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(54) Title: ISOINDOLEDIONE DERIVATIVES AS ADRENERGIC RECEPTOR ANTAGONISTS

(57) Abstract: Provided are isoindoledione derivatives, which can be used of treating a disease or disorder mediated through αla and/or α1(1 adrenergic receptors. Compounds disclosed herein can be used of treating benign prostatic hyperplasia (BPH) and related symptoms thereof, lower urinary tract symptoms (LUTS) associated with or without BPH. Processes for the preparation of described compounds, pharmaceutical compositions thereof, and methods of treating BPH and related symptoms thereof, LUTS associated with or without BPH are also provided.

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ISOINDOLEDIONE DERIVATIVES AS ADRENERGIC RECEPTOR ANTAGONISTS

Field of the Invention

Provided are isoindoledione derivatives, which can be used of treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors. Compounds disclosed herein can be used of treating benign prostatic hyperplasia (BPH) and related symptoms thereof, lower urinary tract symptoms (LUTS) associated with or without BPH. Processes for the preparation of described compounds, pharmaceutical compositions thereof, and methods of treating BPH and related symptoms thereof, LUTS associated with or without BPH are also provided.

Background of the Invention

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

There are two components of BPH, static and a dynamic component. The static component is due to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of the urine from the bladder. The dynamic component is due to increased smooth muscle tone of the bladder neck and prostate itself and is regulated by α_1 adrenergic receptor.

Currently, the most effective treatment for BPH is a surgical procedure of transurethral resection of the prostate (TURP), since it removes the obstructing tissue (C. Chapple, *Br. Med. Journal*, 304: 1198-1199 (1992). TURP is directed to the static and dynamic components of the BPH. However this surgical treatment is associated with mortality (1 % rate) and adverse event (incontinence 2-4%) infection 5-10 %, and impotence 5-10%. A noninvasive alternative treatment is therefore highly desirable. There are some drug therapies, which address the static component of this condition.

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 and 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_1 AR antagonists, for example, terazosin, doxazosin, prazosin, alfuzosin and tamsulosin, 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 adrenoceptor. 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 a better tolerability. Mice deficient in α_{1b} adrenoreceptors show diminished blood pressure response to phenylephrine injection compared to homozygous controls (Decreased blood pressure response in mice deficient of α_{1b} adrenergic receptor. (*Proc. Nat'l Acad Sci USA,* 94: 11589-11594 (1997)). In-vivo studies in healthy subjects comparison of α_{1a} / α_{1d} selective antagonists (for example, tamsulosin) or α_{1a} selective antagonists (for example, urapidil) with non selective antagonists (for example, 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); Naunyn Schmiedeberg's *Arch. Pharmacol.*, 354: 557-561 (1996); *Jpn. J. Pharmacol.* 80: 209-215 (1999); *Br. J. Clin. Pharmacol.* 47: 67-74 (1999). These studies have reported that an antagonist with high affinity for α_{1a} or α_{1a}/α_{1d} can cause some degree

of vasodilation, but that it is much smaller than with non-subtype-selective α_1 adrenoceptor antagonist. Further, there is increased vascular α_{1b} adrenoceptor expression in elderly patients and thus α_{1a}/α_{1d} selective agents with selectivity over α_{1b} adrenoceptor subtype would be of particular importance in benign prostatic hyperplasia, which is generally a disease of old age. Antagonism of both α_{1a} adrenoceptor and α_{1d} adrenoceptor is important to relieve lower urinary tract symptoms especially associated (suggestive of) with BPH. Targeting α_{1a} adrenoceptor with antagonists is important in relaxing prostate smooth muscle and relieving bladder outlet obstruction whereas α_{1d} adrenoceptor antagonism is important to target irritative symptoms.

Over the past decade, there much interest in developing selective antagonists. For example, U.S. Patent Nos. 6,083,950, 6,090,809, 6,410,735, 6,420,559 and 6,420,366, U.S. Patent Application No. 2002/0156085, PCT Publication Nos. WO 02/44151, WO 00/05206, WO 03/084928, WO 03/084541 and WO 00/05205 discloses compounds that exhibited α_1-adrenergic blocking activity and selectivity. The disclosures of these publications are incorporated herein by reference in their entireties. PCT Publication No. WO 2005/037282 discloses 1-alkylpiperazinyl-pyrrolidin-2,5-dione as adrenergic receptor antagonists. U.S. Patent No. 6,914,064 discloses 1,4-disubstituted piperazine derivatives useful as uro-selective α_1-adrenoceptor blockers.

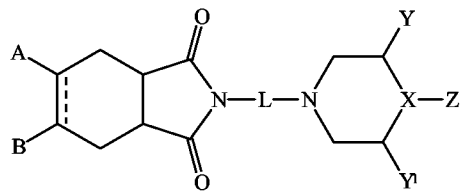
In view of the above, there remains a need for novel adrenergic receptors and particularly selective α_{1a} adrenoceptor antagonists for benign prostatic hyperplasia, which would avoid the cardiovascular side effects, associated with currently used drugs.

Summary of the Invention

Generally provided herein are isoindoledione derivatives, which can be used of treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors. Processes for the synthesis of these compounds, as well as pharmaceutical compositions thereof, are also provided. Described pharmaceutical compositions may also contain one or more pharmaceutically acceptable carriers or diluents. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, conjugates, or prodrugs of such compounds having the same type of activity are also provided, which can be useful to treat a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors.

Pharmaceutical compositions comprising the compounds described herein, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, conjugates or prodrugs in combination with one or more pharmaceutically acceptable carriers, and optionally included excipients, are also included, which can be useful to treat a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors.

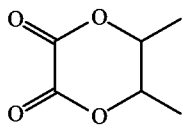
In one aspect, provided herein are compounds having the structure of Formula I,



Formula I

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof, wherein:

A and B can be independently hydrogen, halogen, hydroxy, alkyl, alkoxy, cyano, nitro, amino, alkylamino or thio, or A and B together can form a ring represented by:



L can be $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' can be independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together can form a bridging group (C_{0-3});

X can be N, C, CH or C(OH);

Z can be alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 can be alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') can form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

---- can be an optional bond;

with the provisos that when L is $-(CH_2)_3-$,

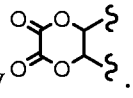
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

In another aspect, provided herein are compounds selected from:

2-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}acetamide and its hydrochloride salt,

Methyl {4-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

Methyl {4-[3-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamido and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.37) and its hydrochloride salt (Compound No.38),

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxooctahydro-2*H*-isoindol-2-yl) acetate and its hydrochloride salt,

7-{3-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]propyl}tetrahydro-4a*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3,6,8(5*H*,7*H*)-tetrone and its hydrochloride salt,

2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetate and its hydrochloride salt,

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

2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

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

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

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof.

In another aspect, provided herein are methods of treating a patient suffering from a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptors, comprising administering to a patient a therapeutically effective amount of one or more compounds or compositions described herein.

In another aspect, provided herein are methods of treating a patient suffering from benign prostatic hyperplasia (BPH) and related symptoms, lower urinary tract symptoms (LUTS) with or without BPH comprising administering to a patient a therapeutically effective amount of one or more compounds or compositions described herein. LUTS may include, for example, irritative symptoms, such as frequent urination, urgent

urination, nocturia and unstable bladder contractions, obstructive symptoms such as hesitancy, poor stream, prolong urination, and feelings of incomplete emptying.

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

In yet another aspect, provided herein are methods of treating a patient suffering from BPH or LUTS with or without BPH, comprising administering to a patient therapeutically effective amount of one or more compounds or compositions described herein in combination with one or more other therapeutic agents selected from muscarinic receptor antagonists (*e.g.*, derifenacin, solifenacin), bladder selective muscarinic receptor antagonists, testosterone 5 alpha-reductase inhibitor (*e.g.*, finasteride or dutasteride), HMG-CoA reductase inhibitors (*e.g.*, atorvastatin, pravastatin or simvastatin), endothelin antagonists (*e.g.*, tracleer, atracentan), nitric oxide donors, cGMP elevators, 5-HT antagonists (*e.g.*, palonosetron) or combinations thereof.

The compounds disclosed herein can be potent adrenergic receptor antagonists. Compounds described herein exhibit affinity towards α_{1a} adrenergic receptor subtypes and good selectivity for α_{1a} over α_{1b}. α_{1a} adrenergic receptors are involved in relieving the obstructive symptoms whereas α_{1d} adrenoreceptor antagonism is associated with alleviation of irritative symptoms. Relatively low affinity at the α_{1b} adrenergic receptor limits the cardiovascular side effects, for example, orthostatic hypotension. The present invention therefore provides pharmaceutical compositions for treating a disease or disorder mediated through α_{1a} and/ or α_{1d} adrenoceptors. Compounds and compositions described herein can be administered by any route, including for example, 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. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulphur, a phenylene, sulphinyl, sulphonyl group or $-NR_{\alpha}-$, wherein R_{α} can be hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_{\lambda}$, SO_mR_{ψ} or $-C(=O)NR_{\lambda}R_{\pi}$. 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, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, -CH=N-O(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)$NR_\lambda R_\pi$ {wherein R_λ and R_π are independently selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or carboxy}, nitro or -SO_mR_ψ (wherein m is an integer from 0-2 and R_ψ is hydrogen, 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, alkenyl, alkynyl, carboxy, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -OC(=O)$NR_\lambda R_\pi$,-NHC(=O)$NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ; or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulphur or -NR_α- (wherein R_α, R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -O-C(=O)$NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the 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 "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans or geminal geometry. Alkenyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulphur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -O-C(=O)$NR_\lambda R_\pi$, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl,

thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$ and $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Groups, such as ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl ($-CH_2CH=CH_2$), iso-propylene ($-C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. Alkynyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulphur, phenylene, sulphinyl, sulphonyl and $-NR_\alpha-$ (wherein R_α is the same as defined earlier). In the event that alkynyl groups are attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$ or $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, cyano or $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier).

