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(54) Title: THIAZOLIDINEDIONE DERIVATIVES

(57) Abstract: The present invention relates to alpha 1a and/or alpha 1d adrenergic receptor antagonists. Compounds described can function as alpha 1a and/or alpha 1d adrenergic receptor antagonists and can be used to treat diseases or disorders mediated through alpha 1a and/or alpha 1d adrenergic receptors. Compounds described can also be used to treat benign prostatic hyperplasia or related symptoms thereof. Compounds described can also be used to treat lower urinary tract symptoms associated with or without benign prostatic hyperplasia. Also described are processes to prepare the described compounds, as well as pharmaceutical compositions thereof and methods of treating benign prostatic hyperplasia or related symptoms thereof.

THIAZOLIDINEDIONE DERIVATIVES

Field of the Invention

The present invention relates to alpha 1a and/or alpha 1d adrenergic receptor antagonists. Compounds described can function as alpha 1a and/or alpha 1d adrenergic receptor antagonists and can be used to treat diseases or disorders mediated through alpha 1a and/or alpha 1d adrenergic receptors. Compounds described can also be used to treat benign prostatic hyperplasia or related symptoms thereof. Compounds described can also be used to treat lower urinary tract symptoms associated with or without benign prostatic hyperplasia. Also described are processes to prepare the described compounds, as well as pharmaceutical compositions thereof and methods of treating benign prostatic hyperplasia or related symptoms thereof.

Background of the Invention

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is highly prevalent in men beyond the age of 50 and increases in severity and incidence with increasing age. It has been reported that the incidence is 70% in 70 years and becomes nearly universal with advancing age with 90% incidence at the age of 80 years. Berry *et al.*, *J. Urol.*, **132**:474-479 (1984).

BPH is characterized by nodular enlargement of prostatic tissue and is associated with variety of lower urinary tract symptoms (LUTS). LUTS in men includes a complex of obstructive (voiding) and irritative (storage or filling) symptoms, which include increased frequency, nocturia, poor urinary stream and hesitancy or delay in starting urinary flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, decompensated bladder and increased incidence of urinary tract infections. Histologically, BPH is characterized by glandular (epithelial) and stromal (fibro muscular) hyperplasia with the latter being the dominant factor in the pathogenesis of clinically significant BPH. Shapiro *et a.l*, *J. Urol.*, **147**:1293-1297 (1992).

Two components - static component and dynamic component contribute to obstruction, although the exact etiology of origin of these symptoms is not distinctly clear. Prostatic enlargement or hyperplasia of prostate gland physically impinges on the free

flow of fluids through the male urethra and leads to varying degrees of bladder obstruction. This component has been referred to as static component (Caine M, *J. Urol.*, **136**:1-4 (1986). Increased adrenergic innervations to the prostate leads to an increased adrenergic tone of the bladder neck or urethra and is referred to as dynamic component. The irritative symptoms have been closely associated with bladder dysfunction, which was believed to be a consequence of bladder outlet obstruction (Anderson K. E., *Brit. J. Urol.*, **85 Suppl**:12-18 (2000)).

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

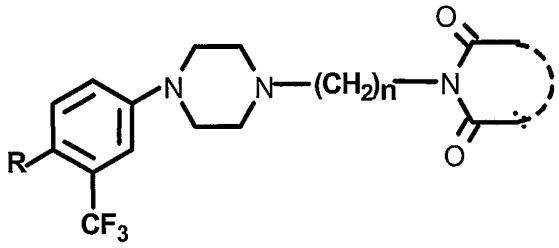
There are some drug therapies that address the static component of this condition. Finasteride is reportedly one such therapy, which is indicated for the treatment of symptomatic BPH. This drug is a competitive inhibitor of the enzyme 5 alpha-reductase, which is responsible for the conversion of testosterone to dihydrotestosterone in the prostate gland. Dihydrotestosterone has been reported as being the major mitogen for prostate growth and agents, which inhibit 5-alpha reductase, reduce the size of the prostate and improve urine flow through the prostatic urethra. Although finasteride is a potent 5-alpha reductase inhibitor and causes a marked decrease in serum and tissue concentrations of dihydrotestosterone, it is moderately effective in treating symptomatic BPH. The effects of finasteride can 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 using adrenergic receptor blocking agents, which decrease smooth muscle tone within the prostate gland. A variety of alpha 1-AR antagonists, such as terazosin, doxazosin, prazosin, alfuzosin and tamsulosin (R. A. Janknegt, op. cit., *et al.*, *J. Urol.*, **145**:65:36-38 (1990) and C. R Chapple *et al.*, *Urol. Inst.*, **45**:47-55 (1990)) 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 alpha 1-adrenoceptor. There are several lines of evidence to suggest that selectivity for alpha-1a adrenoceptor over alpha-1b adrenoceptor will result in relative lack of vascular side effects, thus lead to a better tolerability. *In-vivo* studies in healthy subjects comparison of alpha-1a/1d selective antagonists (*e.g.*, tamsulosin) or alpha-1a selective antagonists (*e.g.*, urapidil) with non selective antagonists (*e.g.*, doxazosin, prazosin, or terazosin) under a variety of experimental conditions (*e.g.*, involving the administration of exogenous agonist or release of endogenous agonist by cold stimulation) in several vascular beds including the skin circulation in finger tips, the dorsal hand vein, or with total peripheral resistance have been reported. (*Eur. J. Clin. Pharmacol.*, **49**:371-375 (1996); *Arch. Pharmacol.*, **354**:557-561 (1996); *Jpn. J. Pharmacol.*, **80**:209-215 (1999); *Br. J. Clin. Pharmacol.*, **47**:67-74 (1999)). Irrespective of the antagonists, agonists and vascular beds under investigation, all of these studies have reported that an antagonist with high affinity for alpha-1a or alpha-1a/1d can cause some degree of vasodilation but that it is much smaller than with non-subtype-selective alpha-1 adrenoceptor antagonists. Further, there reportedly is increased vascular alpha-1b adrenoceptor expression in elderly patients and thus alpha-1a/1d selective agents with selectivity over alpha-1b adrenoceptor subtype would be of particular importance in benign prostatic hyperplasia, which is generally a disease of old age. This viewpoint is widely shared by many others as evident from publications. (Eur. Urol., **39**(Suppl 2):38-41 (2001); *BJU International*, **88**(Suppl 2):27-34 (2001); *BJU International*, **85**(Suppl 2):6-11 (2000)). Antagonism of both alpha-1a adrenoceptor and alpha-1d adrenoceptors is reportedly important to relieve lower urinary tract symptoms especially associated (suggestive of) with BPH. Targeting alpha-1a adrenoceptor with antagonists is reportedly important in relaxing prostate smooth muscle and relieving bladder outlet obstruction whereas alpha-1d adrenoceptor antagonism is reportedly important to target irritative symptoms (*BJU International*, **88**(Suppl 2):27-34 (2001); *BJU International*, **85**(Suppl 2):6-11 (2000); Martin C. Michel, *European Urology Supplements*, **1**:5-13 (2000)).

