulosin) or α_{1a} selective antagonists (*e.g.*, urapidil) with non selective antagonists (*e.g.*, doxazosin, prazosin, or terazosin) under a variety of experimental conditions (*e.g.*, involving the administration of exogenous agonist or release of endogenous agonist by cold stimulation) in several vascular beds including the skin circulation in finger tips, the dorsal hand vein, or with total peripheral resistance have been reported. (*Eur. J. Clin. Pharmacol.*, **49**:371-375 (1996); N. Schmiedeberg, *Arch. Pharmacol.*, **354**:557-561 (1996); *Jpn. J. Pharmacol.*, **80**:209-215 (1999); *Br. J. Clin. Pharmacol.*, **47**:67-74 (1999)). These studies reported that an antagonist with high affinity for α_{1a} or α_{1a}/α_{1d} receptors can cause some degree of vasodilation, although it is much

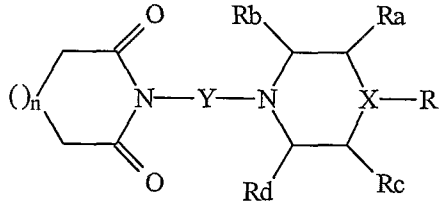
lower than with non-subtype-selective α_{1a} adrenoceptor antagonists. Further, there is increased vascular α_{1b} adrenoceptor expression in elderly patients and thus α_{1a}/α_{1d}-selective agents with selectivity over α_{1b} adrenoceptor subtype would be of particular importance in benign prostatic hyperplasia. Antagonism of both α_{1a} adrenoceptor and α_{1d} adrenoceptor is important to relieve lower urinary tract symptoms especially associated with BPH. Targeting α_{1a} adrenoceptors 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.

The synthesis of 1-(4-arylpiperazin-1-yl)-ω-[N- (α, ω-dicarboximido)]-alkanes useful as uroselective α_1-adrenoceptor blockers are disclosed in US Patent Nos. 6,083,950, 6,090,809, 6,410,735, 6,420,559 and 6,420,366, WO 00/05206, US Patent Appl. No. 2002/0156085 and WO 02/44151. These compounds exhibited α_1-adrenergic blocking activity and selectivity.

Summary of the Invention

Generally provided herein are succinimide and glutarimide derivatives, which can be used to treat disease or disorder mediated through α_{1a} and/or α_{1d} subtype adrenergic receptors. Compounds disclosed herein can be used to treat benign prostatic hyperplasia (BPH) and related symptoms thereof or lower urinary tract symptoms (LUTS) associated with or without BPH. The present invention also provides processes for the synthesis of such compounds. Also provided herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides of such compounds. Also provided are pharmaceutical compositions containing the disclosed compounds and one or more pharmaceutically acceptable carriers, excipients or diluents, which can be used for the treatment of BPH or related symptoms thereof or LUTS with or without BPH.

In one aspect, provided herein are compounds having the structure of Formula 1,



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

n can be an integer 0 or 1; Y can be alkylene; R_a-R_d can be hydrogen; R_a and R_c or R_a and R_d or R_b and R_d together can form $(CH_2)_m$, wherein m can be an integer of from 0 to 2; X-R can be CR_1R_2 or NR_3 {[wherein R_1 and R_2 can be independently hydrogen, hydroxy, alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, cycloalkyl, $NHCOR_4$ or $NHSO_2R_4$ (wherein R_4 can be alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, CH_2OCH_2aryl or OCH_2aryl,); R_3 can be COR_5, SO_2R_5, $CONHR_5$, $CH(aryl)R_5$, aryl, heteroaryl, heterocyclyl, or cycloalkyl]}; further X-R together with R_a can form aryl.

In another aspect, provided herein are compounds selected from:

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(benzyloxy)acetyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

4-[3-(2,6-dioxopiperidin-1-yl)propyl]-*N*,*N*-dimethylpiperazine-1-sulfonamide and its hydrochloride salt,

1-{3-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(trifluoromethyl)sulfonothioyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

ethyl 4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxylate and its hydrochloride salt,

2-{4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}-2-oxoethyl acetate) and its hydrochloride salt,

N-(2,4-difluorophenyl)-4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxamide and its hydrochloride salt,

1-{3-[5-(morpholin-4-ylcarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{5-[(benzyloxy)acetyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(4-nitrophenyl)sulfonyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

1-(3-{[3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}propyl) piperidine-2,6-dione and its hydrochloride salt,

1-[3-({3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)propyl]piperidine-2,6-dione and its hydrochloride salt,

2-(benzyloxy)-*N*-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}acetamide and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}benzamide and its hydrochloride salt,

benzyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}morpholine-4-carboxamide and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}-1,1,1-trifluoromethane sulfonamide and its hydrochloride salt,

methyl {4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}benzamide and its hydrochloride salt,

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide and its hydrochloride salt,

ethyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate and its hydrochloride salt,

1-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

2-(2,6-dioxopiperidin-1-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-l]ethyl}acetamide and its hydrochloride salt,

1-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-((2*R*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-((2*S*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione and its hydrochloride salt,

1-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione hydrochloride salt,

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

In another aspect, provided herein are pharmaceutical compositions comprising therapeutically effective amount of one or more compounds disclosed herein and optionally one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect, provided are methods for treating benign prostatic hyperplasia (BPH) or related symptoms comprising administering to a patient in need thereof a

therapeutically effective amount of a compound or pharmaceutical composition disclosed herein.

In another aspect, provided are methods for treating lower urinary tract symptoms (LUTS) with or without BPH comprising administering to a patient in need thereof a therapeutically effective amount of a compound or pharmaceutical composition disclosed herein. LUTS may include, for example, irritative symptoms (*e.g.*, frequent urination, urgent urination, nocturia and unstable bladder contractions), obstructive symptoms (*e.g.*, hesitancy, poor stream, prolong urination, and feeling of incomplete emptying).

In another aspect, provided are methods for treating BPH or LUTS with or without BPH comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds (or compositions) described herein in combination with one or more muscarnic receptor antagonists (*e.g.* solifenacin or darifinacin), bladder selective muscarinic receptor antagonists (*e.g.* RBx-9841 or RBx-10416), testosterone 5α-reductase inhibitors (*e.g.* finasteride or dutasteride), HMG-COA reductase inhibitors (*e.g.* atorvastatin, pravastatin, RBx-10558 or RBx-11901) , endothelin antagonists, cGMP level elevators, 5-HT antagonists, nitric oxide donors or mixture thereof.

In yet another aspect, provided are processes for preparing compounds disclosed herein.

The compounds disclosed herein are potent adrenergic receptor antagonists. Such compounds exhibit high affinity towards α_{1a} and α_{1d} adrenoceptor subtypes and good selectivity for α_{1a} over α_{1b} adrenoceptor. α_{1a} adrenoceptors are involved in relieving obstructive symptoms of LUTS, whereas α_{1d} adrenoceptor antagonism is associated in alleviation of irritative symptoms of LUTS. The relatively lower affinity to α_{1b} adrenoceptors limits cardiovascular side effects, for example, orthostatic hypotension. Accordingly, pharmaceutical compositions for treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenoceptor subtypes are provided herein. Compounds and pharmaceutical compositions described herein can be administered orally, parenterally, subcutaneously, transdermally or topically.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl,

sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)$NR_fR_{q,}$, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_fR_q {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, or -SO_2R_4 (wherein R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, -NR_fR_q, -C(=O)NR_fR_q, -OC(=O) NR_fR_q, -NHC(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and –SO_2R_4, (wherein R_4 are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_a- {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl,-C(=O)OR_f (wherein R_f is the same as defined earlier), SO_2R_4 (where R_4 is as defined earlier), or -C(=O)NR_fR_q (wherein R_f and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, -NR_fR_q, -C (=O)NR_fR_q, - O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3, cyano, and –SO_2R_4 (where R_4 is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "aryl," unless otherwise specified, refers to carbocyclic aromatic groups, for example, phenyl, biphenyl or napthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_e$ (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), -SO_2R_4 (wherein R_4 is same as defined earlier), carboxy,

heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_fR_q$, CH=NOH, $-(CH_2)_wC(=O)R_g$ {wherein w is an integer from 0-4 and R_g is hydrogen, hydroxy, OR_f, NR_fR_q, $-NHOR_z$ or –NHOH}, $-C(=O)NR_fR_q$ and $-NHC(=O)NR_fR_q$, $-SO_2R_4$, $-O-C(=O)NR_fR_q$, $-O-C(=O)R_f$, $-O-C(=O)OR_f$ (wherein R_4, R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

The term 'heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, $-O-C(=O)R_f$, $-O-C(=O)OR_f$, $-C(=O)NR_fR_q$, SO_2R_6, $-O-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-NR_fR_q$ (wherein R_6, R_f and R_q are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl,

dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

The groups "aryl, heteroaryl and heterocyclyl" can optionally be substituted with substituent(s) selected from alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocycloalkyl, halogen, hydroxy, alkoxy, cyano, nitro, aryloxy, haloalkoxy, COR_b, CSR_b, $COOR_b$, $S(O)_aR_b$, $OCOOR_b$, $NHSO_2R_b$, $NHCOR_b$, $NHCSR_b$, $(CH)_{0-2}C(=O)NR_cR_d$ or NR_cR_d (wherein R_b, R_c and R_d are independently selected from hydrogen, alkyl, aryl, heteroaryl, heterocyclyl and a is an integer of from 0-2. Unless otherwise constrained, all substituents may optionally be further substituted by substituent(s) defined earlier.

The term "alkoxy" stands for a radical represented by Formula O-alkyl and wherein alkyl is the same as defined above. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, and the like.