The term "alkoxy" denotes the group O-alkyl, 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 "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which

may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-OC(=O)NR_\lambda R_\pi$, cyano or $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

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

The term "aryl," unless otherwise specified, refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl 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, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, $-CONHR_\pi$, $-OCOR_\pi$, $-COR_\pi$, $-NHSO_2R_\pi$ or $-SO_2NHR_\pi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group,

wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms or a bicyclic or tricyclic 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, $-NR_\lambda R_\pi$, CH=NOH, $-(CH_2)_wC(=O)R_\eta$ {wherein w is an integer from 0-4 and R_η is hydrogen, hydroxy, OR_λ, $NR_\lambda R_\pi$, $-NHOR_\omega$ or -NHOH}, $-C(=O)NR_\lambda R_\pi$ $-NHC(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, $-O-C(=O)NR_\lambda R_\pi$, $-O-C(=O)R_\lambda$, or $-O-C(=O)OR_\lambda$ (wherein m, R_ψ, R_λ and R_π are as defined earlier and R_ω 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, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl, 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, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, $-O-C(=O)R_\lambda$, $-O-C(=O)OR_\lambda$, $-C(=O)NR_\lambda R_\pi$, SO_mR_ψ, $-O-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NR_\lambda R_\pi$, mercapto, haloalkyl, thioalkyl, $-COOR_\psi$, $-COONHR_\lambda$, $-COR_\lambda$, $-NHSO_2R_\lambda$ or SO_2NHR_λ (wherein m, R_ψ, R_λ and R_π are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Such ring systems can be mono-, bi- or tricyclic. Carbonyl or sulfonyl

group can replace carbon atom(s) of heterocyclyl. 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, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine or piperazinyl and the like.

The groups " alkyl, aryl, heteroaryl and heterocyclyl" can optionally be substituted with substituent(s) selected from one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by substituent(s) defined earlier.

The term “polymorphs” includes all crystalline form as well as amorphous form for compounds described herein and as such are encompassed in the present invention.

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

The term “pharmaceutically acceptable salts” refer to a salt prepared from pharmaceutically acceptable organic or inorganic acids, such salts include hydrochlorides, sulphates, phosphates, tartarates, fumarates, citrates and the like. The free base forms of compounds of the present invention may be prepared from the salt forms, if desired, by contacting the salt with dilute aqueous solution of a base. The acid addition salts may

differ from the free base forms of the compounds of this invention in such physical characteristics as solubility and melting point.

The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for purposes of this invention.

The term "pharmaceutically acceptable" means approved by regulatory agency of the federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

The term "pharmaceutically acceptable solvates" refers to solvates with water (*i.e.*, hydrates, hemihydrate or sesquihydrate) or pharmaceutically acceptable solvents, for example solvates with common organic solvents as ethanol and the like. Such solvates are also encompassed within the scope of the disclosure.

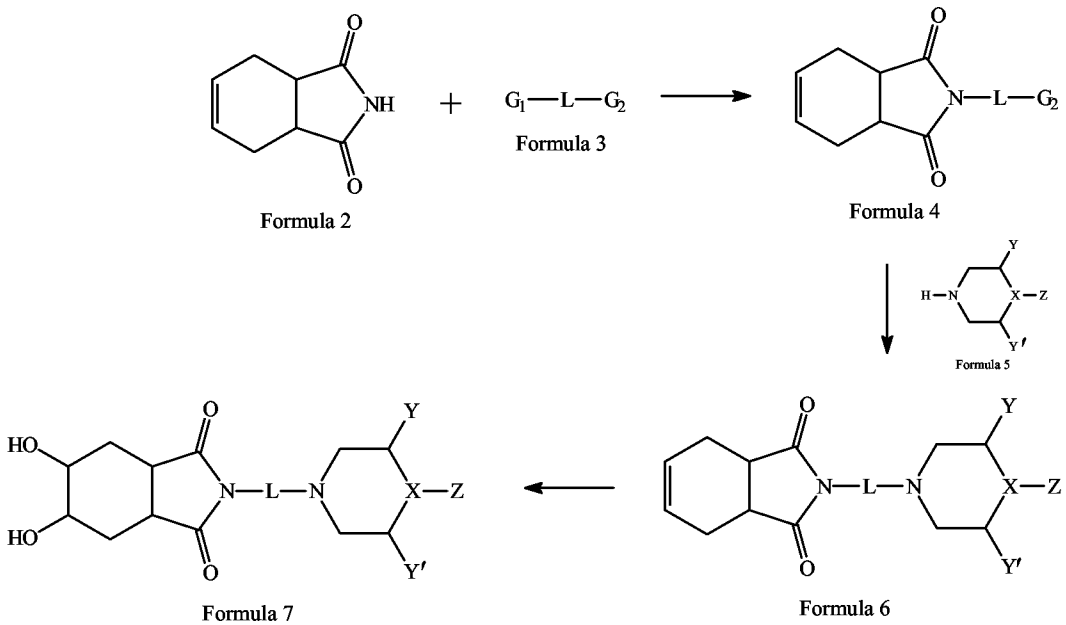
The present invention also includes, within its scope," prodrugs" of these agents. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. They may be carrier-linked or bioprecursors. The carrier-linked prodrugs may be bipartite, tripartite or mutual prodrugs. Prodrugs are intended to improve drug efficacy by improving solubility and consequently absorption and distribution as desired. Conventional procedure for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H Bundgaard and, Elsevier, 1985. Enantiomers and diastereomers, are as defined by the IUPAC 1974 Recommendations for Section E.

Other aspect and properties of this matter will be set forth in description which follows, and will be apparent from the description or may be learnt by the practice thereof.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds described herein may be prepared by the following reaction sequences as depicted in Schemes I, II, III, IV and V.

Scheme I



Compounds of Formula 7 can be prepared according to Scheme I. Thus, compounds of Formula 2 can be reacted with compounds of Formula 3 (wherein, G_1 and G_2 are leaving groups, for example, Cl, Br, I and the like) to form compounds of Formula 4. Compounds of 4 can be treated with compounds of Formula 5 to form compounds of Formula 6 (wherein L, X, Y, Y' and Z are the same as defined earlier). Compounds of Formula 6 can be oxidized to form compounds of Formula 7.

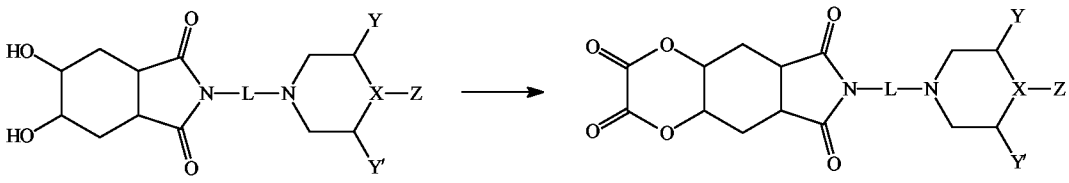
The reaction of a compound of Formula 2 can be carried out in one or more polar aprotic solvents, for example, acetonitrile, acetone, dimethylsulfoxide, dimethylformamide or mixtures thereof. The reaction can also be carried out in the presence of one or more bases, for example, potassium carbonate, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, cesium carbonate, triethylamine or mixtures thereof.

The reaction of a compound of Formula 4 can be carried out in one or more solvents, for example, polar solvent, for example, ethyl methyl ketone, methanol, ethanol, isopropyl alcohol, acetone, 1,4-dioxane, ethyl acetate or mixtures thereof. The reaction can also be carried out in presence of potassium iodide and one or more bases, for example, potassium

carbonate, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, cesium carbonate, triethylamine or mixtures thereof.

The oxidation of a compound of Formula 6 can be carried out in presence of one or more oxidizing agents, for example, potassium permanganate, osmium tetraoxide, periodic acid or mixtures thereof. The reaction can also be carried out in one or more polar protic solvents, for example, methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butanol or mixtures thereof.

Scheme II



Formula 7

Formula 8

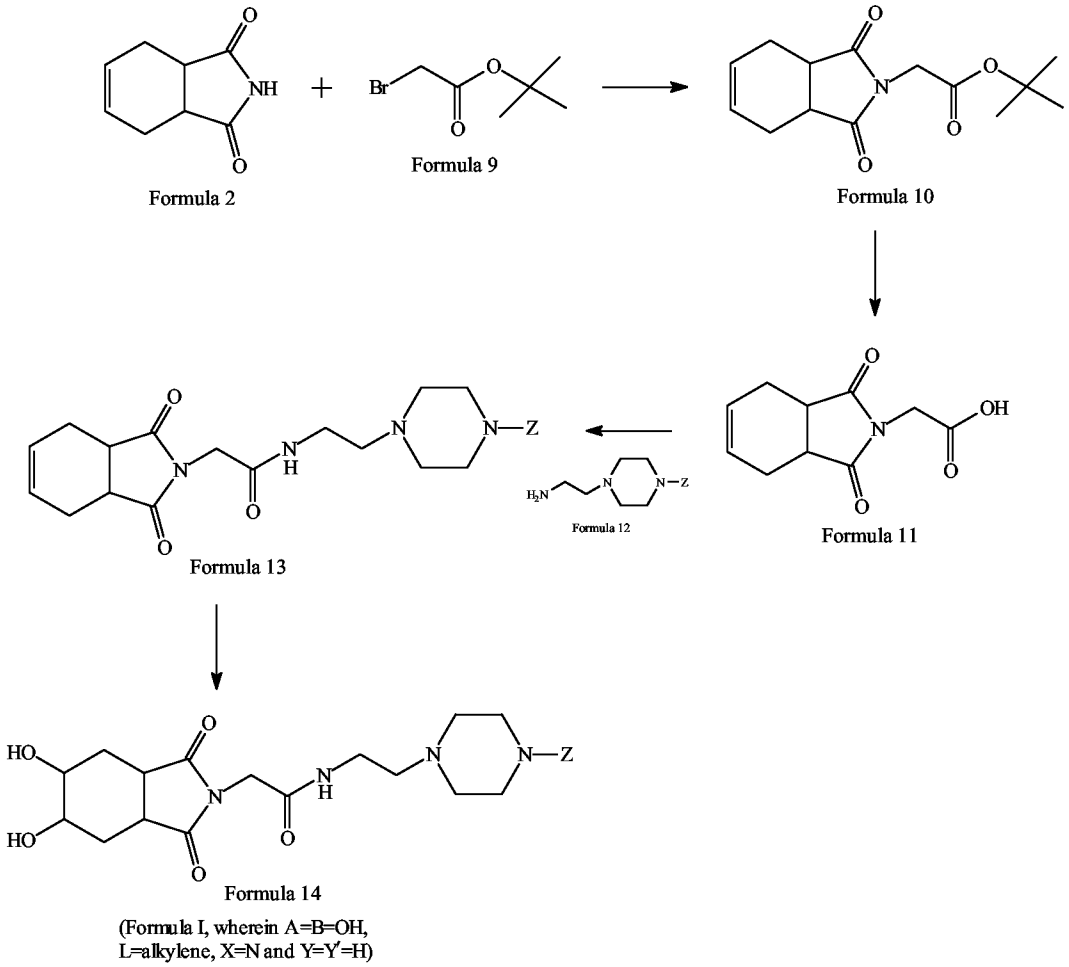
(Formula I, wherein A & B together form)