Over the past decade, there has been an intensive search for selective alpha 1-adrenoceptor antagonists for benign prostatic hyperplasia, which would avoid the cardiovascular side effects, associated with currently used drugs. Many selective antagonist have been disclosed in Hieble *et al. Exp. Opin. Invest. Drugs*, **6**:367-387 (1997)

and by Kenny *et al.*, *J. Med. Chem.*, **40**:1293-1325 (1995). Structure activity relationships in many of these structural series have been studied in details and numerous highly selective compounds have been identified. There are many description in the literature about the pharmacological activities associated with phenyl piperazines, *Eur. J. Med. Chem. – Chimica Therapeutica*, **12**:173-176 (1977), discloses substituted trifluoromethyl phenyl piperazines having cyclo-imido alkyl side chains shown below.



These compounds are potential anorectic agents with no CNS side effects. Other related compounds which have been prepared as anxiolytic, neuroleptic, anti-diabetic and anti-allergic agents have also been disclosed. (PCT Application No. WO 98/37893; Steen *et al.*; *J. Med. Chem.*, **38**:4303-4308 (1995); Ishizumi *et al.*, *Chem. Pharm. Bull.*, **39**(9):2288-2300 (1991); Japanese Patent Publication No. JP 02-235865 (1990); U.S. Patent No. 4,598,078; New *et. al.*; *J. Med. Chem.*, **29**:1476-1482 (1986); Japanese Patent Publication No. JP 60-204784 (1985); U.S. Patent No. 4,524,206; Korgaonkar *et al.*; *J. Indian Chem. Soc.*, **60**:874-876 (1983)).

The synthesis of 1-(4-arylpiperazin-1-yl)-ω-[N-(α, ω-dicarboximido)]-alkanes useful as uro-selective α_1-adrenoceptor blockers are disclosed in 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 and PCT Publication No. WO 02/44151. These compounds reportedly possess good α_1-adrenergic blocking activity and selectivity.

Other reports describing selective alpha 1 adrenoceptor antagonists are U.S. Patents Nos. 6,376,503; 6,319,932; 6,339,090; European Patent No. 711757, and PCT Publication Nos. WO 99/42448, WO 99/42445, WO 98/57940, WO 98/57632, WO 98/30560 and WO 97/23462.

U.S. Patent No. 4,367,335 discloses piperazinyl derivatives containing a 3-alkylene-2,4-thiazolidinedione heterocyclic component with relatively selective psychotropic properties. U.S. Patent No. 4,933,453 discloses 3-[4-(1-substituted-4-piperazinyl)butyl]-4-thiazolidione compounds which are useful as antipsychotic, analgesic, anti convulsant and anxiolytic agents. U.S. Patent No. 4,452,799 discloses disubstituted N,N-piperazinyl derivatives containing one substituent as benzisothiazol-3-yl or benzisoxazol-3-yl and the ether substituent as alkylene attached to heterocycles, for example, thiazolidinedione, spirocyclopentylthia-zolidinediones or butyrophenone like groups with psychotropic properties.

However, there remains a need for novel alpha 1a and alpha 1d adrenergic receptor antagonists, which can be used, for example, to treat BPH or associated symptoms, as well as LUTS with or without BPH.

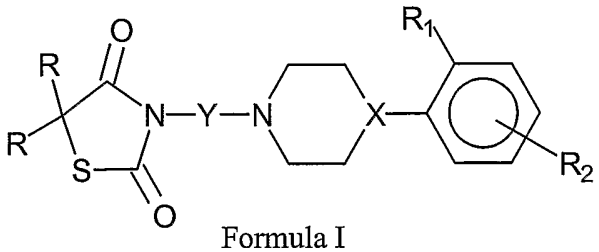
Summary of the Invention

The present invention provides novel alpha 1a and/or alpha 1d adrenergic receptor antagonists, which can be used for treatment of benign prostatic hyperplasia (BPH) or related symptoms thereof or lower urinary tract symptoms (LUTS) with or without BPH, and processes for the syntheses of these compounds.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides of such compounds having the same type of activity are also provided.

Pharmaceutical compositions containing one or more compounds as described herein, and which may also contain pharmaceutically acceptable carriers, excipients or diluents, which can be used for the treatment of BPH or related symptoms thereof or LUTS with or without BPH.

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



Formula I

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

R can be hydrogen, alkyl or aralkyl;

Y can be $-CH_2-Z-CH_2$, wherein Z is $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, and wherein n can be an integer of from 0 to 3, and R_3 can be hydrogen, alkyl, aryl or aralkyl;

X can be CH or nitrogen;

R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

with the proviso that when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen;

and the proviso that when each R is hydrogen or when one R is hydrogen and the other R is alkyl, Z is a bond, $-CH_2-$ or $-CH_2CH_2-$, and R_1 is H, then R_2 cannot be 3-chloro or 3-alkyl.

These compounds can include one or more of the following embodiments. For example in one embodiment, R can be hydrogen or aralkyl; Z can be $-CH_2-$ or -CO-; R_1 can be alkoxy, cycloalkoxy or haloalkoxy; R_2 can be halogen; and X can be nitrogen.

In another aspect, provided herein are compounds selected from:

5,5-Dibenzyl-3-{3[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3{3{4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl}-propyl)-thiazolidine-2,4-dione,

3(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(2-Methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-ethoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione or

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates

enantiomers, diastereomers, N-oxides, polymorphs or metabolites thereof.

In another aspect, provided herein are compounds selected from:

5,5-Dibenzyl-3-{3[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3{4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl}-propyl)-thiazolidine-2,4-dione hydrochloride salt,

3-(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(2-Methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-methoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

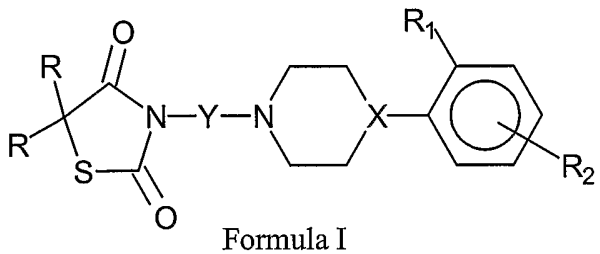
3-{5-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(2-Cyclopentyloxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-propoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt.

In yet another aspect, provided herein are pharmaceutical compositions comprising therapeutically effective amounts of one or more compounds as described herein, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.

In yet another aspect, provided herein are methods for treating a patient suffering from a disease or disorder mediated through alpha 1a or alpha 1d adrenergic receptors comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds having the structure of Formula I,



Formula I

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

R can be hydrogen, alkyl or aralkyl;

Y can be $-CH_2-Z-CH_2$, wherein Z is $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, and wherein n is an integer of from 0 to 3, and R_3 is hydrogen, alkyl, aryl or aralkyl;

X can be CH or nitrogen;

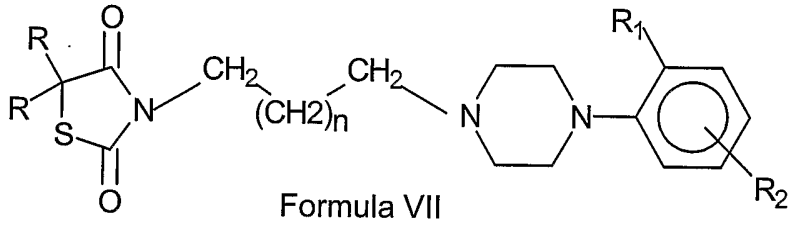
R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

with the proviso that when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and the proviso that when each R is hydrogen or when

one R is hydrogen and the other R is alkyl, Z is a bond, -CH_2- or –CH_2CH_2-, and R_1 is H, then R_2 cannot be 3-chloro or 3-alkyl.