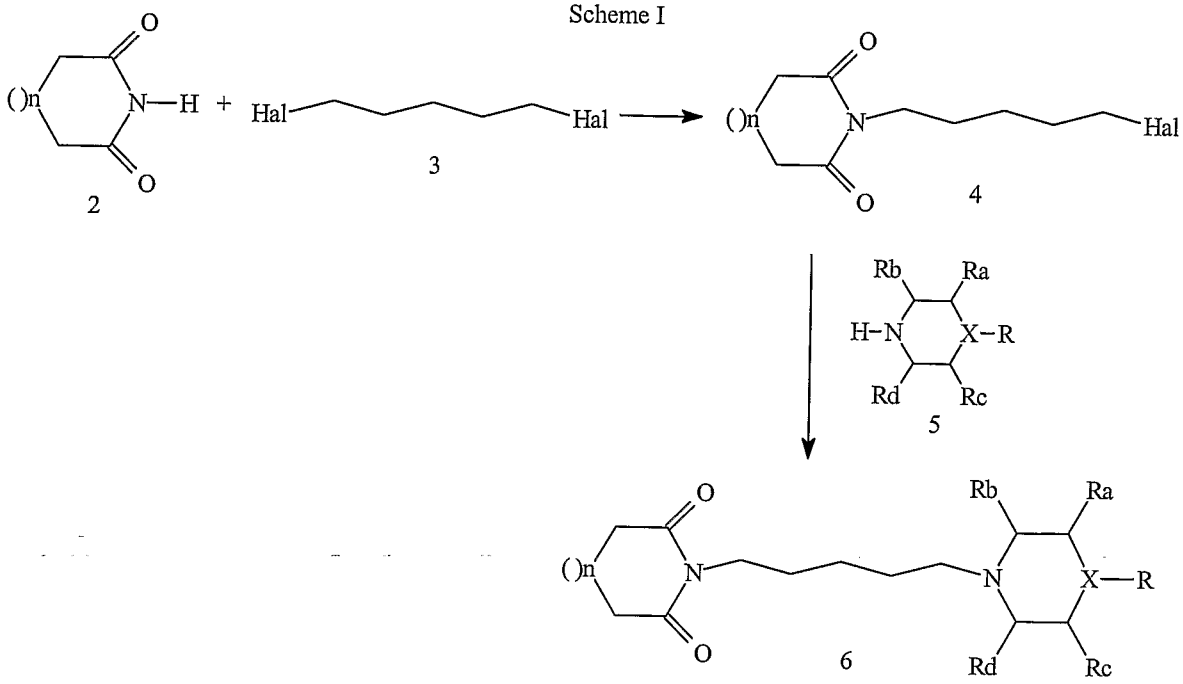
The term "alkylene" herein refers to $-(CH)_{n'}-$ wherein n can be an integer of from 3 to 8 and one or more hydrogen can optionally be substituted with alkyl, hydroxy, halogen or oximes. Alkylene can also be optionally interrupted by -CONH-, -C=O, -NH-, or -O-.

The present invention also encompasses prodrugs of the compounds disclosed herein. In general, such prodrugs will be functional derivatives of such compounds, which are readily convertible *in vivo* into the required compound. Conventional procedures for selecting and preparing suitable prodrug derivatives are described in, for example, "Design of Prodrugs", ed. H. Bundgaard and, Elsevier, 1985. The present invention also encompasses metabolites of the compounds disclosed herein, which become active upon introduction into a biological system. Compounds disclosed herein possess two chiral centers and may therefore exist as enantiomers or diastereomers. It is to be understood that all such isomers or racemic mixtures therefore are encompassed within the scope of the present invention. Crystalline or amorphous forms of compounds disclosed herein may exist as polymorphs and are encompassed in the present invention.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known to one of ordinary skill in the art. In addition, the compounds described herein may be prepared by, for example following the reaction sequences as shown in Schemes I, II, III, IV, V and VI.

Scheme I

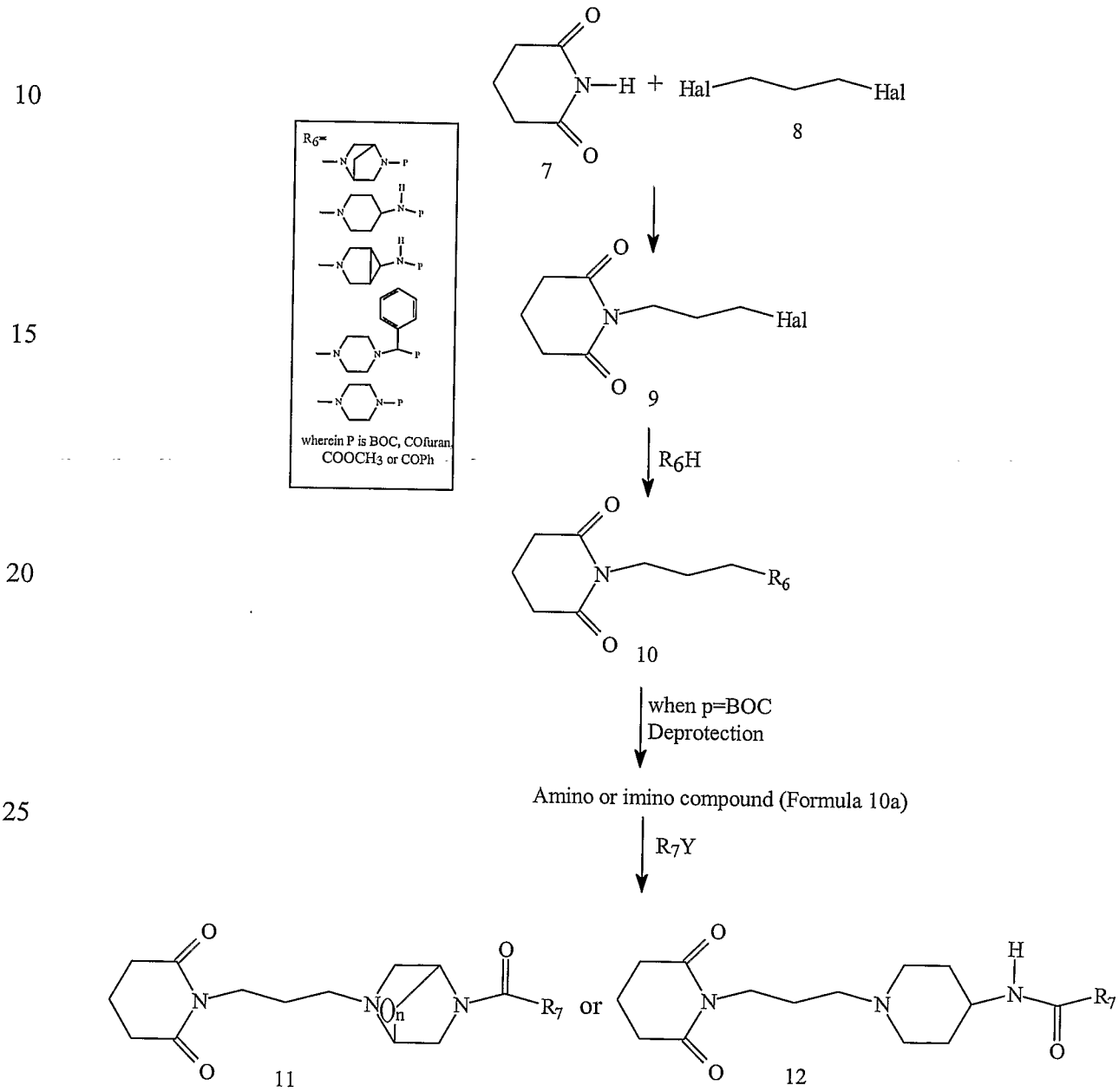


Compounds Formula 6 can be prepared according to scheme I. Thus, compounds of Formula 2 can be reacted with dihalopentane of Formula 3 to form compounds of Formula 4 (wherein Hal is halogen). Compounds of Formula 4 can be reacted with compounds of Formula 5 to form compounds of Formula 6 (wherein R_a-R_d, X and R are the same as defined earlier). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art.

Compounds of Formula 2 can be reacted in the presence of one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof, in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (ethyl acetate or ethylformate). Compounds of Formula 4 can be reacted in the presence of potassium iodide and one or more inorganic

bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof. Compounds of Formula 4 can also be reacted in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (ethyl acetate or ethylformate).

Scheme II



Compounds of Formula 11 or 12 can be prepared, for example according to Scheme II. Thus, glutarimide of Formula 7 can be reacted with dihalopropane of Formula

8 to form compounds of Formula 9. Compounds of Formula 9 can be reacted with compounds of Formula R_6H to form compounds of Formula 10 (wherein R_6 is the same as defined earlier). Compounds of Formula 10 (when P=BOC) can be deprotected to form amino compounds. Amino compounds can be reacted with compounds of Formula R_7Y (Y is hydrogen or halogen) to form compounds of Formula 11 or 12 (wherein R_7 can be morpholinyl, $PhCH_2OCH_2CO$, $PhCO$, CF_3SO_2, $PhCH_2OCO$, C_2H_5OCO, CH_3COOCH_2CO, $N(CH_3)_2SO_2$, $CONHC_6H_3F_2$ or $SO_2C_6H_4NO_2$). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art.

Glutarimide of Formula 7 can be reacted in the presence of one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof, in one or more solvents, for example, ketones (e.g. acetone, ethylmethylketone or diethylketone), ethers (e.g. diethyl ether, tetrahydrofuran or dioxane), acetates (ethyl acetate or ethylformate), chlorinated solvents (dichloromethane, chloroform, carbon tetrachloride or dichloroethane) or mixture thereof.

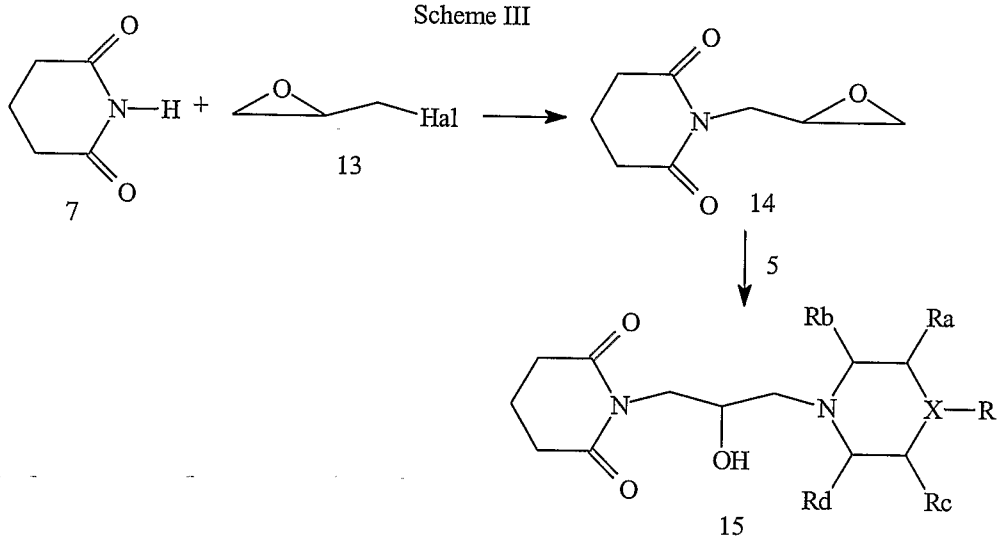
Compounds of Formula 9 can be reacted in the presence of potassium iodide and one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof, in one or more solvents, for example, ketones (e.g. acetone, ethylmethylketone or diethylketone), ethers (e.g. diethyl ether, tetrahydrofuran or dioxane), acetates (e.g. ethyl acetate or ethylformate), chlorinated solvents (e.g. dichloromethane, chloroform, carbon tetrachloride or dichloroethane), nitriles (e.g. acetonitrile or propionitrile) or mixture thereof.

Compounds of Formula 10 can be deprotected (when p=BOC) in the presence of mineral acid, for example, hydrochloric acid or hydrobromic acid, in one or more solvents, for example, ketones (e.g. acetone, ethylmethylketone or diethylketone), ethers (e.g. diethyl ether, tetrahydrofuran or dioxane), acetates (e.g. ethyl acetate or ethylformate), chlorinated solvents (e.g. dichloromethane, chloroform, carbon tetrachloride or dichloroethane), nitriles (e.g. acetonitrile or propionitrile), alcohols (e.g. methanol, ethanol, propanol or butanol) or mixture thereof.