Compounds of Formula 8 can be prepared according to Scheme II. Thus, compounds of Formula 7 can be reacted with oxalyl dichloride to form compounds of Formula 8 (wherein L, Y, Y' and Z are the same as defined earlier).

The reaction of compounds of Formula 7 with oxalyl dichloride can be carried out in one or more nonpolar solvents, such as ethers, for example, tetrahydrofuran, dioxane or

mixtures thereof.

Scheme III



Compounds of Formula 14 can be prepared according to the Scheme III. Thus, compounds of Formula 2 can be reacted with compounds of Formula 9 to form compounds of Formula 10. Compounds of Formula 10 can be treated with one or more acids to form compounds of Formula 11. Compounds of Formula 11 can be reacted with compounds of Formula 12 to form compounds of Formula 13 (wherein Z is the same as defined earlier). Compounds of Formula 13 can be oxidized to form compounds of Formula 14.

Compounds of Formula 2 can be reacted with compounds of Formula 9 in the presence of one or more bases, for example, potassium hydroxide, sodium hydroxide, sodium hydride, potassium carbonate, sodium carbonate or mixtures thereof. The reaction

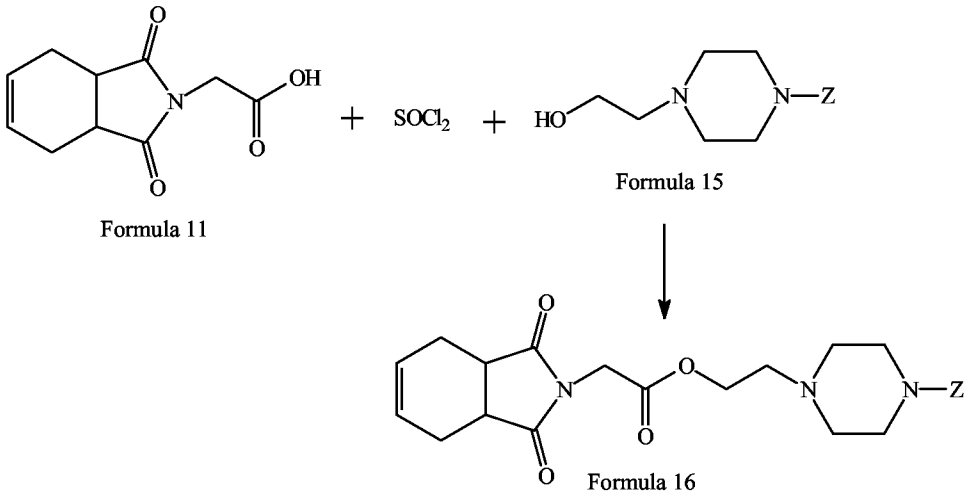
can also be carried out in one or more polar aprotic solvents, for example, dimethylsulfoxide, dimethylformamide, acetonitrile, N-methylpyrrolidone or mixtures thereof.

Compounds of Formula 10 can be deprotected in the presence of one or more acids, for example, acetic acid, trifluoroacetic acid, trichloroacetic acid or mixtures thereof. The deprotection reaction can also be carried out in one or more chlorinated solvents, for example, dichloromethane, dichloroethane, chloroform or mixtures thereof.

Compounds of Formula 11 can be coupled with compounds of Formula 12 in presence of one or more activating agents, for example, 1-hydroxybenzotriazole hydrate, hydroxypyridine, nitrophenol, N-hydroxyphthalimide or mixtures thereof. The coupling reaction can also be carried out in the presence of one or more coupling agents, for example, 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide methiodide, N, N'-diisopropylcarbodiimide, N,N'-Dicyclohexylcarbodiimide or mixtures thereof. The coupling reactions can also be carried out in one or more polar aprotic solvents, for example, acetonitrile, acetone, dimethylsulfoxide, dimethylformamide, N-methylmorpholine or mixtures thereof.

Compounds of Formula 13 can be oxidized in the presence of one or more oxidizing agents, for example, potassium permanganate, osmium tetraoxide, periodic acid or mixtures thereof. The oxidation can also be carried out in one or more solvents, for example, polar protic solvents (*e.g.*, methanol, ethanol, n-propanol, isopropanol, n-butanol, *t*-butanol or mixtures thereof), polar aprotic solvents (*e.g.*, acetonitrile, acetone, dimethylsulfoxide, dimethylformamide or mixtures thereof) or mixtures thereof.

Scheme IV

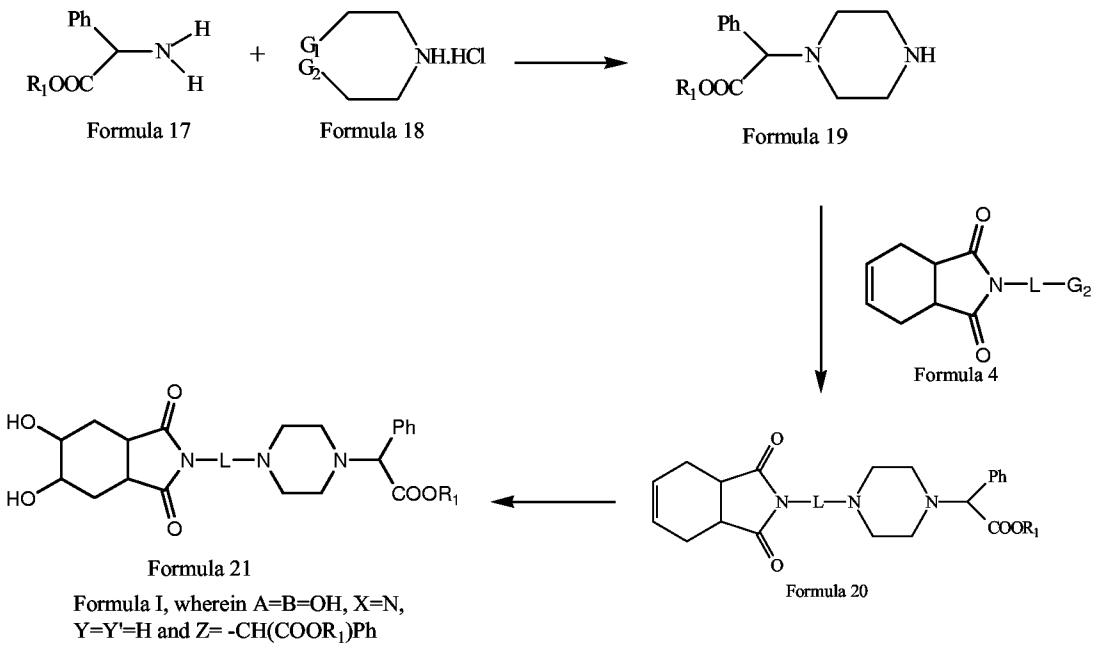


(Formula I, wherein A=B=Y=Y′=H, X=N and L=alkylene)

Compounds of Formula 16 can be prepared according to Scheme IV. Thus, compounds of Formula 11 can be reacted with compounds of Formula 15 and thionyl chloride to form compounds of Formula 16 (wherein Z is the same as defined earlier).

The reaction of compounds of Formula 11 with compounds of Formula 15 and thionyl chloride can be carried out in one or more solvents, for example, ether solvents (*e.g.*, tetrahydrofuran, dioxane or diethylether), halogenated solvents (*e.g.*, chloroform, dichloromethane or dichloroethane) or mixtures thereof. The reaction can also be carried out in presence of one or more acylation catalysts, for example, 4-dimethylaminopyridine, 1,2,4-triazole, 1-methylimidazole, 4(1-pyrrolidino)pyridine or mixtures thereof.

Scheme V



Formula 17 Formula 18 Formula 19

Formula 4

Formula 20

Formula 21

Formula I, wherein A=B=OH, X=N, Y=Y'=H and Z= -CH(COOR$_1$)Ph

Compounds of Formula 21 can be prepared according to the Scheme V. Thus, compounds of Formula 17 can be reacted with compounds of Formula 18 (wherein, G_1 and G_2 are same as defined earlier) to form compounds of Formula 19. Compounds of Formula 19 can be reacted with compounds of Formula 4 to form compounds of Formula 20 (wherein R_1, L and G_2 are the same as defined earlier). Compounds of Formula 20 can be oxidized to form compounds of Formula 21.