The methods can include one or more of the following embodiments. For example, the method can be for treating benign prostatic hyperplasia (BPH) or lower urinary tract symptoms (LUTS).

In another aspect, provided herein are processes of preparing compounds of Formula VII:



Formula VII

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, polymorphs or metabolites thereof, wherein

R can be hydrogen, alkyl or aralkyl;

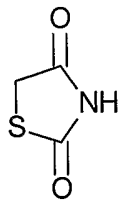
Y can be -CH_2-Z-CH_2, wherein Z is -$(CH_2)_n$-, -$CHOR_3$, -NR_3, -CO- or -CS-, and wherein n can be an integer of from 0 to 3, and R_3 can be hydrogen, alkyl, aryl or aralkyl;

X can be CH or nitrogen;

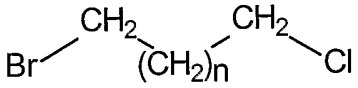
R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

the method comprising the steps of:

(a) reacting 2,4-thiazolidinone of Formula II with compounds of Formula III

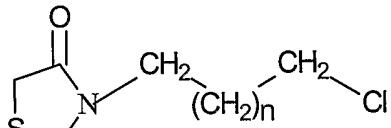


Formula I



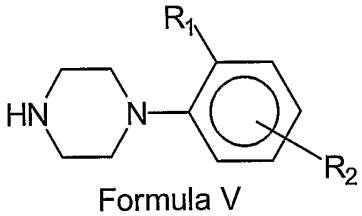
Formula III

to form compounds of Formula IV,



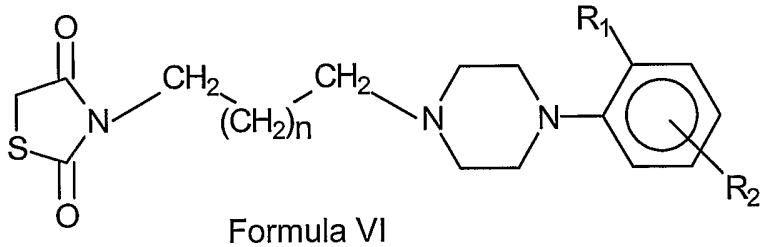
Formula IV

(b) compounds of Formula IV can be treated with compounds of Formula V



Formula V

to form compounds of Formula VI, wherein R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl; and

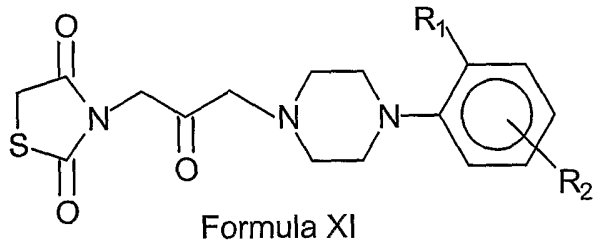


Formula VI

(c) compounds of Formula VI can be treated with compounds of Formula RX (wherein X can be halogen) to form compounds of Formula VII, wherein R can be alkyl or aralkyl.

These processes can include the following embodiments. For example, when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and when each R is hydrogen and Z is a bond, then R_2 cannot be 3-chloro.

In yet another aspect, also provided herein are processes of preparing compounds having the structure of Formula XI,



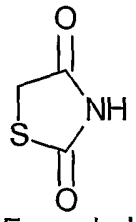
Formula XI

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

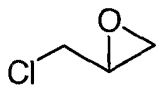
R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl,

which method comprises:

(a) reacting 2,4-thiazolidinedione of Formula II with epichlorohydrin of Formula VIII

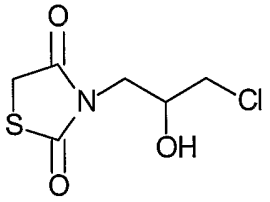


Formula II



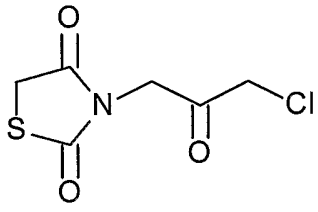
Formula VIII

to form 3-(3-chloro-2-hydroxy propyl)-thiazolidine-2,4-dione of Formula IX



Formula IX

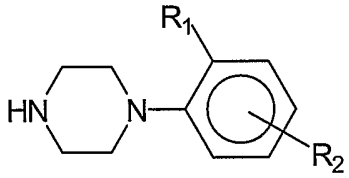
(b) oxidizing the compound of Formula IX to form 3-(3-chloro-2-oxo-propyl)-thiazolidine-2,4-dione of Formula X, and



IV

Formula X

(c) treating the compound of Formula X with compounds of Formula V



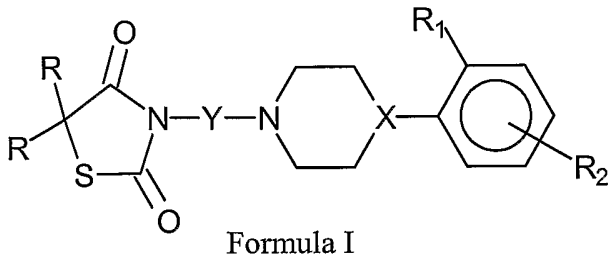
Formula V

to form compounds of Formula XI, wherein R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl.

These processes can include the following embodiments. For example, when R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and when Z is a bond, then R_2 cannot be 3-chloro.

Detailed Description of the Invention

In accordance with one aspect, there are provided compounds having the structure of Formula I,



Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein

R can be hydrogen, alkyl or aralkyl, wherein each R may be same or different;

Y can be $-CH_2-Z-CH_2$, wherein Z can be $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, wherein n can be an integer from 0 to 3, and R_3 can be hydrogen, alkyl, aryl or aralkyl;

X can be CH or nitrogen;

R_1 and R_2 each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl; with the proviso that R_2 cannot be hydrogen when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2.

In one embodiment, there are provided compounds of Formula I, wherein R can be aralkyl; Z can be $-CH_2-$ or -CO-; X can be nitrogen; R_1 can be alkoxy, cycloalkoxy or haloalkoxy; and R_2 can be halogen.

Also provided herein are methods of treating a patient suffering from a disease or disorder mediated through alpha 1a and/or alpha 1d adrenergic receptors comprising administering to a patient in need thereof a therapeutically effective amount of one or more compounds as described herein.

Also provided herein are methods of treating a patient suffering from benign prostatic hyperplasia (BPH) or related symptoms comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds as described herein.

Also provided herein are methods for treating a patient suffering from lower urinary tract symptoms (LUTS) with or without BPH comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds described. LUTS may include, for example, irritative symptoms, *e.g.*, frequent urination, urgent urination, nocturia and unstable bladder contractions; obstructive symptoms, *e.g.*, hesitancy, poor stream, prolong urination, and feelings of incomplete emptying.