Amino compounds can be reacted in the presence or absence of trichloroacetic anhydride, in one or more solvents, for example, ketones (e.g. acetone, ethylmethylketone or diethylketone), ethers (e.g. diethyl ether, tetrahydrofuran or dioxane), acetates (e.g.

ethyl acetate or ethylformate), chlorinated solvents (e.g. dichloromethane, chloroform, carbon tetrachloride or dichloroethane), nitriles (e.g. acetonitrile or propionitrile), alcohols (e.g. methanol, ethanol, propanol or butanol) or mixture thereof. The reaction can also be carried out in the presence of triphosgene and one or more organic bases, for example, triethylamine, trimethylamine, diethylamine, tributylamine, pyridine or 4-dimethylaminopyridine.

Scheme III



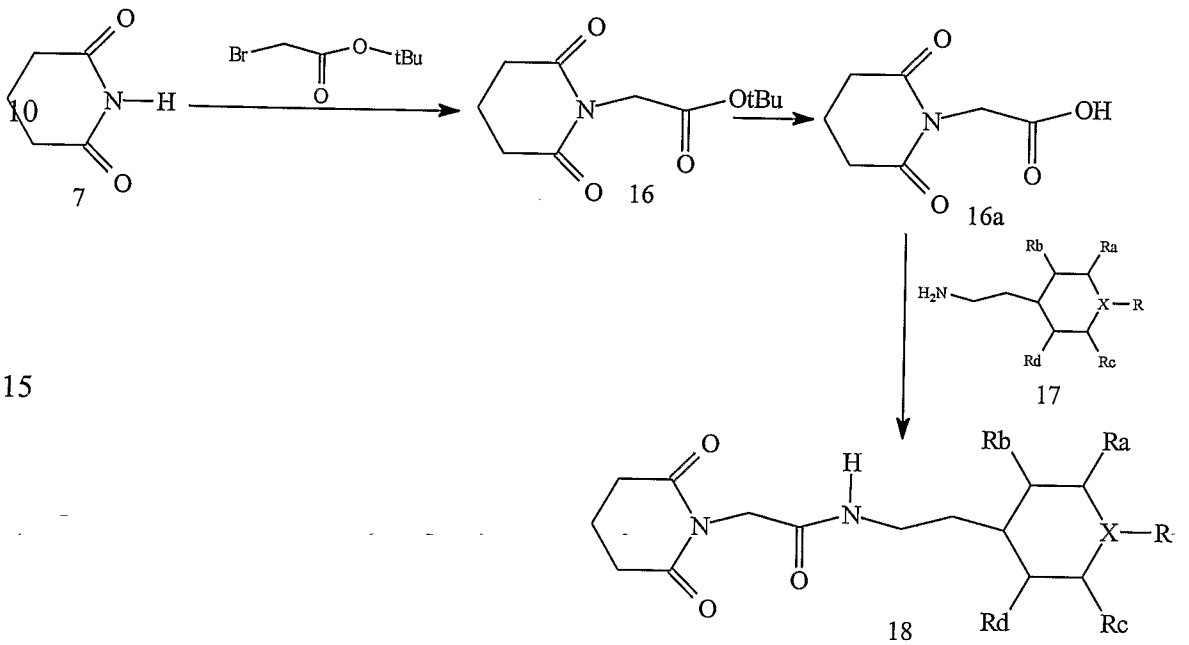
Compounds of Formula 15 can be prepared, for example according to Scheme III. Thus, glutarimide of Formula 7 can be reacted with compounds of Formula 13 (wherein Hal is halogen) to form compound of Formula 14. Compound of Formula 14 can be reacted with compounds of Formula 5 to form compounds of Formula 15 (wherein R_a-R_d, X and R are the same as defined earlier). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art.

Glutarimide of Formula 7 can be reacted in the presence of one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof, in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (ethyl acetate or ethylformate), chlorinated solvents (dichloromethane, chloroform, carbon tetrachloride or dichloroethane) or mixture thereof.

Compound of Formula 14 can be reacted in the presence of one or more organic bases, for example, triethylamine, trimethylamine, diethylamine, tributylamine, pyridine

or 4-dimethylaminopyridine, in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (e.g., ethyl acetate or ethylformate), chlorinated solvents (e.g., dichloromethane, chloroform, carbon tetrachloride or dichloroethane), polar aprotic solvents (e.g., dimethylformamide or dimethylsulfoxide) or mixture thereof.

Scheme IV



Compounds of Formula 18 can be prepared, for example, according to Scheme IV. Thus, glutarimide of Formula 7 can be reacted with bromoacetic acid tert-butyl ester to form (2,6-dioxo-piperidin-1-yl) acetic acid tert-butyl ester of Formula 16. Compound of Formula 16 can be hydrolyzed to form (2,6-dioxo-piperidin-1-yl) acetic acid of Formula 16a. Compound of Formula 16a can be reacted with compounds of Formula 17 to form compounds of Formula 18 (wherein R_a-R_d, X and R are the same as defined earlier). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art.

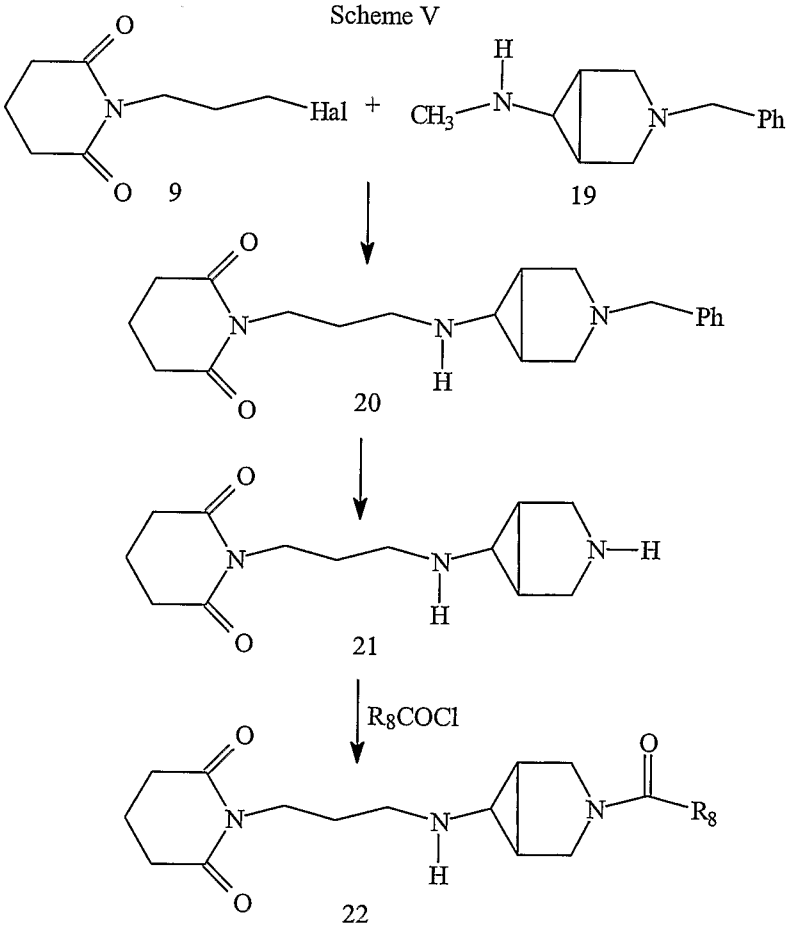
Glutarimide of Formula 7 can be reacted in the presence of one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium hydride, barium carbonate, calcium carbonate or mixture thereof, in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (e.g., ethyl acetate or ethylformate), chlorinated

solvents (e.g., dichloromethane, chloroform, carbon tetrachloride or dichloroethane), polar aprotic solvents (e.g., dimethylformamide or dimethylsulfoxide) or mixture thereof.

Compound of Formula 16 can be hydrolyzed in the presence of acid, for example, trifluroacetic acid, acetic acid, or trichloroacetic acid, in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (e.g., ethyl acetate or ethylformate), chlorinated solvents (e.g., dichloromethane, chloroform, carbon tetrachloride or dichloroethane), polar aprotic solvents (e.g., dimethylformamide or dimethylsulfoxide) or mixture thereof.

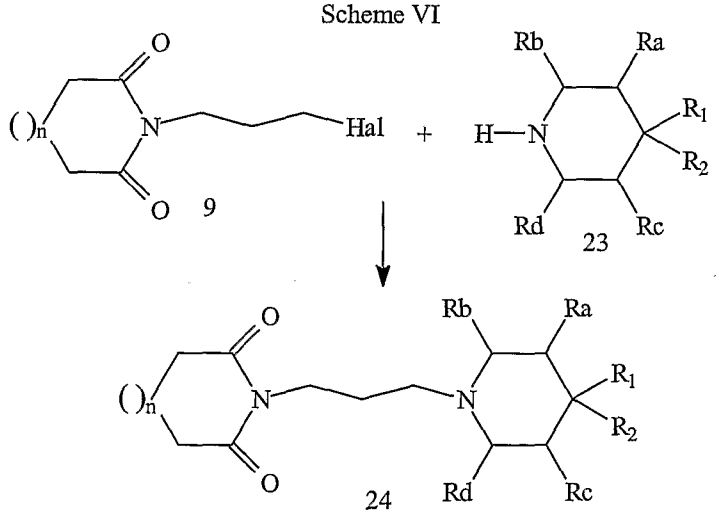
Compound of Formula 16a can be reacted in the presence of coupling agents, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride or DCC in one or more solvents, for example, ketones (e.g., acetone, ethylmethylketone or diethylketone), ethers (e.g., diethyl ether, tetrahydrofuran or dioxane), acetates (e.g., ethyl acetate or ethylformate), chlorinated solvents (e.g., dichloromethane, chloroform, carbon tetrachloride or dichloroethane), polar aprotic solvents (e.g., dimethylformamide or dimethylsulfoxide) or mixture thereof.

Scheme V



Compounds of Formula 22 can be prepared, for example, according to Scheme V. Thus, compounds of Formula can be reacted with (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)methylamine of Formula 19 to form 1-[3-(3-benzyl-3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 20. Compound of Formula 20 can be debenzylated to form 1-[3-(3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 21. Compound of Formula can be reacted with compounds of Formula R_8COCl to form compounds of Formula 22 (wherein R_8 can be CH_2OCH_2aryl, OCH_2aryl,), aryl, heteroaryl or heterocyclyl). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art.

Scheme VI



Compounds of Formula 24 can be prepared, for example, according to Scheme VI. Thus, compounds of Formula 9 can be reacted with compounds of Formula 23 to form compounds of Formula 24 (wherein R_a-R_d, R_1, R_2 and n are the same as defined earlier). Pharmaceutically acceptable salts can be prepared following the methods well known to one of ordinary skilled in the art. The following illustrative compounds were prepared.