Compounds of Formula 17 can be reacted with compounds of Formula 18 in one or more solvents, for example, protic polar solvents (*e.g.*, methanol, ethanol, n-propanol, isopropanol, n-butanol or mixtures thereof), polar aprotic solvents, (*e.g.*, acetonitrile, dimethylformamide, dimethylsulfoxide or mixtures thereof) or mixtures thereof.

Compounds of Formula 19 can be reacted with compounds of Formula 4 in one or more polar aprotic solvents, for example, acetonitrile, dimethylformamide, dimethylsulfoxide or mixtures thereof.

Compounds of Formula 20 can be oxidized in the presence of one or more oxidizing agents, for example, potassium permanganate, osmium tetraoxide, periodic acid or mixtures thereof. The oxidation can also be carried out in one or more polar protic

solvents, for example, methanol, ethanol, n-propyl alcohol, isopropanol, n-butanol or mixtures thereof.

Compounds provided herein include, for example:

2-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.1) and its hydrochloride salt (Compound No. 2),

2-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.3) and its hydrochloride salt (Compound No. 4),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.5) and its hydrochloride salt (Compound No. 6),

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}acetamide (Compound No.7) and its hydrochloride salt (Compound No. 8),

Methyl {4-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate (Compound No.9) and its hydrochloride salt (Compound No. 10),

Methyl {4-[3-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate (Compound No.11) and its hydrochloride salt (Compound No. 12),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No.13) and its hydrochloride salt (Compound No. 14),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.15) and its hydrochloride salt (Compound No. 16),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.17) and its hydrochloride salt (Compound No. 18),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.19) and its hydrochloride salt (Compound No.20),

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide (Compound No.21) and its hydrochloride salt (Compound No.22),

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide (Compound No.23) and its hydrochloride salt (Compound No.24),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.25) and its hydrochloride salt (Compound No.26),

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide (Compound No.27) and its hydrochloride salt (Compound No.28),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.29) and its hydrochloride salt (Compound No.30),

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide (Compound No.31) and its hydrochloride salt (Compound No.32),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No.33) and its hydrochloride salt (Compound No.34),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.35) and its hydrochloride salt (Compound No.36),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide (Compound No.37) and its hydrochloride salt (Compound No.38),

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide (Compound No.39) and its hydrochloride salt (Compound No.40),

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No.41) and its hydrochloride salt (Compound No.42),

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide (Compound No.43) and its hydrochloride salt (Compound No.44),

2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxooctahydro-2*H*-isoindol-2-yl) acetate (Compound No.45) and its hydrochloride salt (Compound No.46),

7-{3-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]propyl}tetrahydro-4a*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3,6,8(5*H*,7*H*)-tetrone (Compound No.47) and its hydrochloride salt (Compound No.48),

2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetate (Compound No.49) and its hydrochloride salt (Compound No.50),

2-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.51) and its hydrochloride salt (Compound No.52),

2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.53) and its hydrochloride salt (Compound No.54),

2-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.55) and its hydrochloride salt (Compound No.56),

2-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.57) and its hydrochloride salt (Compound No.58),

2-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}propyl)-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.59) and its hydrochloride salt (Compound No.60),

2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione (Compound No.61) and its hydrochloride salt (Compound No.62),

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof.

Compounds described herein can be administered to a patient (*e.g.*, human or animal) by any route of administration, including for example, orally, parenterally, topically, rectally, intranasally, subcutaneously or transdermally.

In another aspect, provided are pharmaceutical compositions comprising a therapeutically effective amount of one or more compound described herein and optionally one or more pharmaceutically acceptable carriers, diluents or excipients. Such pharmaceutical compositions are suitable for oral, sublingual, parenteral, topical, nasal, rectal or transdermal administration.

Solid compositions include tablets, capsules, microcapsules, powders, granules, pills, wafers, dragees, catchets, caplets, suppositories and pastilles.

Tablets, capsules, pills are generally administered as a unit dose and may contain one or more suitable excipients, such as dispersing agents, binding agents, fillers, diluents, lubricants, disintegrants, colorants, flavouring agents, sweeteners, preservatives or mixtures thereof.

Tablets, pills and granules may be sugar coated, enteric coated or film coated by standard techniques well-known in the art. Immediate release tablets and tablets having sustained action may also be prepared by methods well known in the art. Capsules may be hard capsules or soft capsules of suitable size, wherein one or more compounds described herein can be mixed with one or more inert solid diluents, for example, sodium carbonate, calcium carbonate, lactose, starch, calcium phosphate, sodium phosphate or mixtures thereof; one or more disintegrants, for example, sodium starch glycolate, croscarmelose sodium or mixtures thereof.

Dispersible powders and granules suitable for reconstitution to form a stable suspension by addition of water are also provided. Such dispersible powders and/or granules can be provided with one or more compounds described herein, one or more dispersing agents and one or more suspending agents. Additional excipients, for example, coloring agents, flavoring agents or sweetening agents may also be added.

Suppositories for rectal administration include carbon dioxide-releasing laxative suppositories. Dosage forms for topical or transdermal administration include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, spot-on or patches. One or more compounds described herein can be admixed under sterile condition with one or more pharmaceutically acceptable carriers and any preservatives or buffers as may be required.

Liquid form preparations for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, aqueous or oily suspensions, syrups, sprays or elixirs. For liquid form preparations, one or more compounds described herein can be mixed with water or one or more other solvents, solubilizing agents, co-solvents, buffers, emulsifiers, for example, ethyl alcohol, isopropanol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1, 3-butylene glycol, dimethylformamide, oils (for example, cottonseed oil, groundnut oil, corn oil, germ oil, olive oil, castor oil, sesame oil or mixtures thereof), glycerol, fatty acid esters of sorbitan or mixtures thereof, suspending agents (for example, sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose or carboxymethylcellulose), preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid), or mixtures thereof. Spray compositions contain one or more suitable propellants.

Injectable preparations may be formulated according to methods known in the art using one or more dispersing agents, wetting agents, suspending agents or mixtures thereof. Injectable preparations include, for example, sterile aqueous or non-aqueous injections, injectable depot forms, aqueous suspensions or emulsions, Among the acceptable vehicles and solvents that may be utilized are water for injection, Ringer's solution and isotonic sodium chloride. Ophthalmic formulations, eardrops, eye ointments, powders and solutions are also provided herein.

Dosage forms for topical or transdermal administration of a compound of the present invention includes ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. One or more compounds described herein can be admixed under sterile conditions with one or more pharmaceutically acceptable carriers and any preservatives or buffers as may be required.

Aerosols for nasal administration can be prepared according to the techniques well known in the art. Nasal aerosols may contain one or more suitable preservatives, anti-oxidants, dispersing agents etc. or mixtures thereof.

Pharmaceutical preparations can be in unit dosage form. In unit dosage form, pharmaceutical preparations can be subdivided into unit doses containing appropriate quantities of active ingredients. Unit dosage forms can be arranged as a packaged preparation, the package containing one or more discrete capsules, powders, vials or ampoules, ointments, capsule, sachet, tablet, gel, cream or any combination of such packaged forms.

Compounds described herein can be formulated and administered in combination with one or more additional therapeutic agents, including but not limited to one or more of muscarinic receptor antagonists, bladder selective muscarinic receptor antagonists, 5α reductase inhibitors, HMG-CoA reductase inhibitors, endothelin antagonists, nitric oxide donors, cGMP elevators, 5-HT antagonists or mixtures thereof to achieve desired therapeutic effects, *i.e.*, combination therapies.

As such, dosage amounts of such active ingredients can be adjusted without undue experimentation and readily by one of ordinary skill in the art. As one of ordinary skill in the art can appreciate, dosage amounts of compounds described herein, as well as bladder selective muscarinic receptor antagonists, 5α reductase inhibitors, HMG-CoA reductase inhibitors, endothelin antagonists, nitric oxide donors, cGMP elevators or 5-HT antagonists, may be independently optimized and the combination of such active ingredients can achieve a synergistic therapeutic effect. Combinations therapies described herein include administering individual active ingredients separately in any sequence, at the same or different times during the course of therapy, or concurrently in divided or single combination forms.

Pharmaceutical compositions described herein can be administered together combined in a single dosage form or they can be administered separately, concurrently or sequentially, each in its dosage form but as part of the same therapeutic treatment program or regimen. Each pharmaceutical composition can be separately administered at different times and by different routes.

Dosage forms disclosed herein can be prepared by conventional methods known to one of ordinary skill in the art. Dosages of pharmaceutical compositions described herein may be appropriately determined with reference to the dosages recommended for respective active components and can be selected according to the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active ingredients, among other factors.

Pharmaceutical compositions described herein can show a synergistic effect compared to administration of either active component alone. Since pharmaceutical compositions described herein can have sufficient efficacy with reduced doses as compared with the administration of any of the active ingredients alone, side effects of the respective components can be reduced.

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

Scheme I

Example 1: Preparation of 2-(5-Chloropentyl)-3a,4,7,7a-tetrahydro-isoindole-1,3-dione

A solution of tetrahydropthalimide (1 equiv.), 1-bromo-5-chloropentane (7 equiv.) and potassium carbonate (3 equiv.) in acetone (25 mL/g) was stirred for about 60 hours at room temperature. The reaction mixture was then filtered washed with acetone. The filtrate was evaporated under reduced pressure to form an oily residue. The oily residue was then stirred in hexane and the solid separated out was dried under vacuum to yield the title product.