Also provided are processes for preparing compounds as described herein.

Also provided are methods for treating a patient suffering from BPH or LUTS with or without BPH comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds (or compositions) as described herein in combination with one or more bladder-selective muscarinic receptor antagonists.

Also provided are methods for treating a patient suffering from BPH or LUTS with or without BPH comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds (or compositions) as described herein in combination with one or more testosterone 5 alpha-reductase inhibitors.

Also provided are methods for treating a patient suffering from BPH or LUTS with or without BPH comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds (or compositions) as described herein in combination with one or more bladder-selective muscarinic receptor antagonists and one or more testosterone 5 alpha-reductase inhibitors.

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, sulfur, a phenylene, sulphinyl, sulphonyl group or $-NR_a-$, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl cycloalkyl or aryl. 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 (referred herein as "substituted alkyl") 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 (for R_6-R_9, alkyl is not substituted with aryl), heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_k, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q,, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_pR_q {wherein R_p and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, hydroxyamino, alkoxyamino or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, -NR_pR_q, -C(=O)NR_pR_q, -OC(=O) NR_pR_q, -NHC(=O)$NR_{fp}R_q$ (wherein R_p and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_a- {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, -C(=O)OR_p (wherein R_p is the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier), or -C(=O)NR_pR_q (wherein R_p and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, -NR_pR_q, -C (=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3, cyano, and $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "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. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_a-, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. 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 (referred to herein as "substituted alkenyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy,

cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -NHC(=O)R_p, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), 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_2R_{66} (wherein R_{66} are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, -CF_3, cyano, -NR_pR_q, -C(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier) and -SO_2R_{66} (where R_{66} is same 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. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-NR_a-$, where R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further (referred to herein as "substituted alkynyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, 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_p, -NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), cyano, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2

and R_{66} is same as defined earlier). Groups such as ethynyl, (-C ≡CH), propargyl (or propynyl, -CH_2C ≡CH), and the like exemplify this term.

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_pR_q, -NHC (=O) NR_pR_q, -NHC (=O) R_p, -C (=O) NR_pR_q, -O-C (=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), cyano or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier).

As used herein, the term "cycloalkenyl," unless otherwise specified, refers to unsaturated carbocyclic ring having three to seven carbon atoms. One or more hydrogen of said alkenyl or alkynyl can be replaced by halogen, hydroxy, cyano, or -$NR_{44}R_{55}$, wherein R_{44} and R_{55} are selected from hydrogen and alkyl. Examples of cycloalkenyl include, but are not limited to, cyclopropenyl and cyclobutenyl, and the like. Multiple cyclic structures are also included. Unless otherwise constrained by the definition, cycloalkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), cyano or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier).

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

The term "hydroxy," unless otherwise specified, refers to –OH.

The term "alkoxy," unless otherwise specified, refers to the group O-alkyl, wherein alkyl is the same as defined above.

The term "cycloalkoxy," unless otherwise specified, refers to –O-cycloalkyl, wherein cycloalkyl is the same as defined above.

The term "haloalkoxy," unless otherwise specified, refers to alkoxy wherein one or more hydrogen atom(s) of alkyl group are replaced by halogen atom(s).

The term "aryl," unless otherwise specified, herein 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, $COOR_s$ (wherein R_s is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), $NHC(=O)R_p$, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl and the like.

The terms "heterocycle" or "heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and

optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, -O-C(=O)R_p, -O-C(=O)OR_p, -C(=O)NR_pR_q, $S(O)_mR_{66}$, -O-C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -NR_pR_q (wherein m, R_{66}, R_p and R_q are as defined earlier) or guanidine. 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 azabicyclohexyl, azetidinyl, benzimidazolyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzoxazinyl, benzthiazinyl, benzothiazolyl, benzothieenyl, carbaxolyl, dihydrobenzofuryl, dihydroimidazolyl, dihydroindolyl,dihydropyranyl, dihydrofuranyl, dihydroisoxazolyl, dihydropyridinyl, dioxanyl, dioxolanyl, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, indolinyl, indolyl, isoindole 1,3-dione, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, napthyridinyl, oxazolidinyl, oxazolyl, phenoxazinyl, phenothiazinyl, piperazinyl, piperidinyl, pyrazinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyridinyl,pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrazolyl, thiazolidinyl, thiazolyl, and thienyl, and the like.

The term "(heterocycle)alkyl" or "(heterocyclyl)alkyl," unless otherwise specified," refers to heterocycle which is bonded to an alkylene chain. Examples of (heterocycle)alkyl include, but are not limited to, isothiazolidinyl ethyl, isothiazolyl propyl, pyrazinyl methyl, pyrazolinyl propyl and pyridyl butyl, and the like.

Aryl or heterocycle may optionally be substituted with one or more substituent(s) independently selected from halogen, hydroxy, nitro, mercapto, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, thioalkyl, cycloalkoxy, -NR_4R_5, -$CONR_4R_5$, -$COOR_5$, -$CONHR_5$, -$OCOR_5$, -COR_5, -$NHSO_2R_5$ and -SO_2NHR_5, wherein R_4 and R_5 are independently selected from hydrogen or alkyl.

The term "pharmaceutically acceptable salts" refers to derivatives of compounds that can be modified by forming their corresponding non-toxic inorganic or organic acid or