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}piperidine-2,6-dione (Compound No. 1) and its hydrochloride salt (Compound No. 2),

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione (Compound No. 3) and its hydrochloride salt (Compound No. 4),

1-(3-{4-[(benzyloxy)acetyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 5) and its hydrochloride salt (Compound No. 6),

4-[3-(2,6-dioxopiperidin-1-yl)propyl]-*N*,*N*-dimethylpiperazine-1-sulfonamide (Compound No. 7) and its hydrochloride salt (Compound No. 8),

1-{3-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]propyl}piperidine-2,6-dione (Compound No. 9) and its hydrochloride salt (Compound No. 10),

1-(3-{4-[(trifluoromethyl)sulfonothioyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 11) and its hydrochloride salt (Compound No. 12),

ethyl 4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxylate (Compound No. 13) and its hydrochloride salt (Compound No. 14),

2-{4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}-2-oxoethyl acetate (Compound No. 15) and its hydrochloride salt (Compound No. 16),

N-(2,4-difluorophenyl)-4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxamide (Compound No. 17) and its hydrochloride salt (Compound No. 18),

1-{3-[5-(morpholin-4-ylcarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]propyl}piperidine-2,6-dione (Compound No. 19) and its hydrochloride salt (Compound No. 20),

1-(3-{5-[(benzyloxy)acetyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}propyl)piperidine-2,6-dione (Compound No. 21) and its hydrochloride salt (Compound No. 22),

1-(3-{4-[(4-nitrophenyl)sulfonyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 23) and its hydrochloride salt (Compound No. 24),

1-(3-{[3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}propyl) piperidine-2,6-dione (Compound No. 25) and its hydrochloride salt (Compound No. 26),

1-[3-({3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)propyl]piperidine-2,6-dione (Compound No. 27) and its hydrochloride salt (Compound No. 28),

2-(benzyloxy)-*N*-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}acetamide (Compound No. 29) and its hydrochloride salt (Compound No. 30),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}benzamide (Compound No. 31) and its hydrochloride salt (Compound No. 32),

benzyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate (Compound No. 33) and its hydrochloride salt (Compound No. 34),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}morpholine-4-carboxamide (Compound No. 35) and its hydrochloride salt (Compound No. 36),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}-1,1,1-trifluoromethane sulfonamide (Compound No. 37) and its hydrochloride salt (Compound No. 38),

methyl {4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}(phenyl)acetate (Compound No. 39) and its hydrochloride salt (Compound No. 40),

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}benzamide (Compound No. 41) and its hydrochloride salt (Compound No. 42),

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide (Compound No. 43) and its hydrochloride salt (Compound No. 44),

ethyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate (Compound No. 45) and its hydrochloride salt (Compound No. 46),

1-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]piperidine-2,6-dione (Compound No. 47) and its hydrochloride salt (Compound No. 48),

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 49) and its hydrochloride salt (Compound No. 50),

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione (Compound No. 51) and its hydrochloride salt (Compound No. 52),

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 53) and its hydrochloride salt (Compound No. 54),

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 55) and its hydrochloride salt (Compound No. 56),

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 57) and its hydrochloride salt (Compound No. 58),

1-(5-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione (Compound No. 59) and its hydrochloride salt (Compound No. 60),

1-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 61) and its hydrochloride salt (Compound No. 62),

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 63) and its hydrochloride salt (Compound No. 64),

2-(2,6-dioxopiperidin-1-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No. 65) and its hydrochloride salt (Compound No. 66),

1-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 67) and its hydrochloride salt (Compound No. 68),

1-((2*R*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 69) and its hydrochloride salt (Compound No. 70),

1-((2*S*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 71) and its hydrochloride salt (Compound No. 72),

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}pyrrolidine-2,5-dione (Compound No. 73) and its hydrochloride salt (Compound No. 74),

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione (Compound No. 75) and its hydrochloride salt (Compound No. 76),

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 77) and its hydrochloride salt (Compound No. 78),

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 79) and its hydrochloride salt (Compound No. 80),

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 81) and its hydrochloride salt (Compound No. 82),

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 83) and its hydrochloride salt (Compound No. 84),

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 85) and its hydrochloride salt (Compound No. 86),

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)pyrrolidine-2,5-dione (Compound No. 87) and its hydrochloride salt (Compound No. 88),

1-{5-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 89) and its hydrochloride salt (Compound No. 90),

1-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 91) and its hydrochloride salt (Compound No. 92),

1-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione (Compound No. 93) and its hydrochloride salt (Compound No. 94),

1-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione (Compound No. 95) hydrochloride salt (Compound No. 96), and

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

The compounds described herein are basic and can form organic or inorganic acid addition salts, which can be suitably administerable in humans and other animals without undue toxicity, irritation, allergic response, and the like. The resulting addition salts are useful alone or in pharmaceutical compositions. These salts may be prepared by methods known to one of ordinary skill in the art, for example, suspending the compound in water and then adding one equivalent of one or more organic acids, *e.g.*, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, malonic acid, adipic acid, ascorbic acid, camphoenic acid, nicotinic acid, butyric acid, lactic acid, glucuronic acid or mixtures thereof, and/or one or more inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, boric acid, perchloric acid or mixtures thereof.

Neutral solutions of addition salts can be subjected to rotary evaporation under reduced pressure to volumes sufficient to facilitate precipitation of the salt upon cooling, which is then filtered and dried. The salts of the present invention may also be prepared under strictly non-aqueous conditions. For example, free base can be dissolved in one or

more suitable organic solvents, for example, ethanol, methanol, isopropanol, dichloromethane, diethyl ether or mixtures thereof, to form a solution; one equivalent of a suitable acid can be added to the solution; and the solution can be stirred at temperatures of between about 0 °C to 5 °C, precipitating corresponding acid addition salts, which can then be filtered, washed with one or more solvents and dried. In another example, solvent can be completely removed by reduced pressure to obtain addition salts. Such salts are typically preferable for use in formulating pharmaceutical compositions of the invention because they are crystalline, relatively more stable and water-soluble.

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 include 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 particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

Example 1: Preparation of compounds of Formula 4

A compound of Formula 2, potassium carbonate (2.0 equiv.) and a compound of Formula 3 were dissolved in acetone and heated at about 60°C for about 24 hours. The reaction mixture was cooled to room temperature, filtered, washed with acetone and ethyl acetate. The filtrate thus obtained was concentrated and purified by column chromatography to form a compound of Formula 4.

Example 2: Preparation of a compound of Formula 6

A compound of Formula 4, potassium carbonate (3.0 equiv.), potassium iodide (0.05 g) and compound of Formula 5 (1.1 equiv.) were taken in ethyl methyl ketone and then heated at about 80 °C for about 16 hours. The reaction mixture was filtered though G-3 sintered funnel, washed with dichloromethane and then the solvent was evaporated. The

crude product thus formed was purified by preparative thin layer chromatography to form a compound of Formula 6.

Example 3: Preparation of a compound of Formula 9

A mixture of glutarimide of Formula 7 (1.0 equiv.), compound of Formula 8 (7.0 equiv.) and potassium carbonate (2.0 equiv.) in acetone was stirred at an ambient temperature for about 60 hours. The solvent was evaporated. Poured water on it, extracted with ethyl acetate, washed with water, brine solution and then dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product thus obtained was purified by column chromatography to form a compound of Formula 9.

Example 4: Preparation of a compound of Formula 10

A mixture of a compound of Formula R_6H (1.0 equiv.), potassium carbonate (2.0 equiv.), compound of Formula 9 (1.1 equiv.) and potassium iodide in acetonitrile was refluxed for about 5 hours. The solvent was evaporated, extracted with ethyl acetate, washed with water, brine solution and dried over anhydrous sodium sulfate. The solvent was evaporated and the product thus obtained was purified by column chromatography to form a compound of Formula 10.

Example 5: Prepration of amino compound of Formula 10a

A compound of Formula 10 was dissolved in dichloromethane followed by adiition of ethanol-hydrochloric acid (3.5 N, 1.1 equiv.). The solvent was evaporated completely. Hexane was added and then sonicated. The solvent was then evaporated to form amino compound of Formula 10a.

Example 6: Preparation of a compound of Formula 11

Method A: Amino compound (example 5) was dissolved in dichloromethane and then triethylamine (3.0 equiv.) was added to it. The reaction mixture was stirred at 0 °C. Triphosgene (0.5 equiv.) was added at about 0°C and the reaction mixture was stirred for at 0 °C about 2 hours. A compound of Formula R_7Y (1.1 equiv.) was added at 0 °C. The reaction mixture was slowly brought to an ambient temperature and stirred for about 12 hours. Sodium bicarbonate solution was added to it and stirred for about 15 minutes. The reaction mixture was extracted with dichloromethane, washed with water, brine. The

solvent was evaporated and the product thus obtained was purified by column chromatography to form a compound of Formula 11.

Method B: Amino compound of Formula 10a was dissolved in dichloromethane and added triethylamine (2.0 equiv.) to it, cooled to 0 °C and then a compound of Formula R_7Y (1.5 equiv.) was added, stirred at an ambient temperature for about 16 hours. Sodium bicarbonate solution was added to it and stirred for about 15 minutes. The reaction mixture was extracted with dichloromethane, washed with water, and brine. The solvent was evaporated and the product thus obtained was purified by column chromatography to form a compound of Formula 11.

Example 7: Preparation of a compound of Formula 12

Same as described in method B of example 6.

Example 8: Preparation of a compound of Formula 14

A mixture of glutarimide of Formula 7 (1.0 equiv.), compound of Formula 13 (2.0 equiv.) and potassium carbonate (3.0 equiv.) in ethyl methyl ketone was refluxed for about 42 hours. Cooled the reaction mixture to an ambient temperature, filtered, washed the residue with ethyl acetate. The solvent was evaporated to form a compound of Formula 14.

Example 9: Preparation of a compound of Formula 15

A mixture of a compound of Formula 14 (1.0 equiv.), compound of Formula 5 (1.0 equiv.), and triethylamine (2.0 equiv.) in dimethylformamide was heated at about 50 °C for about 12 hours. The reaction mixture was cooled to room temperature and water was added to it, extracted with ethyl acetate, washed with water, brine solution, and then dried over anhydrous sodium sulfate. The solvent was evaporated and the product thus obtained was purified by column chromatography to form a compound of Formula 15.

Example 10: Preparation of (2,6-dioxo-piperidin-1-yl) acetic acid tert-butyl ester of Formula 16

Sodium hydride (1.2 equiv.) was added to dimethylformamide and stirred at about 0-5°C. Glutarimide (1.0 equiv.) of Formula 7 was added and the reaction mixture was stirred at an ambient temperature for about 1 hour. The reaction mixture was cooled to about 0-5°C and bromo-acetic acid tert-butyl ester (1.0 equiv.) was added dropwise. The reaction mixture

was heated at about 50°C for about 15 hours. The reaction mixture was quenched with water, extracted with ethyl acetate, washed with water, brine and purified by column chromatography to form (2,6-dioxo-piperidin-1-yl) acetic acid tert-butyl ester of Formula 16.