Yield: 92 %

Example 2: Preparation of 2-{5-(3,4-Dihydro-1H-isoquinoline-2-yl)-pentyl]-3a,4,7,7a-tetrahydro-isoindole-1,3-dione

A solution of 2-(5-Chloropentyl)-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (1 equiv.), 1,2,3,4-tetrahydro-isoquinoine (1.1 equiv.), potassium carbonate (3 equiv.) and potassium iodide (0.1 equiv.) in ethyl methyl ketone (40 mL) was refluxed for about 6-7 hours. The reaction mixture was then filtered through a sintered funnel and washed with dichloromethane. The filtrate was concentrated under reduced pressure and the solid obtained was then purified to yield the title product. Yield 90 %.

Example 3: Preparation of 2-{5-(3,4-Dihydro-1H-isoquinoline-2-yl)-pentyl]-5,6-dihydroxy-hexahydro-isoindole-1,3-dione

To a clear solution of 2-{5-(3,4-dihydro-1H-isoquinoline-2-yl)-pentyl]-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (1 equiv.) in ethanol (20 mL) was added potassium permanganate solution (1 equiv. in water 5 mL) dropwise at about 0-5 °C. The reaction mixture was stirred at room temperature for about 6-8 hours. After completion, the reaction was filtered through a celite pad and washed with ethanol. The filtrate thus obtained was concentrated to yield the crude product, which was purified by column chromatography using methanol in dichloromethane to yield the title product. Yield 10 % w/w.

Scheme II

Example 4: Preparation of 2-{3-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-propyl}-hexahydro-5,8-dioxa-2-aza-cyclopenta[b]naphthalene-1,3,6,7-tetraone

The title compound was prepared according to the procedure disclosed in *Chem.Pharm.Bull.*, 50 (3), 2002, 346-363. In particular, 2-{3-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-propyl}-5,6-dihydroxy-hexahydro-isoindole-1,3-dione (1eq)(prepared according to the procedure described in WO2005/118537) was taken in benzene(20ml / 1g) with pyridine(5 eq) and cooled to 0-5^{0}C. Solution of Oxalyl chloride (1.2eq) in benzene (10ml) was added dropwise. Reaction mixture was warmed up to room temperature and refluxed for about 4-5 hrs. Solvent was evaporated and the compound

dissolved in ethyl acetate. Organic layer was washed with water, dried over sodium sulphate and concentrated. The crude product was purified by column chromatography using methanol in dichloromethane. Yield: 40 % w/w

Scheme III

Example 5: Preparation of 3-[4-(2-Methoxyphenyl)-piperazine-1-yl-]-propylamine (Compound of Formula 12)

i) Preparation of 1-(2-Isocyano-ethyl)-4-(2-methoxyphenyl)-piperazine

Triethylamine (1.3 equiv.) and acrylonitrile (1.5 equiv.) were added to a solution of 1-(2-Methoxyphenyl) piperazine (1.18 equiv.) in methanol at room temperature and the reaction mixture was stirred overnight. The solvent was removed and the resulting residue was taken in water followed by extraction with dichloromethane. The organic extract was concentrated and then purified by column chromatography using methanol in dichloromethane to yield the title compound. Yield: 90 %

ii) Preparation of 3-[4-(2-Methoxyphenyl)-piperazine-1-yl-]-propylamine

To a solution of 1-(2-Isocyano-ethyl)-4-(2-methoxyphenyl)-piperazine (1 equiv.) in methanol was added Raney Ni (135 mg) followed by addition of methanol-ammonia. The reaction mixture was hydrogenated in a Parr apparatus for about 2 hours. The reaction mixture was filtered through a bed of celite, and the bed was washed with methanol. The filtrate was then concentrated to yield the desired product. Yield: 75 %

Example 6: Preparation of (1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid tert-butyl ester

Sodium hydride (1.2 equiv.) was added to dimethylformamide and stirred at about 0-5°C. 3a,4,7,7a-Tetrahydro-isoindole-1,3-dione of Formula 2 (1.0 equiv.) 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 bromoacetic acid tert-butyl ester (1.0 equiv.) was added dropwise. The reaction mixture was heated to about 50 °C for about 15 hours. The reaction mixture was quenched with water, extracted with ethyl acetate, washed with water and brine and purified by column chromatography to yield (1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid tert-butyl ester of Formula 10.

Example 7: Preparation of (1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid

(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid tert-butyl ester of Formula 10 was dissolved in dichloromethane and trifluoroacetic acid (5.0 equiv.) was added. The reaction mixture was stirred overnight at ambient temperature. The solvent was evaporated, followed by addition of dichloromethane. The solvent was then evaporated under vacuum to yield (1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid of Formula 11.

Example 8: Preparation of Compound of Formula 13

To a solution of (1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isoindol-2-yl)-acetic acid of Formula 11 (1 equiv.) in dimethylformamide was added a compound of Formula 12 (1 equiv.). The reaction mixture was cooled to about 0-5°C and stirred for about 10 minutes. N-methyl morpholine (2 equiv.) and hydroxy benzotriazole (1 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 overnight at ambient temperature. The reaction was quenched with water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and evaporated the solvent to yield a compound of Formula 13.

Example 9: Preparation of Compound of Formula 14

To a clear solution of a compound of Formula 13 (1 equiv.) in ethanol (20 ml) was added potassium permanganate solution (1 equiv. in water 5 ml) dropwise at about 0-5°C. The reaction mixture was stirred at room temperature for about 6-8 hours. After completion, the reaction was filtered through a celite pad and washed with ethanol. The filtrate thus obtained was concentrated to yield the crude product which was then purified by column chromatography to yield a compound of Formula 14.

Scheme IV

Example 10: Preparation of Compound of Formula 16

A solution of a compound of Formula 11 (1 equiv.) with thionyl chloride (5 equiv.) in dichloromethane was refluxed for about 2 hours. The reaction mixture was distilled under reduced pressure. Hexane was added and the mixture was distilled under reduced

pressure. Reaction mixture was dissolved in dichloromethane and 4-Dimethylaminopyridine was added (1.2 equiv.) followed by compound of Formula 15. The reaction mixture was then stirred at room temperature for about 3 hours. Sodium bicarbonate washings were given to the reaction mixture followed by water. The solvent was then concentrated under reduced pressure. The solid thus obtained was then purified by column chromatography to yield the title compound.

Scheme V

Example 11: Preparation of Compound of Formula 19

A solution of a compound of Formula 17 (1 equiv.) and a compound of Formula 18 (2 equiv.) in n-butanol was refluxed for about 15 hours. The reaction mixture was concentrated under reduced pressure. To the oily residue thus obtained was added sodium hydroxide and the product was then extracted with chloroform. The organic layer was concentrated and purified by column chromatography to yield the title compound.

Example 12: Preparation of Compound of Formula 20

A suspension of 2-(3-Chloropropyl)-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (55 equiv.), phenyl-piperazin-1-yl-acetic acid methyl ester (46.25 equiv.), anhydrous potassium carbonate (108.75 equiv.) and potassium iodide (1 equiv.) in dimethylformamide was heated to about 70-75 °C for about 6-8 hours. The reaction was quenched by adding water. The solid thus obtained was extracted with ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulphate and concentrated to yield the crude product, which was purified over silica gel column by using dichloromethane and methanol as eluent to yield the title compound.

Example 13: Preparation of Compound of Formula 21

To a clear solution a compound of Formula 20 (1 equiv.) in ethanol was added potassium permanganate solution (1 equiv. in water 5 ml) dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for about 6-8 hours. After completion, the reaction was filtered through a celite pad and washed with ethanol. The filtrate thus obtained was concentrated to yield the crude product which was then purified by column chromatography to yield the title compound.

Example 14: Preparation of Hydrochloride Salt

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to the base of the compound of Formula 7, the compound of Formula 8, the compound of Formula 14, the compound of Formula 16 and the compound of Formula 21. A solid which precipitates was filtered to yield the hydrochloride salt of the corresponding compound.

The following compounds were prepared by following the above procedures:

Compound No. 1: 2-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 2)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.68 (bs, 4H), 1.98 (bs, 3H), 2.20-2.25 (m, 2H), 2.45-2.50 (m, 2H), 2.92-2.95 (m, 4H), 3.27-3.31 (m, 7H), 3.55-3.59 (m, 5H), 3.80 (s, 3H), 7.08-7.35 (m, 4H),

Mass (m/z): 425 (M^++1),

Compound No. 3: 2-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 4)

^{1}H NMR (300 MHz, HCl salt $DMSOd^6$): δ 1.63-1.67 (m, 2H), 2.01-2.02 (m, 2H), 2.18-2.28 (m, 2H), 2.44-2.49 (m, 2H), 3.04-3.06 (m, 2H), 3.23-3.32 (m, 4H), 3.46-3.51 (m, 2H), 3.88-3.93 (m, 3H), 3.97 (s, 3H), 5.95-5.96 (m, 2H), 6.99-7.06 (m, 2H), 7.29-7.60 (m, 1H), 7.60-7.63 (m, 1H)

Mass (m/z): 399 (M^++1),

Compound No. 5: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 6)

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22-2.26 (m, 2H), 2.55-2.60 (m, 2H), 3.21-3.23 (m, 4H), 3.43-3.44 (m, 2H), 3.53-3.54 (m, 4H), 3.61-3.73 (m, 4H), 3.87 (s, 3H), 4.22 (s, 2H), 5.89 (s, 2H), 6.88-6.99 (m, 3H), 7.06-7.12 (m, 1H), 8.57 (s, 1H)

Mass (m/z): 427.21(M^++1),

Compound No. 7: *N*-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}acetamide and its hydrochloride salt (Compound No. 8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48-1.55 (m, 4H), 1.91 (s, 3H), 2.29-2.57 (m, 6H), 2.57-2.60 (m, 2H), 2.90 (m, 1H), 3.05-3.14 (m, 4H), 3.44-3.49 (m, 2H), 5.88-5.89 (bs, 2H)

Mass (m/z): 332 (M^++1),

Compound No. 9: Methyl {4-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt (Compound No. 10)