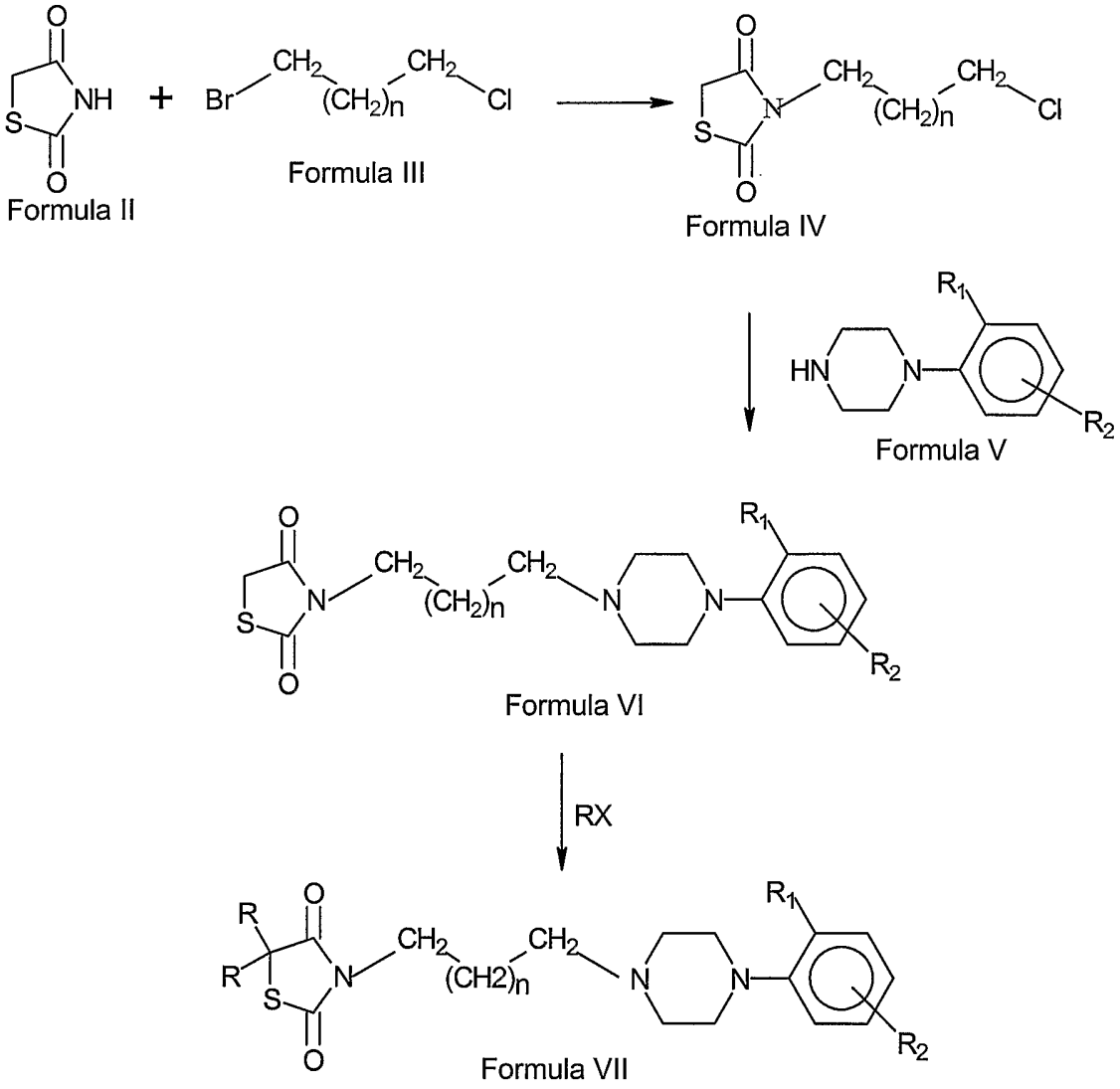
base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like. Examples of inorganic acids used to prepare inorganic acid salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitrous, nitric, carbonic, sulfuric, phosphoric acid, and the like. Examples of organic acids used to prepare organic acid salts include, but are not limited to aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic, methansulfonic, ethanesulfonic, benzenesulfonic, panthenic, toluenesulfonic and 2-hydroxyethanesulfonic acid, and the like.

The term "pharmaceutically acceptable solvates" refers to solvates with waters (*i.e.*, hydrates, hemihydrates or sesquihydrates) or pharmaceutically acceptable organic solvents. Such solvates are also encompassed within the scope of the present invention. Further, some crystalline forms of the compounds described may exist as polymorphs and as such are encompassed by the present invention.

It is to be understood that all optically active isomers and racemic mixtures of the compounds as described herein are encompassed within the scope of the present invention.

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

Scheme I



The compound of Formula VII can be prepared according to Scheme I. Thus, 2,4-thiazolidinone of Formula II can be alkylated with compounds of Formula III to form compounds of Formula IV (wherein n is the same as defined earlier). Compounds of Formula IV can be treated with compounds of Formula V to form compounds of Formula VI (wherein R_1 and R_2 are the same as defined earlier). Compounds of Formula VI can be treated with compounds of Formula RX (wherein X is halogen) to form compounds of Formula VII (wherein R is the same as defined earlier except R cannot be hydrogen).

The reaction of 2,4-thiazolidinones of Formula II with compounds of Formula III can be carried out in one or more solvents, for example, chloroform, acetone, methanol, ethanol, cyclohexane, n-butanol, acetonitrile, dichloromethane, dimethylsulfoxide,

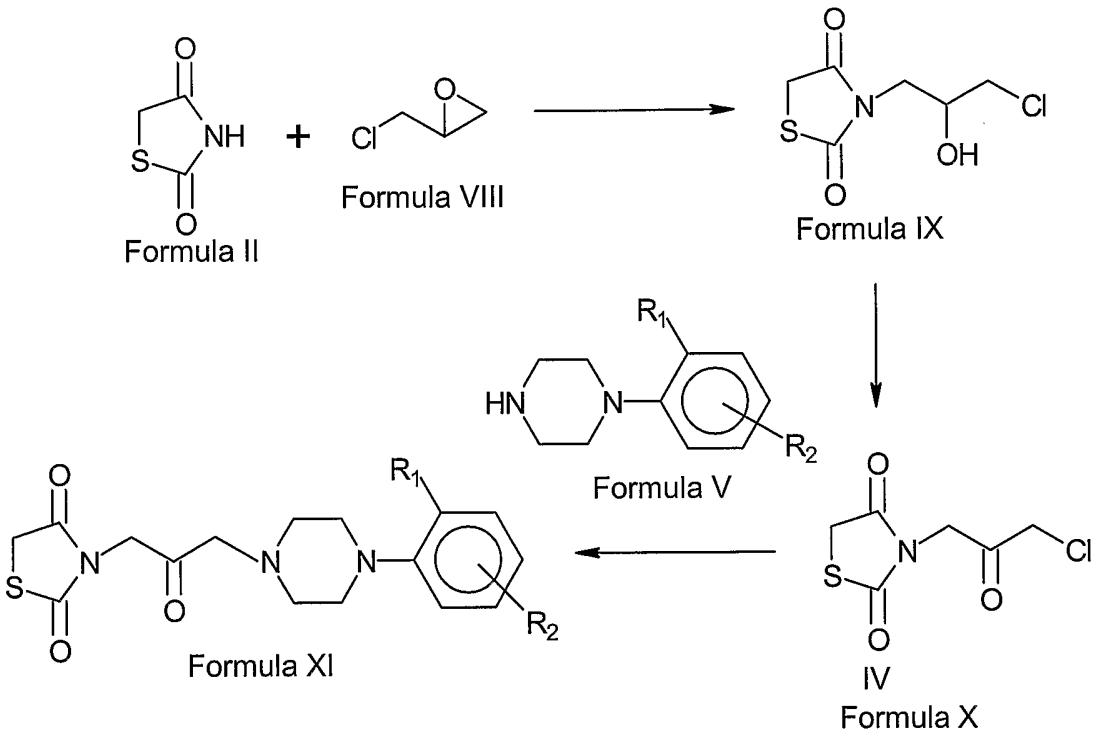
tetrahydrofuran, dimethylformamide, chlorobenzene, hexamethylphosphoramide or mixtures thereof. This reaction can also be carried out in the presence of one or more bases, for example, potassium carbonate, sodium carbonate, sodium bicarbonate, cesium carbonate, barium carbonate, calcium carbonate, sodium hydride, potassium t-butoxide, lithiumhexamethyl disilazane, lithium diisopropylamide or mixtures thereof.

The reaction of compounds Formula IV with compounds of Formula V can be carried out in one or more solvents, for example, methanol, ethanol, isopropanol, acetone, dimethylsulfoxide, tetrahydrofuran, acetonitrile, dimethylformamide or mixtures thereof. This reaction can also be carried out in the presence of one or more inorganic bases, for example, potassium carbonate, sodium carbonate, sodium bicarbonate, barium carbonate, calcium carbonate or mixtures thereof. This reaction can also be carried out in the presence of one or more phase transfer catalysts, for example, potassium iodide, tetra butylammonium bromide, butylammonium iodide or mixtures thereof.