Example 11: Preparation of (2,6-dioxo-piperidin-1-yl) acetic acid of Formula 16a

(2,6-dioxo-piperidin-1-yl) acetic acid tert-butyl ester of Formula 16 was dissolved in dichloromethane and trifluro acetic acid (5.0 equiv.) was added to it and then the reaction mixture was stirred at an ambient temperature for overnight. The solvent was evaporated, followed by addition of dichloromethane. The solvent was then evaporated under vacuum to form (2,6-dioxo-piperidin-1-yl) acetic acid of Formula 16a.

Example 12: Preparation of a compound of Formula 18

To a solution of (2,6-dioxo-piperidin-1-yl) acetic acid of Formula 16a (1.0 equiv.) in dimethylformamide was added a compound of Formula 17 (1.0 equiv.). The reaction mixture was cooled to about 0-5°C and stirred for about 10 minutes. N-methyl morpholine (2.0 equiv.), hydroxy benzotriazole (1.0 equiv.) were added to the reaction mixture at about 0-5°C and stirred for about 10 minutes. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride was added at about 0-5°C and stirred at an ambient temperature for overnight. The raction was quenched with water, extracted with ethylacetate, washed with water, dried over anhydrous sodium sulfate and evaporated the solvent to form a compound of Formula 18.

Example 13: Preparation of 1-[3-(3-benzyl-3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 20

A compound of Formula 9 (1.0 equiv.), (3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)methylamine of Formula 19 (1.0 equiv.) and potassium carbonate (2.0 equiv.) were taken in dimethylformamide and heated under argon at about 90°C for overnight. The reaction mixture was cooled, poured in to water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated and then purified by column chromatography to form 1-[3-(3-benzyl-3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 20.

Example 14: Preparation of 1-[3-(3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 21

1-[3-(3-benzyl-3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 20 was taken in methanol. Palladium-carbon was added and hydrogenated at 60 psi of hydrogen in parr apparatus for about 4 hours. The reaction mixture was filtered through celite bed, washed with methanol, concentrated to form 1-[3-(3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 21.

Example 15: Preparation of a compound of Formula 22

1-[3-(3-azabicyclo[3.1.0]hex-6ylamino)-propyl]-piperidine-2,6-dione of Formula 21 was dissolved in dichloromethane and then triethylamine (3.0 equiv.) was added to it. The reaction mixture was stirred at 0 °C. Triphosgene (0.5 equiv.) was added at about 0°C and the reaction mixture was stirred for about 2 hours at 0 °C. A compound of Formula R_8COCl (1.1 equiv.) was added at 0 °C. The reaction mixture was slowly brought to an ambient temperature and stirred for about 12 hours. Sodium bicarbonate solution was added to it and stirred for about 15 minutes. The reaction mixture was extracted with dichloromethane, washed with water, and brine. The solvent was evaporated and the product thus obtained was purified by column chromatography to form a compound of Formula 22.

Example 16: Preparation of a compound of Formula 24

A mixture of a compound of Formula 9 (1.0 equiv.), compound of Formula 23 (1.1 equiv.), potassium carbonate (2.0 equiv.) and potassium iodide in dimethylformamide was heated at about 90 ^{0}C for overnight. The reaction mixture was cooled, poured into water, extracted with ethyl acetate and then purified by column chromatography to form a compound of Formula 24.

The following compounds were prepared analogously, following the procedures described above.

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}piperidine-2,6-dione (Compound No. 1),

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione (Compound No. 3),

1-(3-{4-[(benzyloxy)acetyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 5),

4-[3-(2,6-dioxopiperidin-1-yl)propyl]-*N*,*N*-dimethylpiperazine-1-sulfonamide (Compound No. 7),

1-{3-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]propyl}piperidine-2,6-dione (Compound No. 9),

1-(3-{4-[(trifluoromethyl)sulfonothioyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 11),

ethyl 4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxylate (Compound No. 13),

2-{4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}-2-oxoethyl acetate (Compound No. 15),

N-(2,4-difluorophenyl)-4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxamide (Compound No. 17),

1-{3-[5-(morpholin-4-ylcarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]propyl}piperidine-2,6-dione (Compound No. 19),

1-(3-{5-[(benzyloxy)acetyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}propyl)piperidine-2,6-dione (Compound No. 21),

1-(3-{4-[(4-nitrophenyl)sulfonyl]piperazin-1-yl}propyl)piperidine-2,6-dione (Compound No. 23),

1-(3-{[3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}propyl) piperidine-2,6-dione (Compound No. 25),

1-[3-({3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)propyl]piperidine-2,6-dione (Compound No. 27),

2-(benzyloxy)-*N*-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}acetamide (Compound No. 29),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}benzamide (Compound No. 31),

benzyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate (Compound No. 33),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}morpholine-4-carboxamide (Compound No. 35),

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}-1,1,1-trifluoromethane sulfonamide (Compound No. 37),

methyl {4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}(phenyl)acetate (Compound No. 39),

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}benzamide (Compound No. 41),

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide (Compound No. 43),

ethyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate (Compound No. 45),

1-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]piperidine-2,6-dione (Compound No. 47),

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 49),

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione (Compound No. 51),

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 53),

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 55),

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 57),

1-(5-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione (Compound No. 59),

1-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 61),

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione (Compound No. 63),

2-(2,6-dioxopiperidin-1-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No. 65),

1-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 67),

1-((2*R*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 69),

1-((2*S*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione (Compound No. 71),

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}pyrrolidine-2,5-dione (Compound No. 73),

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione (Compound No. 75),

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 77),

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 79),

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 81),

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 83),

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 85),

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)pyrrolidine-2,5-dione (Compound No. 87),

1-{5-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 89),

1-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione (Compound No. 91),

1-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione (Compound No. 93),

1-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione (Compound No. 95),

Example 17: Preparation of hydrochloride salt of a compound of Formula 6, 11, 12, 15, 18, 22 or 24

A compound of Formula 6, 11, 12, 15, 18, 22 or 24 was dissolved in dichloromethane followed by addition of ethanol-hydrochloric acid (3.5 N, 1.1 equiv.). The solvent was evaporated completely. Hexane was added and then sonicated. The solvent was then evaporated to form the desired product.

The following compounds were prepared analogously, following the procedures described above:

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}piperidine-2,6-dione hydrochloride salt (Compound No. 2)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.429-1.55 (m, 2H), 1.56-1.57 (m, 2H), 1.959-2.001 (m, 2H), 2.158-2.20 (m, 4H), 2.67-2.74 (m, 2H), 2.98-3.03 (m, 2H), 3.29-3.39 (m, 4H), 3.86-3.92 (m, 4H), 4.39 (brs, 1H), 6.92-7.00 (m, 2H), 7.27-7.31 (m, 2H). Mass (m/z): 361 (M+1)

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione hydrochloride salt (Compound No. 4)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.22-1.83 (bs, 4H), 2.00-2.11 (m, 4H), 2.79-2.81 (m, 4H), 3.06 (bs, 2H), 3.20-3.23 (m, 2H), 3.40-3.46 (m, 2H), 3.73-3.77 (m, 2H), 3.86-3.90 (m, 2H), 3.92 (s, 3H), 7.06-7.11 (m, 1H), 7.18-7.21 (d, J=9Hz, 1H), 7.18-7.21 (d, J=9Hz, 1H), 7.40-7.50 (m, 2H). Mass (m/z): 387 (M^++1)

1-(3-{4-[(benzyloxy)acetyl]piperazin-1-yl}propyl)piperidine-2,6-dione hydrochloride salt (Compound No. 6)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.70 (s, 2H), 1.93-2.01 (m, 2H), 2.08-2.14 (t, 2H), 2.62-2.70 (m, 6H), 2.97 (s, 2H), 3.48-3.51 (m, 2H), 3.86-3.88 (m, 2H), 3.97-4.02 (t, 2H), 4.14 (d, 2H), 4.56 (s, 2H), 7.32-7.40 (m, 5H). Mass (m/z): 388 (M+1)

4-[3-(2,6-dioxopiperidin-1-yl)propyl]-*N*,*N*-dimethylpiperazine-1-sulfonamide hydrochloride salt (Compound No. 8)

1-{3-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]propyl}piperidine-2,6-dione hydrochloride salt (Compound No. 10)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 19.6-2.01 (m, 2H), 2.14 (m, 2H), 2.66-2.70 (t, 4H), 2.82 (t, 2H), 3.28-3.30 (t, 4H), 3.42-3.47 (t, 4H), 3.66-3.67 (t, 4H), 3.74 (t, 2H), 3.85-3.89 (t, 4H). Mass (m/z): 353 (M+1)

1-(3-{4-[(trifluoromethyl)sulfonothioyl]piperazin-1-yl}propyl)piperidine-2,6-dione hydrochloride salt (Compound No. 12)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.96-2.00 (m, 2H), 2.12-2.17 (m, 2H), 2.67-2.71 (t, 4H), 2.85 (s, 2H), 3.05 (t, 2H), 3.60 (t, 2H), .69-3.74 (t, 2H), 3.86-3.93 (t, 4H). Mass (m/z): 356 (M+1)

ethyl 4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxylate hydrochloride salt (Compound No. 14)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.30 (t, 3H), 1.96-2.08 (m, 2H), 2.14-2.19 (m, 2H), 2.67-2.71 (t, 6H), 3.013 (t, 2H), 3.48-3.52 (t, 2H), 3.758 (t, 2H), 3.86-3.91 (t, 2H), 4.14-4.16 (m, 2H), 4.18-4.2 (m, 2H). Mass (m/z): 312 (M+1)

2-{4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}-2-oxoethyl acetate hydrochloride salt (Compound No. 16)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.66 (s, 2H), 1.96-2.01 (m, 2H), 2.18-2.11 (m, 5H), 2.67-2.69 (m, 4H), 2.71-2.78 (s, 2H), 3.05 (s, 2H), 3.59 (m, 3H), 3.82-3.91 (m, 3H), 4.56 (m, 2H). Mass (m/z): 340 (M+1)

N-(2,4-difluorophenyl)-4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxamide hydrochloride salt (Compound No. 18),

^{1}H NMR (DMSO, 300 MHz): δ 1.84-1.88 (m, 4H), 2.50 (s, 2H), 2.60-2.64 (m, 4H), 2.96-3.08 (m, 4H), 3.67-3.72 (m, 4H), 4.17-4.21 (m, 2H), 7.04-7.06 (m, 1H), 7.22-7.29 (m, 1H), 7.36-7.45 (m, 1H), 8.61 (s, 1H). Mass (m/z): 395 (M+1)

1-{3-[5-(morpholin-4-ylcarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]propyl}piperidine-2,6-dione hydrochloride salt (Compound No. 20)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.94-2.09 (m, 6H), 2.18-2.77 (m, 6H), 3.32-3.38 (m, 4H), 3.34-3.48 (m, 2H), 3.67-3.71 (m, 2H), 3.75-3.87 (m, 4H), 4.56-4.89 (m, 4H). Mass (m/z): 365.0 (M+1)

1-(3-{5-[(benzyloxy)acetyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}propyl)piperidine-2,6-dione hydrochloride salt (Compound No. 22)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.22-1.29 (m, 6H), 1.91-1.97 (m, 3H), 2.32-3.3 (m, 1H), 3.64-3.75 (m, 6H), 4.23-4.68 (m, 3H), 7.2-7.49 (m, 4H). Mass (m/z): 400.9 (M+1)