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18-2.24 (m, 4H), 2.59-2.64 (m, 2H), 2.77-3.13 (m, 10H), 3.34 (bs, 2H), 3.44 (m, 2H), 3.67 (s, 3H), 4.10 (s, 1H), 5.91 (bs, 2H), 7.36 (bs, 4H)

Mass (m/z): 426(M^++1),

Compound No. 11: Methyl {4-[3-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt (Compound No. 12)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68-1.70 (m, 2H), 2.14 (bs, 4H), 2.86-2.93 (m, 12H), 3.56 (bs, 2H), 3.67 (s, 3H), 3.82 (bs, 3H), 4.11 (s, 1H), 7.36 (bs, 5H)

Mass (m/z): 460 (M^++1),

Compound No. 13: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 14)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43-1.48 (m, 3H), 2.22-2.26 (m, 2H), 2.55-2.60 (m, 2H), 3.11-3.22 (m, 4H), 3.44-3.49 (m, 2H), 3.54-3.56 (m, 4H), 3.67-3.73 (m, 4H), 4.04-4.11 (m, 2H), 4.22 (s, 2H), 5.88-5.90 (t, 2H), 6.86-6.93 (m, 3H), 7.02-7.08 (m, 1H), 8.57 (s, 1H)

Mass (m/z): 441.34 (M^++1),

Compound No. 15: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 16)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.34-1.39 (m, 4H), 1.73-1.77 (m, 2H), 1.90-1.92 (m, 2H), 3.04-3.06 (m, 6H), 3.22 (m, 6H), 4.02-4.07 (m, 6H), 6.89-6.99 (m, 4H), 8.56 (s, 1H)

Mass (m/z): 475 (M^++1),

Compound No. 17: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 18)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.39-1.44 (m, 6H), 2.22 (m, 1H), 2.26 (m, 1H), 2.54 (m, 1H), 2.54 (m, 1H), 2.59 (m, 1H), 3.24 (m, 2H), 3.41 (m, 4H), 3.54-3.58 (m, 2H), 3.64-3.73 (m, 6H), 4.22 (s, 2H), 4.61-4.65 (m, 1H) 5.89 (s, 2H), 6.90-6.95 (m, 2H), 7.08-7.13 (m, 2H), 8.51 (s, 1H)

Mass (m/z): 455.2 (M^++1),

Compound No. 19: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 20)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.14-1.25 (m, 2H), 1.67-1.92 (m, 13H), 2.09-2.13 (m, 3H), 2.59 (m, 2H), 3.19-3.31 (m, 8H), 4.18 (m, 2H), 4.83 (m, 1H), 6.89-6.91 (m, 2H), 7.00-7.07 (m, 2H), 8.75 (s, 1H)

Mass (m/z): 489.2 (M^++1),

Compound No. 21: *N*-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt (Compound No. 22)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.68-1.84 (m, 4H), 1.91-1.98 (m, 4H), 2.27 (m, 2H), 2.55 (m, 2H), 3.22 (m, 2H), 3.42-3.44 (m, 2H), 3.55-3.74 (m, 10H), 4.22 (s, 2H), 4.82 (s, 1H), 5.89 (s, 2H), 6.87-6.93 (m, 2H), 7.00-7.09 (m, 2H), 8.57 (s, 1H)

Mass (m/z): 481.22 (M^++1),

Compound No. 23: *N*-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt (Compound No. 24)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.18-1.25 (m, 3H), 1.37-1.43 (m, 5H), 2.01-2.17 (m, 8H), 3.29 (m, 5H), 3.44-3.82 (m, 9H), 4.23 (m, 2H), 4.61 (m, 1H), 6.90 (m, 2H), 7.05 (m, 2H), 8.57 (s, 1H)

Mass (m/z): 515.23 (M^++1),

Compound No. 25: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 26)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.77 (m, 2H), 1.92 (m, 2H), 2.94-2.97 (m, 6H), 3.49 (m, 8H), 3.80 (m, 6H), 4.02 (m, 3H), 6.93-7.00 (m, 4H), 8.49 (s, 1H)

Mass (m/z): 461.21 (M^++1),

Compound No. 27: *N*-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide and its hydrochloride salt (Compound No. 28)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.79 (s, bs, 5H), 1.92 (bs, 2H), 2.35-2.40 (m, 4H), 2.45-2.50 (m, 2H), 2.98 (bs, 2H), 3.08-3.13 (4H), 3.39-3.72 (m, 5H), 4.15 (s, 1H), 5.86 (bs, 2H)

Mass (m/z): 388 (M^++1),

Compound No. 29: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 30)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.37-1.39 (m, 6H), 2.04 (m, 2H), 2.22-2.27 (m, 2H), 2.55-2.59 (m, 2H), 3.13 (m, 4H), 3.44 (m, 4H), 3.60-3.64 (m, 6H), 4.19 (s, 2H), 4.58-4.66 (m, 1H), 5.89-5.90 (m, 2H), 6.88-6.93 (m, 2H), 7.04-7.09 (m, 2H), 8.20 (s, 1H)

Mass (m/z): 470.17 (M^++1),

Compound No. 31: *N*-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt (Compound No. 32)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.68-1.97 (m, 8H), 2.14 (m, 2H), 2.22-2.27 (m, 2H), 2.55-2.60 (m, 2H), 3.10 (m, 4H), 3.45-3.64 (m, 10H), 4.19 (s, 2H), 4.80-4.83 (m, 1H), 5.89-5.90 (m, 2H), 6.89-7.04 (m, 4H), 8.20 (s, 1H)

Mass (m/z): 496 (M^++1),

Compound No. 33: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 34)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.45-1.48 (m, 3H), 2.14-2.16 (m, 2H), 2.26-2.27 (m, 2H), 2.55-2.56 (m, 2H), 3.09-3.12 (m, 4H), 3.44-3.45 (m, 4H), 3.54-3.65 (m, 6H), 4.06-4.10 (m, 2H), 4.19 (s, 2H), 5.89-5.90 (m, 2H), 6.87-6.96 (m, 3H), 7.06 (m, 1H), 8.18-8.21 (m, 1H)

Mass (m/z): 455 (M^++1),

Compound No. 35: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 36)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.34-1.37 (m, 3H), 1.80-1.82 (m, 2H), 1.87-1.89 (m, 4H), 3.02-3.16 (m, 10H), 3.46-3.48 (m, 8H), 3.97 (s, 2H), 4.02-4.04 (m, 2H), 6.89-6.99 (m, 4H), 8.37-8.40 (m, 1H)

Mass (m/z): 489 (M^++1),

Compound No. 37: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 38)

^{1}H NMR (300MHz, $CDCl_3$): δ 1.23-1.28 (m, 6H), 1.76-1.77 (m, 2H), 1.87-1.91 (m, 4H), 3.01-3.18 (m, 10H), 3.95-3.97 (m, 8H), 3.97 (s, 2H), 4.59-4.63 (m, 1H), 6.88-6.98 (m, 4H), 8.38-8.40 (m, 1H)

Mass (m/z): 504 (M^++1),

Compound No. 39: *N*-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt (Compound No. 40)

^{1}H NMR (300MHz, DMSO): δ 1.23-1.28 (m, 8H), 1.75-1.76 (m, 2H), 1.85-1.90 (m, 4H), 3.00-3.18 (m, 12H), 3.50-3.54 (m, 6H), 3.97 (s, 2H), 4.59-4.63 (m, 1H), 6.86-6.98 (m, 4H), 8.37-8.39 (m, 1H)

Mass (m/z): 529 (M^++1),

Compound No. 41: 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 42)

^{1}H NMR (300MHz, $CDCl_3$): δ 2.122-2.151 (m, 2H), 2.228-2.271 (m, 2H), 2.556-2.600 (m, 2H), 3.076-3.105 (m, 4H), 3.426-3.646 (m, 10H), 3.878 (s, 3H), 4.190 (s, 2H), 5.89-5.903 (m, 2H), 6.890-6.977 (m, 3H), 7.068-7.089 (m, 1H), 8.175-8.203 (m, 1H)

Mass (m/z): 441 (M^++1),

Compound No. 43: 2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt (Compound No. 44)

^{1}H NMR (300MHz, DMSO): 1.75-1.76 (m, 2H), 1.88-1.91 (m, 4H), 3.04-3.16 (m, 10H), 3.47-3.53 (m, 6H), 3.80-3.81 (s, 3H), 3.98 (m, 4H), 6.89-7.05 (m, 4H), 8.38-8.40 (m, 1H)

Mass (m/z): 475 (M^++1),

Compound No. 45: 2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetate and its hydrochloride salt (Compound No. 46)

^{1}H NMR (300MHz, $CDCl_3$): 2.25-2.30 (m, 2H), 2.58-2.62 (m, 2H), 3.18-3.24 (m, 4H), 3.33 (m, 2H), 3.47-3.52 (m, 4H), 3.61-3.63 (m, 2H), 3.88 (s, 3H), 4.28 (s, 2H), 4.79 (m, 2H), 5.90-5.94 (m, 2H), 6.88-6.95 (m, 3H), 7.06-7.10 (m, 1H)

Mass (m/z): 428 (M^++1),

Compound No. 47: 7-{3-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]propyl} tetrahydro-4a*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3,6,8(5*H*,7*H*)-tetrone and its hydrochloride salt (Compound No. 48)

^{1}H NMR (300 MHz, $CDCl_3$)δ: 1.20-1.25 (d, 6H), 1.60 (s, 2H), 1.60-2.52 (m, 4H), 3.01-3.08 (m, 6H), 3.10-3.41 (m, 6H), 3.62-3.65 (m, 2H), 4.48-4.51 (m, 1H), 5.08 (s, 2H), 6.59-6.80 (m, 3H)

Mass (m/z): 518 (M^++1),

Compound No. 49: 2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetate and its hydrochloride salt (Compound No. 50)