The reaction of compounds of Formula VI with compounds of Formula RX can be carried out in one or more solvents, for example, diethylether, tetrahydrofuran, hexane, cyclohexane, dimethylformamide or mixtures thereof.

The reaction of a compound of Formula VI with a compound of Formula RX can be carried out in the presence of a base, for example, lithium diisopropylamide or n-butyl lithium.

Scheme II



Compounds of Formula XI can be prepared according to Scheme II. Thus, 2,4-thiazolidinone of Formula II can be contacted with epichlorohydrin of Formula VIII and heated to form 3-(3-chloro-2-hydroxy propyl)-thiazolidine-2,4-dione of Formula IX. The compound of Formula IX can be oxidized to form 3-(3-chloro-2-oxo-propyl)-thiazolidine-2,4-dione of Formula X. The compound of Formula X can be treated with compounds of Formula V to form compounds of Formula XI (wherein R_1 and R_2 are the same as defined earlier).

The reaction of 2,4-thiazolidinedione of Formula II with epichlorohydrin of Formula VIII can be carried out at temperatures ranging from 120-170 °C.

Oxidation of 3-(3-chloro-2-hydroxypropyl)-thiazoldine-2,4-dione of Formula IX can be carried out in one or more solvents, for example, dichloromethane, dimethylsulfoxide, tetrahydrofuran, acetonitrile, ethanol, n-butanol, chloroform or mixtures thereof. This reaction can also be carried out in the presence of one or more oxidizing agents, for example, pyridinium dichromate, pyridinium chlorochromate or mixtures thereof.

The reaction of 3-(3-chloro-2-oxo-propyl)-thiazoldine-2,4-dione of Formula X with compounds of Formula V can be carried out in one or more solvents, for example, methanol, ethanol, isopropanol, dimethylformamide or mixtures thereof. This reaction can also be carried out in the presence of one or more inorganic bases, for example, potassium carbonate, sodium hydride, sodium carbonate sodium bicarbonate, barium carbonate, calcium carbonate or mixtures thereof.

In the above schemes, where specific reagents, for example, solvents, bases, oxidizing agents, catalysts and other reagents, are described, it is to be understood that other reagents, *e.g.*, solvents, bases, oxidizing agents, catalysts and other reagents known to one of ordinary skill in the art, may be used. Similarly, reaction temperatures and durations may be adjusted according to the desired needs without undue experimentation and well within the abilities of one of ordinary skill in the art.

Specific compounds can include, for example:

5,5-Dibenzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 1) and its hydrochloride salt (Compound No. 2),

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 3) and its hydrochloride salt (Compound No. 4),

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

3-(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 7) and its hydrochloride salt (Compound No. 8),

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione (Compound No. 9) and its hydrochloride salt (Compound No. 10),

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 11) and its hydrochloride salt (Compound No. 12),

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione (Compound No. 13) and its hydrochloride salt (Compound No. 14),

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 15) and its hydrochloride salt (Compound No. 16),

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 17) and its hydrochloride salt (Compound No. 18),

3-{3-[4-(2-Methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione (Compound No. 19) and its hydrochloride salt (Compound No. 20),

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione (Compound No. 21) and its hydrochloride salt (Compound No. 22),

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione (Compound No. 23) and its hydrochloride salt (Compound No. 24),

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 25) and its hydrochloride salt (Compound No. 26),

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 27) and its hydrochloride salt (Compound No. 28),

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 29) and its hydrochloride salt (Compound No. 30),

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione (Compound No. 31) and its hydrochloride salt (Compound No. 32),

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione (Compound No. 33) and its hydrochloride salt (Compound No. 34),

3-{5-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione (Compound No. 35) and its hydrochloride salt (Compound No. 36),

3-{5-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione (Compound No. 37) and its hydrochloride salt (Compound No. 38),

3-{5-[4-(5-Fluoro-2-ethoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione (Compound No. 39) and its hydrochloride salt (Compound No. 40),

3-{5-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione (Compound No. 41) and its hydrochloride salt (Compound No. 42),

3-{5-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione (Compound No. 43) and its hydrochloride salt (Compound No. 44),

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, polymorphs or metabolites.

Compounds described are pharmacologically active and thus may be administered to an animal for treatment orally, parenterally, topically, rectally, internasally, subcutaneously or transdermally. Pharmaceutical compositions described comprise

therapeutically effective amounts of one or more compounds described formulated together with one or more pharmaceutically acceptable carriers.

The term "pharmaceutically acceptable carriers," as used herein, refers to non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Solid form preparations for oral administration include capsules, tablets, pills, powder, granules, cachets and suppository. For solid form preparations, active compounds can be mixed with one or more inert, pharmaceutically acceptable excipients or carriers (for example, sodium citrate, dicalcium phosphate or mixtures thereof) and/or one or more fillers or extenders (for example, starch, lactose, sucrose, glucose, mannitol, silicic acid or mixtures thereof); binders (for example, carboxymethylcellulose, alginates, gelatins, polyvinylpyrolidinone, sucrose, acacia or mixtures thereof); disintegrating agents (for example, agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates, sodium carbonate or mixtures thereof); absorption accelators (for example, quaternary ammonium compounds); wetting agents (for example, cetyl alcohol, glycerol, monostearate or mixtures thereof); adsorbents (for example, kaolin); lubricants (for example, talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulphate or mixture thereof) or mixtures thereof.

Capsules, tablets, or pills may also comprise buffering agents.

Tablets, capsules, pills, or granules can be prepared with one or more coatings or shells, for example, enteric coatings or other coatings known to one of ordinary skill in the art.

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

agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents or mixtures thereof.

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

Dosage forms for topical or transdermal administration include ointments, pastes, creams, lotions, gel, powders, solutions, spray, inhalants or patches. Active compounds can be admixed under sterile conditions with one or more pharmaceutically acceptable carriers, and optionally any preservative or buffer as may be required. Ophthalmic formulations, eardrops, eye ointments, powders and solutions are also encompassed within the scope of this invention.

Pharmaceutical preparations may be in unit dosage form. In unit dosage form, pharmaceutical preparations may be subdivided into unit doses containing appropriate quantities of active ingredients. Unit dosage forms can be packaged preparations containing discrete capsules, powders, in vials or ampoules, ointments, capsules, cachets, tablets, gel creams or any combination and number of such packaged forms.

Formulations described may be formulated to provide immediate, sustained, or delayed release of active ingredients after administration to patients by employing procedures well known to one of ordinary skill in the art.

Dosages of compounds described, bladder selective muscarinic receptor antagonists or 5 alpha-reductase inhibitors can be adjusted accordingly when formulated in any combination to achieve desired effects. As one of ordinary skill in the art will appreciate, dosages of compounds described, bladder selective muscarinic receptor antagonists or 5 alpha-reductase inhibitors may be independently optimized and combined to achieve synergistic results, such that the pathology is reduced more than it would be if each agent are used alone, *i.e.*, the cumulative effect are greater than when each agent are used alone. In accordance with the formulations and methods described, individual components in any combination can be administered concurrently in divided or single

combination forms or sequentially in any order and at different times during the course of therapy .