1-(3-{4-[(4-nitrophenyl)sulfonyl]piperazin-1-yl}propyl)piperidine-2,6-dione hydrochloride salt (Compound No. 24)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.92-1.96 (m, 2H), 2.08 (m, 2H), 2.63-2.67 (m, 4H), 2.99 (m, 4H), 3.54 (m, 4H), 3.83-3.87 (m, 4H), 7.91-7.94 (m, 2H), 8.38-8.41 (m, 2H). Mass (m/z): 425 (M+1)

1-(3-{[3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}propyl) piperidine-2,6-dione hydrochloride salt (Compound No. 26)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.35 (bs, 1H), 1.66-1.73 (m, 5H), 1.91-1.95 (m, 2H), 2.31 (s, 3H), 2.54 (bs, 2H), 2.62-2.66 (m, 3H), 2.20-2.23 (m, 3H), 3.31-3.35 (m, 2H), 3.66-3.89 (m, 8H). Mass (m/z): 379 (M^++1)

1-[3-({3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)propyl]piperidine-2,6-dione hydrochloride salt (Compound No. 28)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.82-1.86 (m, 3H), 2.59-2.63 (m, 3H), 2.73-2.78 (m, 2H), 3.13 (bs, 2H), 3.57-3.68 (m, 5H), 4.06 (s, 3H), 4.50 (s, 1H), 4.51-4.54 (m, 4H), 4.81 (s, 1H), 5.02 (s, 1H), 7.25-7.37 (m, 5H). Mass (m/z): 414 (M^++1)

2-(benzyloxy)-*N*-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}acetamide hydrochloride salt (Compound No. 30)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.29-2.12 (m, 8H), 2.74-2.78 (m, 3H), 3.09-3.19 (m, 6H), 3.63-3.82 (m, 4H), 3.84-4.11 (m, 4H), 4.67-4.82 (m, 2H), 7.48-7.05 (m, 4H). Mass (m/z): 402.0 (M+1)

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}benzamide hydrochloride salt (Compound No. 32)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.95 (m, 4H), 1.98-2.04 (m, 4H), 2.18-2.5 (m, 3H), 2.75-2.79 (m, 3H), 3.14-3.28 (m, 4H), 3.69-3.88 (m, 4H), 4.18-4.74 (m, 1H), 7.4-8.06 (m, 4H). Mass (m/z): 358.17 (M+1)

benzyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate hydrochloride salt (Compound No. 34)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.29 (m, 2H), 1.42-1.44 (m, 2H), 1.66-1.73 (m, 2H), 1.90-1.96 (m, 2H), 2.04-2.08 (m, 2H), 2.32-2.37 (m, 2H), 2.61-2.65 (m, 4H), 2.79-2.82 (m, 2H), 3.50-3.52 (m, 1H), 3.78-3.81 (m, 2H), 5.08 (s, 2H), 7.26-7.35 (m, 5H). Mass (m/z): 388 (M+1)

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}morpholine-4-carboxamide hydrochloride salt (Compound No. 36)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 0.85-0.88 (m, 2H), 1.28-1.33 (m, 6H), 1.70-1.77 (m, 2H), 1.91-1.98 (m, 4H), 1.99-.05 (m, 3H), 2.63-2.67 (m, 4H), 3.00 (1H, s), 3.56-3.68 (m, 4H), 3.75-3.79 (m, 4H). Mass (m/z): 367 (M+1)

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}-1,1,1-trifluoromethane sulfonamide hydrochloride salt (Compound No. 38)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.2-1.32 (m, 2H), 1.97-2.02 (m, 4H), 2.34-2.78 (m, 4H), 3.16-3.31 (m, 2H), 3.39-3.84 (m, 4H), 4.6-4.9 (m, 4H). Mass (m/z): 386.06 (M+1)

methyl {4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}(phenyl)acetate hydrochloride salt (Compound No. 40)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.94-2.00 (m, 2H), 2.08-2.13 (m, 2H), 2.65-2.75 (m, 5H), 2.94-2.99 (m, 6H), 3.17 (broad temperature, 2H), 3.67 (s, 3H), 3.67-3.88 (m, 2H), 4.10 (s, 1H), 7.27-7.36 (m, 5H). Mass (m/z) 388 (M+1)

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}benzamide hydrochloride salt (Compound No. 42)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.96 (bs, 3H), 2.12-2.22 (bs, 3H), 2.67 (bs, 1H), 2.67 (bs, 4H), 3.03-3.53 (broad temperature, 4H), 3.54 (bs, 1H), 3.82 (bs, 2H), 4.00 (bs, 1H), 7.41 (m, 3H), 7.81 (m, 2H). Mass (m/z): 356 (M^++1)

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide hydrochloride salt (Compound No. 44)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.79-1.84 (m, 7H), 2.58-2.62 (m, 4H), 3.05-3.10 (m, 4H), 3.05-3.10 (m, 2H), 3.57-3.58 (m, 5H), 3.62-3.64 (m, 1H), 3.72-3.74 (m, 2H), 4.15-4.16 (m, 1H). Mass (m/z): 350 (M+1)

ethyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate hydrochloride salt (Compound No. 46)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.23-1.25 (m, 3H), 1.38-1.44 (m, 8H), 1.66-1.75 (m, 2H), 1.90-2.05 (m, 4H), 2.31-2.36 (m, 2H), 2.61-2.65 (m, 4H), 2.79-2.83 (m, 2H), 3.76-3.81 (m, 2H). Mass (m/z): 326 (M+1)

1-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]piperidine-2,6-dione hydrochloride salt (Compound No. 48)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.79-1.90 (m, 4H), 2.54-2.62 (m, 6H), 2.69-2.72 (m, 2H), 2.87-2.90 (m, 2H), 3.59 (s, 2H), 3.85-3.89 (m, 2H), 7.00-7.12 (m, 4H).

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 50)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.41-1.43 (m, 2H), 1.47-1.49 (m, 6H), 1.60 (m, 2H), 1.97 (m, 4H), 2.67 (m, 4H), 3.08 (m, 2H), 3.63 (m, 4H), 3.78 (m, 2H), 3.89 (m, 2H), 4.38 (m, 2H), 4.65-4.68 (m, 1H), 6.94-6.97 (m, 2H), 7.52 (m, 1H). Mass (m/z): 420 (M+1)

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione hydrochloride salt (Compound No. 52)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.59-1.69 (m, 8H), 1.92-1.97 (m, 8H), 2.65-2.68 (m, 4H), 3.02 (m, 4H), 3.55-3.66 (m, 6H), 3.76-3.79 (m, 2H), 4.75-4.76 (m, 1H), 6.65-6.78 (m, 3H). Mass (m/z): 446 (M+1)

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 54)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.40-1.42 (m, 2H), 1.59 (m, 6H), 1.90-1.97 (m, 6H), 2.65-2.68 (m, 4H), 3.00 (m, 2H), 3.30-3.31 (m, 2H), 3.56-3.59 (m, 4H), 3.75-3.79 (m, 2H), 4.01-4.02 (m, 3H), 6.90-6.96 (m, 2H), 7.11-7.15 (m, 2H). Mass (m/z): 402 (M+1)

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 56)

Mass (m/z): 388 (M+1), melting point: 201-205 °C

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 58)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.04-1.07 (3H, t), 1.25 (6H, s), 1.95 (6H, s), 2.66 (4H, s), 3.04-3.48 (6H, m), 3.77-4.03 (6H, m), 6.43-7.26 (4H, m). Mass (m/z): 401 (M^++1)

1-(5-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione hydrochloride salt (Compound No. 60)

Mass (m/z): 428 (M+1), IR KBr: 1692.7 cm^{-1}

1-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 62)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.26-1.60 (7H, m), 1.97 (4H, s), 2.68-3.09 (8H, m), 3.63-3.84 (8H, m), 4.34 (2H, s), 4.66 (2H, s), 6.95-7.27 (3H, m). Mass (m/z): 392 (M+1)

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione hydrochloride salt (Compound No. 64)

Mass (m/z): 373 (M+1), Melting point: 192-195 °C

2-(2,6-dioxopiperidin-1-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide hydrochloride salt (Compound No. 66)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 2.02-2.07 (m, 2H), 2.86-2.89 (m, 4H), 3.25 (m, 2H), 3.51-3.54 (m, 4H), 3.67-3.75 (m, 4H), 3.90 (m, 5H), 4.51 (s, 2H), 6.91-6.98 (m, 2H), 7.12-7.14 (m, 2H), 8.34 (m, 1H). Mass (m/z): 389 (M+1)

1-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione hydrochloride salt (Compound No. 68)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.98-2.01 (m, 2H), 2.30-2.41 (m, 1H), 2.43-2.54 (m, 1H), 2.71-2.74 (m, 4H), 2.81-2.85 (m, 2H), 3.11-3.13 (m, 2H), 3.17-3.21 (m, 6H), 3.24-3.27 (m, 1H), 3.50-3.51 (m, 1H), 3.93-3.98 (m, 1H), 4.02 (m, 1H), 4.51-4.52 (m, 1H), 5.05-5.06 (s, 1H), 5.13 (s, 1H), 6.71-6.72 (m, 1H), 6.91-6.95 (m, 1H), 7.22-7.29 (m, 5H). Mass (m/z): 482 (M+1)

1-((2*R*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione hydrochloride salt (Compound No. 70)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.98-2.01 (m, 2H), 3.35-3.38 (m, 1H), 3.50-3.55 (m, 1H), 2.71-2.74 (m, 4H), 2.80-2.91 (m, 2H), 3.07-3.13 (m, 2H), 3.17-3.28 (m, 6H), 3.35-3.38 (m, 1H), 3.49-3.51 (m, 1H), 3.71-3.73 (m, 1H), 4.00-4.02 (m, 1H), 4.30-4.34 (m, 1H), 4.95-4.97 (s, 1H), 5.13-5.14 (s, 1H), 6.71-6.72 (m, 1H), 6.93-6.94 (m, 1H), 7.22-7.29 (m, 5H). Mass (m/z): 482 (M+1)

1-((2*S*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione hydrochloride salt (Compound No. 72)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.97-2.01 (m, 2H), 2.66-2.74 (m, 6H), 2.84-2.86 (m, 4H), 2.09-3.13 (m, 2H), 3.18-3.24 (m, 6H), 3.76 (m, 1H), 3.98-4.00 (m, 1H), 4.33-4.40 (m, 1H), 4.81 (s, 1H), 5.13 (s, 1H), 6.71-6.72 (m, 1H), 6.91-6.93 (m, 1H), 7.22-7.27 (m, 5H). Mass (m/z): 482 (M+1)

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 74)

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 76)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 0.85-0.89 (m, 1H), 1.25 (s, 2H), 1.58-1.61 (m, 3H), 1.99-2.01 (m, 3H), 2.51-2.55 (m, 3H), 2.73 (bs, 2H), 2.87-2.90 (m, 2H), 3.14-3.21 (m, 2H),