^{1}H NMR (300MHz, $CDCl_3$): 1.46-1.49 (m, 3H), 2.25-2.30 (m, 2H), 2.62-2.63 (m, 2H), 3.16-3.22 (m, 4H), 3.34 (m, 2H), 3.54-3.61 (m, 6H), 4.06-4.11 (m, 2H), 4.28 (s, 2H), 4.79 (m, 2H), 5.93-5.94 (m, 2H), 6.86-6.94 (m, 3H), 7.03-7.05 (m, 1H)

Mass (m/z): 442 (M^++1),

Compound No. 51: 2-[5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 52)

^{1}H NMR (300MHz, $CDCl_3$): 1.28-1.33 (m, 2H), 1.55-1.64 (m, 4H), 2.14-2.18 (m, 2H), 2.51-2.59 (m, 4H), 2.78-2.85 (m, 4H), 3.06-3.07 (m, 2H), 3.46-3.49 (m, 2H), 3.61 (s, 2H), 3.84 (s, 6H), 5.87-5.88 (m, 2H), 6.52 (s, 1H), 6.59 (s, 1H)

Mass (m/z): 413 (M^++1),

Compound No. 53: 2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 54)

^{1}H NMR (300MHz, $CDCl_3$): 1.25-1.30 (m, 2H), 1.55-1.63 (m, 4H), 2.16-2.20 (m, 2H), 2.50-2.59 (m, 4H), 2.77-2.78 (m, 2H), 2.91-2.92 (m, 2H), 3.05-3.06 (m, 2H), 3.45-3.49 (m, 2H), 3.66 (s, 2H), 5.84-5.88 (m, 2H), 7.01-7.15 (m, 4H)

Mass (m/z): 353 (M^++1),

Compound No. 55: 2-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 56)

^{1}H NMR (300 MHz, $CDCl_3$)δ: 1.32-1.34 (d, 6H), 1.38 (s, 2H), 1.62-1.64 (m, 2H), 2.01-2.05 (m, 4H), 2.50 (s, 2H), 3.02-3.08 (m, 8H), 3.45-3.56 (m, 6H), 3.59-3.81 (m, 4H), 4.48-4.50 (m, 1H), 6.64-6.79 (m, 3H)

Mass (m/z): 492 (M^++1),

Compound No. 57: 2-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 58)

^{1}H NMR (300MHz, $CDCl_3$): 1.80-1.82 (m, 2H), 2.14-2.28 (m, 9H), 2.53-2.58 (m, 2H), 3.01-3.02 (m, 2H), 3.12-3.13 (m, 2H), 3.38-3.42 (m, 2H), 3.61-3.64 (m, 2H), 4.01-4.03 (m, 1H), 4.55-4.56 (m, 1H), 5.63-5.74 (m, 2H), 7.10-7.30 (m, 4H)

Mass (m/z): 325 (M^++1),

Compound No. 59: 2-(3-{4-[2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-fluorophenyl]piperazin-1-yl}propyl)-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 60)

^{1}H NMR (300MHz, $CDCl_3$): 1.25-1.37 (m, 4H), 1.74-2.18 (m, 6H), 2.34-2.42 (m, 7H), 2.95-3.26 (m, 8H), 3.50-3.79 (m, 4H), 6.57-6.84 (m, 3H), 7.17-7.19 (m, 4H)

Mass (m/z): 538.0 (M^++1),

Compound No. 61: 2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt (Compound No. 62)

^{1}H NMR (300MHz, $CDCl_3$): 1.25-1.33 (m, 4H), 1.59-1.62 (m, 2H), 1.59-1.68 (m, 2H), 2.16-2.20 (m, 2H), 2.63-2.66 (m, 2H), 2.91-3.01 (m, 6H), 3.47-3.50 (m, 2H), 3.66-3.69 (m, 2H), 3.88 (s, 2H), 7.04-7.23 (m, 4H)

Mass (m/z): 387 (M^++1),

and pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof.

Example 15: Pharmacological testing

A) 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) Hydrochloride compounds disclosed herein exhibited α_{1a} Ki (nM) values of between about 1 nM to about greater than 2500 nM, between about 1 nM to about 280 nM, between about 1 nM to about greater than 95 nM, and even between about 1 nM to about 10 nM

b) Hydrochloride compounds disclosed herein exhibited α_{1b} Ki (nM) values of between about 4.8 nM to about greater than 1333 nM, between about 4.8 nM to

about greater than 900 nM, between 4.8 nM to 478 nM, and even between about 4.8 nM to about 175 nM.

B) Receptor binding assays

Receptor binding assays are performed using native α-1 adrenoceptors. The affinity of different compounds for α_{1a} and α_{1b} adrenoceptor subtypes is evaluated by 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 hydrochloric acid 50 mM, sodium chloride 100 mM, ethylene diamine tetra acetic acid 10 mM, pH 7.4). The homogenate is filtered through two layers of wet guaze and filtrate is centrifuged at 500g for 10 min. The supernatant is subsequently centrifuged at 40, 000g for 45 min. The pellet thus obtained is resuspended in the same volume of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) and are stored at –70 ^{0}C until the time of assay.

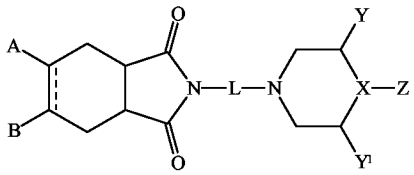
The membrane homogenates (150-250 μg protein) are incubated in 250 μl of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) at 24-25 ^{0}C for I hour. Non-specific binding is determined in the presence of 300 nM prazosin. The incubation is terminated by vacuum filtration over GF/B fibre filters. The filters 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, 1973, 22:3099-3108), $Ki = IC_{50} /(1+L/Kd)$ where L is the concentration of [^{3}H] prazosin used in the particular experiment.

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

In order to study selectivity of action of compounds described herein towards different α_{1a} adrenoreceptor subtypes, the ability of such 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 thiopentane anaesthetized (≈ 300 mg/Kg) male wistar rats. Isolated tissues are mounted in organ bath containing Krebs Henseleit buffer of the following composition (mM): sodium chloride (NaCl) 118; potassium chloride (KCl) 4.7; calcium chloride ($CaCl_2$) 2.5; magnesium sulphate heptahydrate ($MgSO_4 \cdot 7H_2O$) 1.2; sodium bicarbonate ($NaHCO_3$) 25; potassium dihydrogen phosphate (KH_2PO_4) 1.2; glucose 11.1. Buffer is maintained at 37 ^{0}C and aerated with a mixture of 95 % oxygen (O_2) and 5 % carbon dioxide (CO_2). A resting tension of 2 g (aorta and spleen) or 1 g (prostate) is applied to tissues. Contractile response is monitored using a force displacement transducer and is 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:

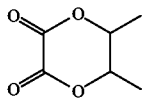
1. A compound having the structure of Formula I,



Formula I

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolites thereof, wherein:

A and B are independently hydrogen, halogen, hydroxy, alkyl, alkoxy, cyano, nitro, amino, alkylamino or thio, or A and B together form a ring represented by:



L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH);

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

----- is optional bond;

with the provisos that when L is $-(CH_2)_3-$,

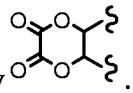
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

2. A compound selected from:

2-{3-[8-hydroxy-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and it's hydrochloride salt,

2-{3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]propyl}-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}acetamide and its hydrochloride salt,

Methyl {4-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

Methyl {4-[3-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)propyl]piperazin-1-yl}(phenyl)acetate and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-{3-[3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}tetrahydrofuran-2-carboxamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-ethoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-isopropoxyphenyl) piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

N-(2-{4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl}ethyl)-2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)acetamide and its hydrochloride salt,

2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-isoindol-2-yl)-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}acetamide and its hydrochloride salt,

2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxooctahydro-2*H*-isoindol-2-yl) acetate and its hydrochloride salt,

7-{3-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]propyl} tetrahydro-4a*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3,6,8(5*H*,7*H*)-tetrone and its hydrochloride salt,

2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl (1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetate and its hydrochloride salt,

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

2-[5-(3,4-dihydroisoquinolin-2(1*H*)-yl)pentyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

2-{5-[4-(5-fluoro-2-isopropoxyphenyl)piperazin-1-yl]pentyl}-5,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

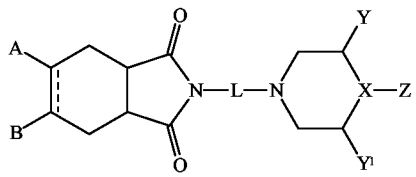
2-[3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propyl]-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and its hydrochloride salt,

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

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

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof.

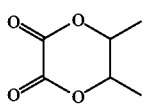
3. A method of treating a disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptor comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds having the structure of Formula I,



Formula I

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolites thereof, wherein:

A and B are independently hydrogen, halogen, hydroxy, alkyl, alkoxy, cyano, nitro, amino, alkylamino or thio, or A and B together form a ring represented by:



L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH);

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

----- is optional bond;

with the provisos that when L is $-(CH_2)_3-$,

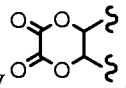
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

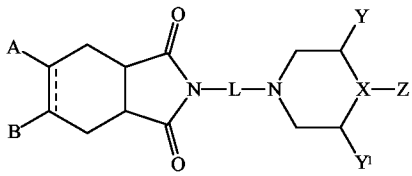
vi) A and B together form a ring represented by  .

4. The method of claim 3, wherein the disease or disorder mediated through α_{1a} and/or α_{1d} adrenergic receptor is benign prostatic hyperplasia.

5. The method of claim 4, wherein the one or more compounds of Formula I causes minimal fall or no fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

6. The method of claim 4, further comprising administering one or more other therapeutic agents selected from muscarinic receptor antagonists, bladder selective muscarinic receptor antagonists, testosterone 5 alpha-reductase inhibitor, endothelin, antagonists, nitric oxide donors, cGMP elevators, 5-HT antagonists or mixtures thereof.