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

Example 1: Preparation of 3-(2-chloropropyl)-thiazolidine-2,4-dione

A solution of 2,4 thiazolidinedione (10 g, 0.085 mols) in dimethylformamide was added dropwise to a suspension of sodium hydride, 60 % (3.41 g, 0.085 mol) in dry dimethyl formamide to form a reaction mixture. The reaction mixture was heated for about 1 hour after which 1-bromo-3-chloropropane (20.16 g, 0.128 mol) was added. The reaction mixture was heated for an additional 4 about hours, quenched with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and solvent was removed by rotary evaporation to form a crude product. The crude product was purified by silica gel column using ethyl acetate:hexane mixture as eluent.

Yield: 12.0 g (72.7%)

Example 2: Preparation of 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl] propyl}-thiazolidine-2,4-dione

A mixture of 1-(3-chloropropyl) thiazolidine-2,4 dione (5.0 g, 0.026 mol), 2-methoxyphenylpiperazine monohydrochloride (5.90 g, 0.026 mol), anhydrous potassium carbonate (7.13 g, 0.052 mol) and potassium iodide (0.257 g, 0.0015 mol) in dry dimethyl formamide was heated for about 20 hours. After the reaction was completed, water was added and the reaction mixture was then extracted with ethyl acetate. Combined organic layers were dried over anhydrous sodium sulphate and concentrated under vacuum to form a thick crude residue. The crude residue was purified by column chromatography using silica gel (60-120 mesh) and dichloromethane:methanol mixture as eluent.

Yield: 20 g (22%) oil.

Example 3: Preparation of 5,5- Dibenzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1yl]-propyl}-thiazolidine-2,4-dione (Compound No. 1)

Dry tetrahydrofuran (10 mL) was added to a well-dried 3 neck round bottom flask under nitrogen atmosphere followed by adding lithium diisopropylamide (0.368 g, 0.0034 mL). The reaction mixture was cooled to -78 °C. A solution of 1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(2,4-dioxothiazolidine-1-yl]propane (1.0 g, 0.0028 mol) in tetrahydrofuran (5 mL) was then added dropwise under nitrogen atmosphere. The reaction mixture was stirred for about 1 hour and then allowed to come at room temperature. The reaction mixture was then cooled to -78 °C and benzyl iodide (0.4 g, 0.0028 mol) was added. The reaction mixture was stirred further for about 4 hours, quenched with water and extracted with ethyl acetate. The organic layer dried over anhydrous sodium sulphate and concentrated to yield a crude product. The crude product was purified on silica gel column using hexane:ethyl acetate mixture as eluent.

Example 4: Preparation of 5,5- Dibenzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 2)

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to 5,5-Dibenzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1yl]-propyl}-thiazolidine-2,4-dione. A solid precipitates and was then filtered to yield the title compound.

IR (KBr) cm^{-1}: 1739.0, 1672.3.

^1H NMR (300MHz, $CDCl_3$)δ: 1.81 (2H, brs), 2.65 (2H, brs), 3.13-3.17 (2H, m), 3.45-3.51 (10H, m), 4.07 (3H, s), 4.20 (2H, brs), 7.06-7.46 (14H, m), 13.8 (1H, brs).

Mass (m/z): 565.5 (M^++1).

The following compounds were prepared following the above procedure of Example 4:

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 4)

IR (KBr) cm^{-1}: 1743.2, 1670.8.

^{1}H NMR (300MHz, $CDCl_3$)δ: 2.17-2.24 (2H, m), 2.90-2.96 (4H, m), 3.16-3.23 (1H, m), 3.49-3.53 (7H, m), 3.69-3.73 (2H, m), 3.87 (3H, s), 4.55-4.59 (1H, m), 6.87-7.37 (9H, m), 13.6 (1H, brs).

Mass (m/z): 475.5 (M^++1).

3{3{4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl}-propyl)-thiazolidine-2,4-dione hydrochloride salt (Compound No. 6)

IR (KBr) cm^{-1}: 1745.2, 1673.7.

^{1}H NMR (300MHz, $CDCl_3$)δ: 2.33 (2H, m), 3.00-3.08 (4H, m), 3.50-3.57 (6H, m), 3.77-3.81 (2H, m), 4.04 (3H, s), 4.33-4.41 (2H, m), 6.83-7.06 (4H, m), 12.8 (1H, brs).

Mass (m/z): 453.5 (M^++1).

3-(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 8)

IR (KBr) cm^{-1}: 1745.8, 1679.5.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.67-1.94 (8H, m), 2.30-2.32 (2H, m), 3.03-3.05 (4H, m), 3.49-3.59 (6H, m), 3.76-3.80 (2H, m), 4.03 (2H, s), 4.80 (2H, s), 6.84-7.01 (4H, m), 12.8 (1H, brs).

Mass (m/z): 404.0 (M^++1).

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 10)

IR (KBr) cm^{-1}: 1749.7, 1686.9.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.34-1.36 (6H, d), 1.70-1.77 (2H, m), 1.95-2.00 (2H, m), 3.01-3.03 (4H, m), 3.35-3.39 (2H, m), 3.47-3.69 (6H, m), 4.02 (2H, s), 4.49-4.53 (1H, m), 6.53-6.59 (3H, m), 6.81-6.86 (1H, m), 12.90 (1H, brs).

Mass (m/z): 410.3 (M^++1).

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 12)

IR (KBr) cm^{-1}: 1748.1, 1679.5.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.41-1.43 (6H, d), 2.31 (2H, brs), 3.10 (2H, brs), 3.33-3.78 (12H, m), 4.03 (2H, s), 4.56-4.60 (1H, m), 6.58-6.65 (2H, m), 7.19 (1H, m),12.90 (1H, brs).

Mass (m/z): 396.3 (M^++1).

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 14)

IR (KBr) cm^{-1}: 1749.2, 1682.2.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.75 (2H, m), 2.01 (2H, m), 3.06 (4H, m), 3.47-3.70 (8H, m), 4.05 (2H, s), 4.35-4.44 (2H, m), 6.84-7.08 (4H, m), 12.90 (1H, brs).

Mass (m/z): 432.3 (M^++1).

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 16)

IR (KBr) cm^{-1}: 1748.9, 1677.1.

^{1}H NMR (300MHz, DMSO-d_6)δ: 2.00 (2H, m), 2.98-3.60 (8H, m), 3.81 (3H, s), 4.18 (2H, s), 6.66-6.71 (1H, m), 6.86-6.95 (2H, m), 10.56 (1H, brs).

Mass (m/z): 368.2 (M^++1).

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 18)

IR (KBr) cm^{-1}: 1746.6, 1678.4.

^{1}H NMR (300MHz, $CDCl_3$)δ: 2.32 (2H, m), 3.09 (4H, m), 3.47-3.64 (8H, m), 3.76-3.80 (2H, m), 3.83 (3H, s), 4.04 (2H, s), 6.65-6.81 (3H, m), 10.50 (1H, brs).

Mass (m/z): 368.3 (M^++1).