3.77 (m, 2H), 3.90 (s, 3H), 6.93-6.98 (m, 2H), 7.25-7.30 (m, 2H). Mass (m/z): 248 (M-OH)

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 78)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.64 (m, 8H), 2.41-2.70 (m, 8H), 3.13-3.53 (m, 6H), 3.86 (singlet 3H), 6.85-7.01 (m, 4H). Mass (m/z): 360.2 (M+1)

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 80)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.26-1.47 (m, 7H), 1.56-1.65 (m, 4H), 2.42-2.70 (m, 8H), 3.16-3.54 (m, 6H), 4.04-4.09 (m, 2H), 6.83-6.99 (m, 4H). Mass (m/z): 374.2 (M+1)

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 82)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.05-1.36 (m, 7H), 1.57-1.89 (m, 6H), 2.42-2.70 (m, 8H), 3.16-3.53 (m, 6H), 3.94-3.97 (m, 2H), 6.83-6.96 (m, 4H). Mass (m/z): 388.2 (M+1)

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 84)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.3-1.38 (m, 8H), 1.57-1.65 (m, 4H), 2.43-2.75 (m, 10H), 3.16-3.54 (m, 6H), 4.57-4.62 (m, 1H), 6.35-6.96 (m, 4H). Mass (m/z): 388.3 (M+1)

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 86)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.29-1.41 (m, 8H), 1.57-1.63 (m, 4H), 2.43-2.71 (m, 10H), 3.16-3.54 (m, 6H), 4.49-4.52 (m, 1H), 6.57-6.79 (m, 3H). Mass (m/z): 406.3 (M+1)

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)pyrrolidine-2,5-dione hydrochloride salt (Compound No. 88)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.36 (m, 6H), 1.6-1.66 (m, 6H), 1.79-1.87 (m, 4H), 2.46-2.711 (m, 8H), 3.14-3.54 (m, 6H), 4.74-4.78 (m, 1H), 6.57-6.75 (m, 3H). Mass (m/z): 432.3 (M+1)

1-{5-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 90)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.25-1.37 (m, 4H), 1.57-1.63 (m, 4H), 2.41-2.71 (m, 8H), 3.11-3.54 (m, 6H), 3.11-3.54 (m, 6H), 3.83 (singlet 3H), 6.62-6.86 (m, 3H). Mass (m/z): 378.3 (M+1)

1-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione hydrochloride salt (Compound No. 92)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.35-1.72 (m, 6H), 2.60-2.86 (m, 10H), 3.28-3.54 (m, 6H), 4.31-4.37 (m, 2H), 6.64-6.86 (m, 3H). Mass (m/z): 446.3 (M+1)

1-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione hydrochloride salt (Compound No. 94)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.29-1.4 (m, 2H), 1.60-1.65 (m, 4H), 2.49-2.83 (m, 10H), 3.50-3.57 (m, 4H), 3.84 (singlet, 6H), 6.52-6.59 (m, 2H). Mass (m/z): 361.3 (M+1)

1-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione hydrochloride salt (Compound No. 96)

^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.33-1.65 (m, 6H), 2.46-2.5 (m, 2H), 2.68-2.72 (m, 6H), 2.87-2.90 (m, 2H), 3.49-3.60 (m, 4H), 7.00-7.12 (m, 4H). Mass (m/z): 301.3 (M+1)

Pharmacological testing

Human Recombinant Assay

Receptor Binding Assay: Receptor binding assays were performed using recombinant cells expressing human alpha-1a and alpha-1b adrenoceptors. The affinity of different compounds for α_{1a} and α_{1b} adrenoceptor subtypes was evaluated by studying their ability to displace specific [^{3}H] prazosin binding from the membranes of recombinant clones expressing alpha-1a and alpha-1b adrenoceptors. The binding assays were performed according to U'Prichard *et al.*, *Eur J Pharmacol*, **50**:87-89 (1978) with minor modifications.

Human embryonic kidney (HEK) cells which had been stably transfected with human alpha–1a and alpha-1b adrenoceptors were cultured in an atmosphere of 5 % CO_2 at 37 °C in DMEM medium supplemented with 10%heat inactivated fetal calf serum, 1 mM glutamine, 100 U/mL penicillin and 0.1 mg/mL streptomycin. Selection pressure was maintained by regular addition of puromycin (3 μg/mL) to the culture medium.

The cells were homogenized in 5-10 volumes of buffer (Tris HCl 5 mM, EDTA 5 mM, pH 7.4) using a polytron homogenizer. The homogenate was centrifuged at 40,000 g for 20 min at 4 °C. The pellet thus obtained was resuspended in assay buffer (Tris HCl 5 mM, EDTA 5 mM, pH 7.4) and were stored at -70 °C until the time of assay.

Competition radioligand binding to the cloned subtypes of α_1-adrenoceptors was performed using [^{3}H] prazosin as the radioligand. The membrane homogenates (5-10 μg protein) were incubated in 250 μL of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) at 24-25 ^{0}C for 1 hour. Non-specific binding was determined in the presence of 10-μM terazosin. The incubation was terminated by vacuum filtration over GF/B fiber filters. The filters were then washed with ice-cold 50 mM Tris HCl buffer (pH 7.4). The filter mats were dried and bounded radioactivity retained on filters was counted. The IC_{50} and Kd were estimated by using the non-linear curve-fitting program using Graph pad prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng and Prusoff equation (Cheng and Prusoff, *Biochem Pharmacol*, **22**:3099-3108 (1973)), $Ki = IC_{50} /(1+L/Kd)$ where L is the concentration of [^{3}H] prazosin used in the particular experiment.

Reference: Michel, M. C., Grübbel, B., Taguchi, K. et al: Drugs for treatment of benign prostatic hyperplasia: affinity comparison at cloned α_1-adrenoceptor subtypes and in human prostate. *J Auton Pharmacol*, **16**:21 (1996).

The results of the human recombinant assays of the compounds disclosed herein are as follows:

a) The compounds specifically disclosed herein exhibited α_{1a} Ki (nM) values of between about 0.3 nM to about greater than 2500 nM, for example, between about 0.3 nM to about 1000 nM, or between about 0.3 nM to about 100 nM, and for example between about 0.3 nM to about 10 Nm,

b) The compounds specifically disclosed herein exhibited α_{1b} Ki (nM) values of between about 5.3 nM to about greater than 1333 nM, for example, between about 5.3 nM to about 1000 nM, between about 5.3 nM to about 600 nM, and for example, between about 5.3 nM to about 100 nM.

Receptor Binding Assay

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 studying 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 gauze and the filtrate is centrifuged at 500 g for 10 min. The supernatant is subsequently centrifuged at 40,000 g 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 °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 °C for 1 hour. Non-specific binding is determined in the presence of 300 nM prazosin. The incubation is terminated by vaccum filtration over GF/B fiber filters. The filters are then washed with ice-cold 50 mM Tris HCl buffer (pH 7.4). The filtermats are 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*, 22:3099-3108 (1973)), $Ki = IC_{50} /(1+L/Kd)$ where L is the concentration of [^{3}H] prazosin used in the particular experiment.

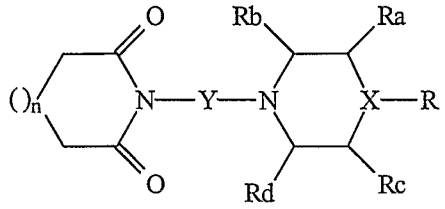
In vitro functional studies (In vitro α_{1a} Adrenoceptor selectivity)

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 thiopentone-

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 sulfate heptahydrate ($MgSO_4$. $7H_2O$) 1.2; sodium bicarbonate ($NaHCO_3$) 25; potassium dihydrogen phosphate (KH_2PO_4) 1.2; glucose 11.1. The buffer is maintained at 37 °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 norepinephrine (aorta) and phenylepinephrine (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. Compounds having the structure of Formula I,



1

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

n is an integer 0 or 1; Y is alkylene; R_a-R_d are hydrogen; R_a and R_c or R_a and R_d or R_b and R_d together forms $(CH_2)_m$ wherein m is an integer of from 0 to 2; X-R is CR_1R_2 or NR_3 {[wherein R_1 and R_2 are independently hydrogen, hydroxy, alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, cycloalkyl, $NHCOR_4$ or $NHSO_2R_4$ (wherein R_4 is CH_2OCH_2phenyl, phenyl, OCH_2phenyl, morpholinyl, trifluoromethyl, furanyl or alkoxy); R_3 is COR_5, SO_2R_5, $CONHR_5$, CH(phenyl)R_5, aryl, heteroaryl, heterocyclyl, or cycloalkyl]}; further R_a and X-R can together form aryl.

2. A compound, which is:

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(benzyloxy)acetyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

4-[3-(2,6-dioxopiperidin-1-yl)propyl]-*N*,*N*-dimethylpiperazine-1-sulfonamide and its hydrochloride salt,

1-{3-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(trifluoromethyl)sulfonothioyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

ethyl 4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxylate and its hydrochloride salt,

2-{4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}-2-oxoethyl acetate) and its hydrochloride salt,

N-(2,4-difluorophenyl)-4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazine-1-carboxamide and its hydrochloride salt,

1-{3-[5-(morpholin-4-ylcarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]propyl}piperidine-2,6-dione and its hydrochloride salt,

1-(3-{5-[(benzyloxy)acetyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

1-(3-{4-[(4-nitrophenyl)sulfonyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its hydrochloride salt,

1-(3-{[3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}propyl) piperidine-2,6-dione and its hydrochloride salt,

1-[3-({3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)propyl]piperidine-2,6-dione and its hydrochloride salt,

2-(benzyloxy)-*N*-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}acetamide and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}benzamide and its hydrochloride salt,

benzyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}morpholine-4-carboxamide and its hydrochloride salt,

N-{1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}-1,1,1-trifluoromethane sulfonamide and its hydrochloride salt,

methyl {4-[3-(2,6-dioxopiperidin-1-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}benzamide and its hydrochloride salt,

N-{3-[3-(2,6-dioxopiperidin-1-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide and its hydrochloride salt,

ethyl {1-[3-(2,6-dioxopiperidin-1-yl)propyl]piperidin-4-yl}carbamate and its hydrochloride salt,

1-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}pentyl)piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}piperidine-2,6-dione and its hydrochloride salt,

2-(2,6-dioxopiperidin-1-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

1-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-((2*R*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-((2*S*)-3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}-2-hydroxypropyl)piperidine-2,6-dione and its hydrochloride salt,

1-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-(5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl}pentyl)pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}pyrrolidine-2,5-dione and its hydrochloride salt,

1-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione and its hydrochloride salt,

1-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]pyrrolidine-2,5-dione hydrochloride salt, or

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

3. Use of a compound as defined in claim 1 for the manufacture of a medicament for treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors.