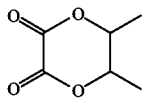
7. A method of treating a lower urinary tract symptom associated with or without benign prostatic hyperplasia comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds having the structure of Formula I,



Formula I

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolites thereof, wherein:

A and B are independently hydrogen, halogen, hydroxy, alkyl, alkoxy, cyano, nitro, amino, alkylamino or thio, or A and B together form a ring represented by:



L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH);

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

----- is optional bond;

with the provisos that when L is $-(CH_2)_3-$,

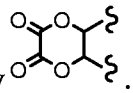
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

iii) Z is $CH(COOR_1)R_1$,

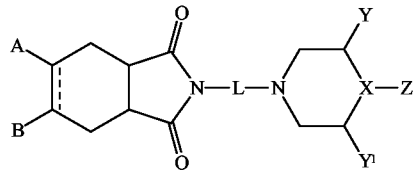
iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

8. The method of claim 7, further comprising administering one or more other therapeutic agents selected from muscarinic receptor antagonists, bladder selective muscarinic receptor antagonists, testosterone 5 alpha-reductase inhibitor, endothelin, antagonists, nitric oxide donors, cGMP elevators, 5-HT antagonists or mixtures thereof.

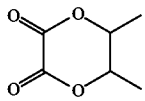
9. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of Formula I and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the one or more compounds Formula I are represented by:



Formula I

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolites thereof, wherein:

A and B are independently hydrogen, halogen, hydroxy, alkyl, alkoxy, cyano, nitro, amino, alkylamino or thio, or A and B together form a ring represented by:



L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH);

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

----- is optional bond;

with the provisos that when L is $-(CH_2)_3-$,

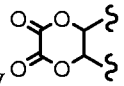
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

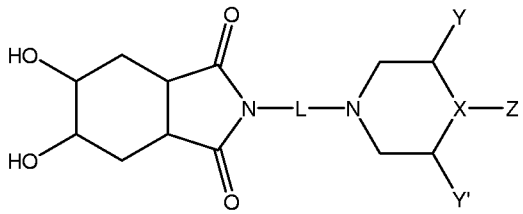
iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

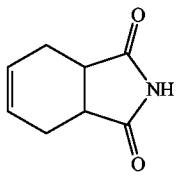
10. A method for preparing a compound of Formula 7,



Formula 7

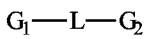
comprising the steps of:

a) reacting a compound of Formula 2



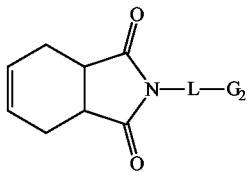
Formula 2

with a compound of Formula 3



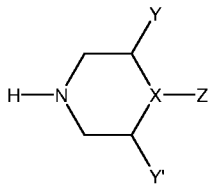
Formula 3

to form a compound of Formula 4,



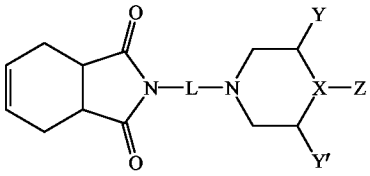
Formula 4

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



Formula 5

to form a compound of Formula 6, and



Formula 6

c) oxidizing the compound of Formula 6 to form a compound of Formula 7,

wherein

L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH);

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated; and

G_1 and G_2 are leaving groups;

with the provisos that when L is $-(CH_2)_3-$,

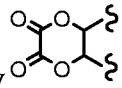
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

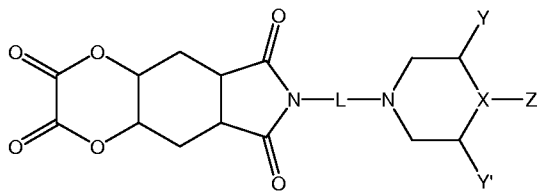
iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

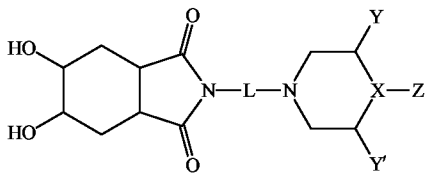
11. A method for preparing a compound of Formula 8,



Formula 8

comprising the step of:

a) reacting a compound of Formula 7



Formula 7

with oxalyl chloride to form a compound of Formula 8,

wherein

L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

Y and Y' are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl, or Y and Y' together form a bridging group (C_{0-3});

X is N, C, CH or C(OH); and

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl, or X and Z together with Y (or Y') form a 5-7 membered ring, which may be partially saturated, saturated or unsaturated;

with the provisos that when L is -$(CH_2)_3$-,

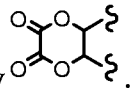
i) Y and Y' together form a bridging group (C_{0-3}),

ii) X is –COH,

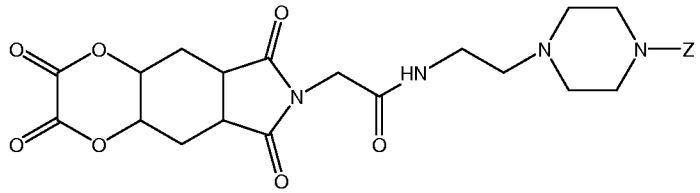
iii) Z is $CH(COOR_1)R_1$,

iv) X and Z together with Y (or Y') form phenyl ring,

v) Z is 2-(2,3-dihydro-1H-inden-2-yloxy)-5-fluorophenyl, or

vi) A and B together form a ring represented by  .

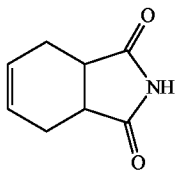
12. A method for preparing a compound of Formula 14,



Formula 14

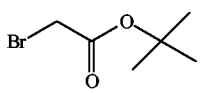
comprising the steps of:

a) reacting the a compound of Formula 2



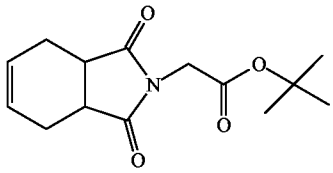
Formula 2

with a compound of Formula 9



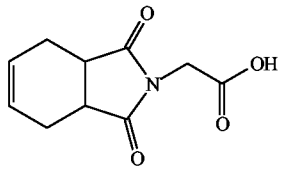
Formula 9

to form a compound of Formula 10,



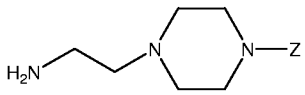
Formula 10

b) reacting the compound of Formula 10 with one or more acids to form a compound of Formula 11,



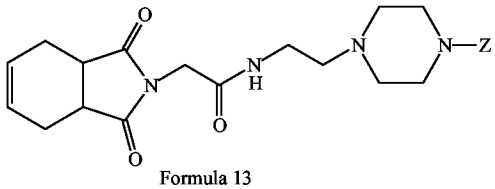
Formula 11

c) coupling the compound of Formula 11 with a compound of Formula 12



Formula 12

to form compounds of Formula 13, and



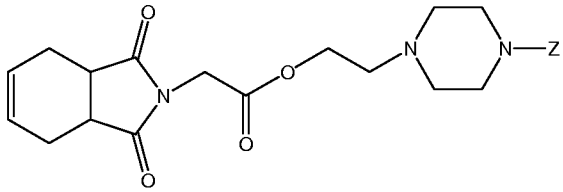
Formula 13

d) oxidizing the compound of Formula 13 to form a compound of Formula 14,

wherein:

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl.

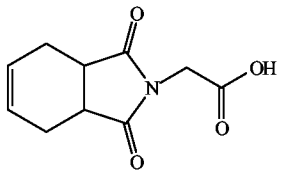
13. A method for the preparing a compound of Formula 16,



Formula 16

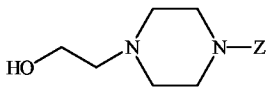
comprising the step of:

a) reacting a compound of Formula 11



Formula 11

with thionyl chloride and compound of Formula 15



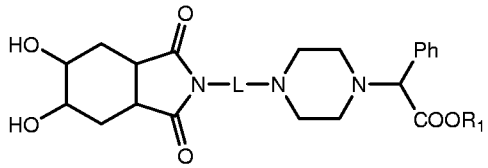
Formula 15

to form a compound of Formula 16,

wherein:

Z is alkyl, cycloalkyl, aryl, $NHCOR_1$, $CH(COOR_1)R_1$ or $NHCONHR_1$, wherein R_1 is alkyl, aryl or heterocyclyl.

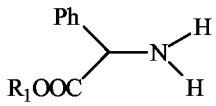
14. A method for preparing a compound of Formula 21,



Formula 21

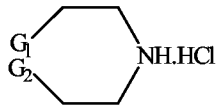
comprising the steps of:

a) reacting a compound of Formula 17



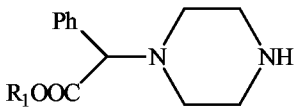
Formula 17

with a compound of Formula 18



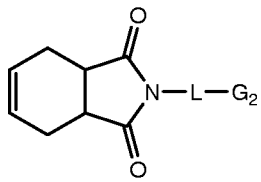
Formula 18

to form a compound of Formula 19,



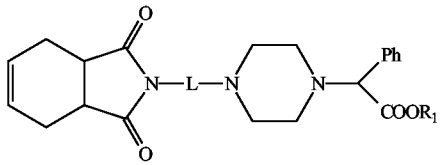
Formula 19

b) reacting the compound of Formula 19 with a compound of Formula 4



Formula 4

to form compounds of Formula 20.



Formula 20

c) oxidizing the compound of Formula 20 to form a compound of Formula 21,

wherein

L is $(CH_2)_3$, $(CH_2)_5$, $CH_2CONHCH_2CH_2$ or $CH_2COOCH_2CH_2$;

R_1 is alkyl, aryl or heterocyclyl; and

G_2 is a leaving group.