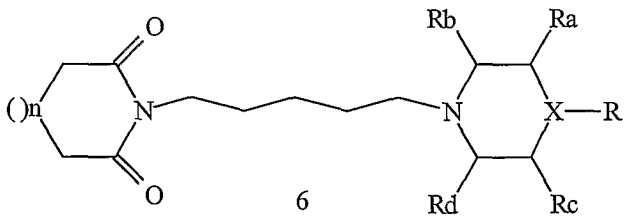
4. The use according to claim 3 wherein disease or disorder is benign prostatic hyperplasia.

5. The use according to claim 4 wherein compound causes minimal decrease or no decrease in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

6. Use of a compound as defined in claim 1 for the manufacture of a medicament for treating lower urinary tract symptoms associated with or without benign prostatic hyperplasia.

7. A pharmaceutical composition for treating benign prostatic hyperplasia or lower urinary tract symptoms associated with or without BPH, which comprises a therapeutically effective amount of a compound according to claim 1 and optionally one or more pharmaceutically acceptable carriers, excipients or diluents.

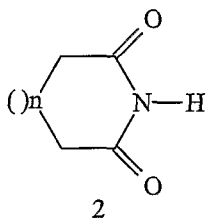
8. A method of preparing a compound of Formula 6,



6

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_a-R_d, X, R and n are the same as defined in claim 1, which method comprises:

(a) reacting a compound of Formula 2 with dihalopentane of Formula 3



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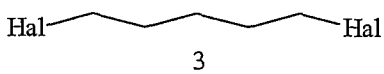
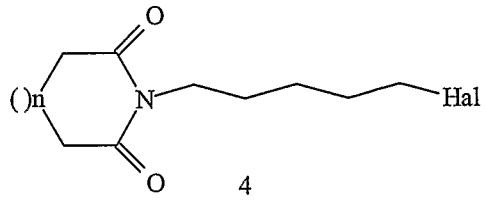


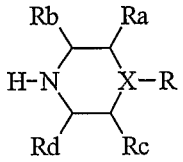
3

to form a compound of Formula 4; and



4

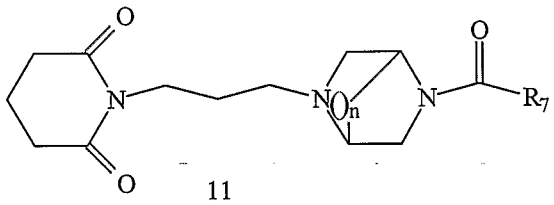
(b) reacting the compound of Formula 4 with a compound of Formula 5



5

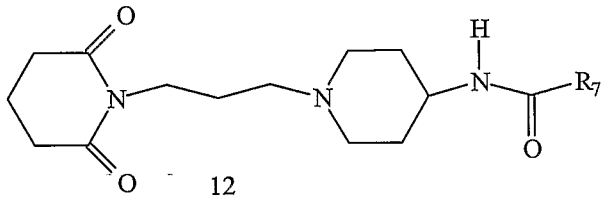
to form compound of Formula 6.

9. A method of preparing a compound of Formula 11 or 12,



11

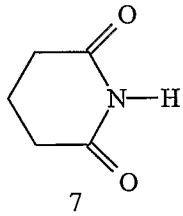
or



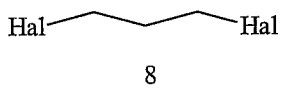
12

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_7 is morpholinyl, $PhCH_2OCH_2CO$, PhCO, CF_3SO_2, $PhCH_2OCO$, C_2H_5OCO, CH_3COOCH_2CO, $N(CH_3)_2SO_2$, $CONHC_6H_3F_2$ or $SO_2C_6H_4NO_2$).and n is an integer of from 0 or 1, which method comprises

(a) reacting glutarimide of Formula 7 with dihalopropane of Formula 8

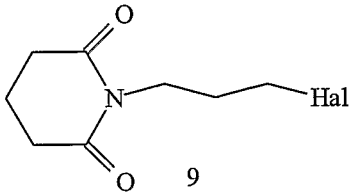


7



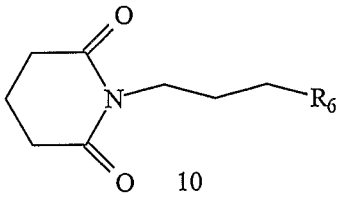
8

to form a compound of Formula 9;

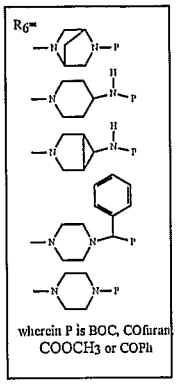


9

(b) reacting the compound of Formula 9 with a compound of Formula R_6H to form a compound of Formula 10 (wherein R_6 is as given below in the box);



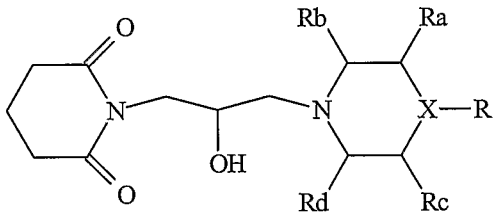
10



(c) deprotecting the compound of Formula 10 (when P=BOC) to form an amino or imino compound; and

(d) reacting the amino or imino compound with a compound of Formula R_7Y (wherein Y is hydrogen or halogen) to form a compound of Formula 11 or 12.

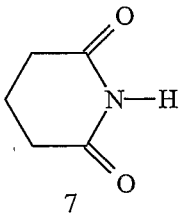
10. A method of preparing a compound of Formula 15,



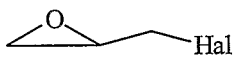
15

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_a-R_d, X and R are the same as defined in claim 1, which method comprises:

(a) reacting glutarimide of Formula 7 with a compound of Formula 13

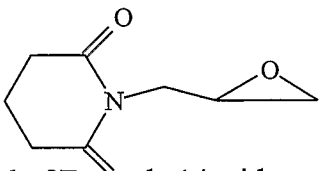


7



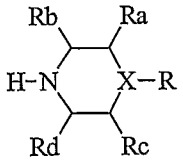
13

to form a compound of Formula 14; and



14

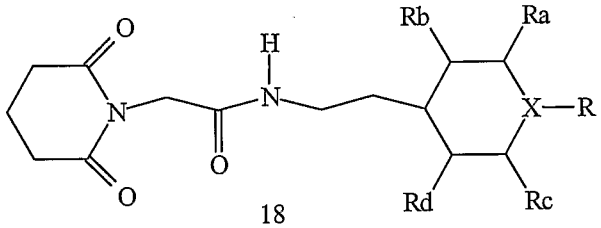
(b) reacting the compound of Formula 14 with a compound of Formula 5



5

to form a compound of Formula 15.

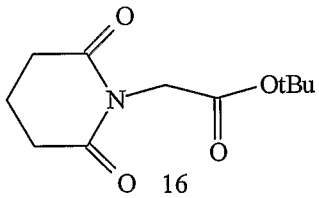
11. A method of preparing a compound of Formula 18,



18

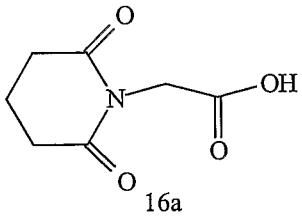
pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_a-R_d, X and R are the same as defined in claim 1, which method comprises:

(a) reacting glutarimide of Formula 7 with bromo-acetic acid tert-butyl ester to form a compound of Formula 16;



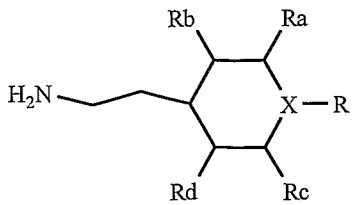
16

(b) hydrolyzing the compound of Formula 16 to form a compound of Formula 16a; and



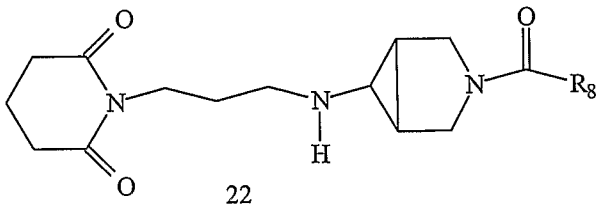
16a

(c) reacting the compound of Formula 16a with a compound of Formula 17



to form a compound of Formula 18.

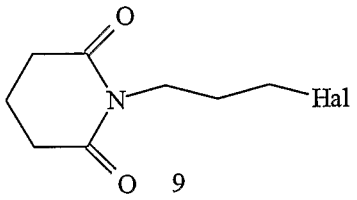
12. A method of preparing a compound of Formula 22,



22

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_8 is CH_2OCH_2aryl, OCH_2aryl, aryl, heteroaryl or heterocyclyl, which method comprises:

(a) reacting a compound of Formula 9 with a compound of Formula 19



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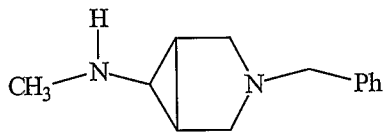
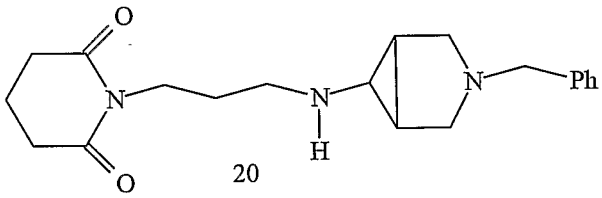


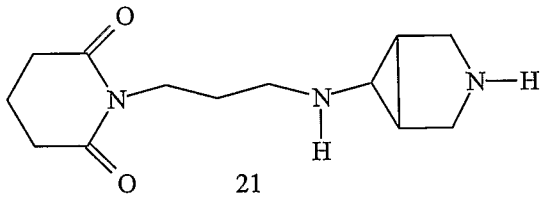
19

to form a compound of Formula 20;



20

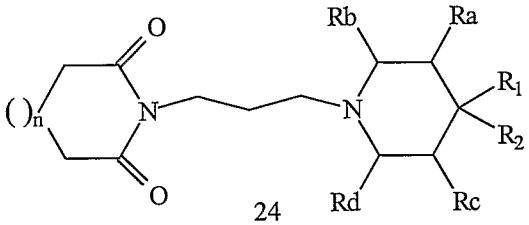
(b) debenzylating the compound of Formula 20 is debenzylated to form a compound of Formula 21; and



21

(c) reacting the compound of Formula 21 with a compound of Formula R_8COCl to form a compound of Formula 22.

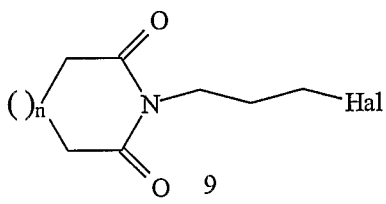
13. A method of preparing a compound of Formula 22,



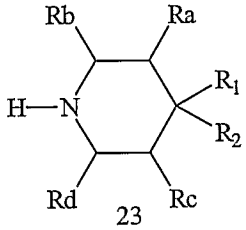
24

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites thereof, wherein R_a-R_d, R_1, R_2 and n are the same as defined in claim 1, which method comprises:

reacting a compound of Formula 9 with a compound of Formula 23



9



23

to form a compound of Formula 24.