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 26)

IR (KBr) cm^{-1}: 1676.8.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.28-1.30 (6H, d), 2.34 (2H, m), 2.96-3.09 (4H, m), 3.61 (6H, m), 3.79 (2H, m), 4.04 (2H, m), 4.49 (1H, m), 6.69-6.71 (1H, m), 6.80-6.86 (1H, m), 6.94-6.97 (1H, m), 13.0 (1H, brs).

Mass (m/z): 396.4 (M^++1).

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 28)

IR (KBr) cm^{-1}: 1741.8, 1678.5.

^{1}H NMR (300MHz, $CDCl_3$)δ: 1.69-1.90 (8H, m), 2.26 (2H, m), 3.01 (4H, m), 3.32-3.45 (6H, m), 3.75-3.79 (2H, m), 4.02 (2H, s), 6.61-6.78 (3H, m), 13.7 (1H, brs).

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 30)

IR (KBr): 1678.8 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: 2.332 (2H, s), 3.11-3.23 (4H, d), 3.55-3.59 (4H, d), 3.79 (4H, s), 3.97-4.03 (5H, d), 6.87-6.99 (3H, m)

Mass (m/z): 368 (M^++1)

3-{5-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 36)

IR (DCM): 1677 cm^{-1}, 1746 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: 1.41-1.43 (m, 3H), 1.52-1.58 (m, 3H), 1.68-1.69 (m, 2H), 1.80-1.82 (m, 2H), 1.98-2.00 (m, 2H), 2.85 (m, 2H), 3.00 (m, 2H), 3.64-3.66 (m, 6H), 3.75 (m, 4H), 3.99 (m, 1H), 6.64-6.69 (m, 1H), 6.80-6.89 (m, 2H)

Mass (m/z): 424 (M+1)

3-{5-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 38)

IR (DCM): 1675 cm^{-1}, 1744 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: 1.41-1.45 (m, 2H), 1.70 (m, 2H), 2.01 (m, 2H), 3.04 (m, 2H), 3.46-3.56 (m, 4H), 3.66 (m, 4H), 4.00 (s, 3H), 4.10 (m, 4H), 6.87-6.88 (m, 2H), 7.13 (m, 1H)

Mass (m/z): 396 (M+1)

3-{5-[4-(5-Fluoro-2-ethoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 40)

IR (DCM): 1677 cm^{-1}, 1747 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: .41 (m, 2H), 1.59-1.60 (m, 2H), 1.91-1.92 (m, 2H), 3.11-3.15 (m, 4H), 3.63-3.75 (m, 6H), 4.00 (s, 2H), 4.36-4.40 (m, 4H), 6.76-6.86 (m, 3H)

Mass (m/z): 464 (M+1)

3-{5-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 42)

IR (DCM): 1673 cm^{-1}, 1741 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: 1.41-1.43 (m, 2H), 1.68-1.69 (m, 2H), 1.93-2.03 (m, 8H), 2.1-2.11 (m, 2H), 3.10 (m, 2H), 3.61-3.68 (m, 6H), 4.01 (m, 2H), 4.31 (m, 2H), 4.67 (m, 2H), 4.92 (m, 1H), 6.98-7.06 (m, 3H), 7.35-7.39 (m, 1H).

Mass (m/z): 432 (M+1)

3-{5-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 44)

IR (DCM): 1676 cm^{-1}, 1746 cm^{-1}

H^1 NMR (300 MHz, $CDCl_3$)δ: 1.27-1.30 (m, 3H), 1.41-1.44 (m, 2H), 1.70 (m, 2H), 1.99-2.02 (m, 4H), 3.11-3.13 (m, 2H), 3.62-3.71 (m, 8H), 4.02 (m, 2H), 4.09-4.13 (m, 2H), 4.39 (m, 2H), 6.95-7.05 (m, 3H)

Mass (m/z): 424 (M+1)

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 32)

IR (DCM): 1705.6 cm^{-1}

^{1}H NMR ($CDCl_3$):δ 1.21-1.34 (m, 6H), 2.23 (s, 2H), 2.96-2.98 (d, 2H), 3.45-3.49 (m, 8H), 3.75-3.80 (t, 2H), 3.99-4.02 (d, 2H), 4.48-4.52 (m, 1H), 6.61-6.80 (m, 3H).

Mass: 396 (M+1)

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 34)

IR (DCM): 1695.8 cm^{-1}

^{1}H NMR ($CDCl_3$):δ 1.221-1.326 (m, 6H), 1.72-1.97 (m, 2H), 1.94-2.01 (m, 2H), 2.99 (brs, 4H), 3.39-3.48 (m, 4H), 3.67-3.71 (t, 2H), 4.04 (s, 2H), 4.48-4.50 (m, 2H), 4.52-4.71 (m, 1H), 6.62-6.81 (m, 3H)

Mass: 410 (M+1)

Example 5: Preparation of 3-(3-chloro –2-oxo-propyl)-thiazolidin-2,4-dione

A mixture of 2,4-thiazolidinedione (8.0 g, 0.068 mol) and epichlorohydrin (6.32 g, 0.068) was heated for about 6 hours. After completion of the reaction, a gummy crude product was formed, which was then purified on a silica gel column using dichloromethane:methanol mixture as eluent. The compound (4.0 g, 0.019 mol) thus obtained was dissolved in dichloromethane (140 mL), pyridinium chlorochromate (8.23 g, 0.038 mol) was added, and the resulting reaction mixture was refluxed for about 10 hours. After completion of the reaction, the reaction mixture was filtered through a celite pad and washed with dichlromethane. A filtrate thus obtained was concentrated under vacuum and purified on silica gel column using dichloromethane and methanol mixture as eluent to yield the title compound.

Yield: 2.0 g (50%), oil

Example 6: Preparation of 3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-oxo-propyl}thiazolidine-2,4-dione (Compound No. 19)

A mixture of 3-(3-chloro-2-oxo-propyl) thiazolidin-2,4-dione (0.5 g, 0.0024 mol), 2-methoxyphenyl piperazine-monohydrochloride (0.55 g, 0.0024 mol) and anhydrous potassium carbonate (0.665 g, 0.0048 mol) in dry dimethylformamide was heated for about 6 hours. The reaction mixture was quenched with water and extracted with ethyl

acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to yield a crude product. The crude product was purified on silica gel column using dichloromethane and methanol mixture as eluent.

Example 7: Preparation of 3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-oxo-propyl}thiazolidine-2,4-dione hydrochloride salt (Compound No. 20)

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to 3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-oxo-propyl}thiazolidine-2,4-dione. After completion of the reaction, a solid precipitated and was filtered to yield the title compound.

IR (KBr) cm^{-1}: 1743.4, 1685.6.

^1H NMR (300MHz, $CDCl_3$)δ: 3.37-3.51 (10H, m), 3.88 (3H, s), 4.07 (2H, s), 4.69 (2H, s), 4.69 (2H, s), 6.89-7.10 (3H, m), 10.8 (1H, s).

Mass (m/z): 364.2 (M^++1).

The following compounds were prepared following the above procedure:

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 22)

IR (KBr) cm^{-1}: 1747.4, 1690.3.

^1H NMR (300MHz, DMSO-d_6)δ: 3.07-3.40 (8H, m), 3.81 (3H, s), 4.35 (2H, s), 4.64 (4H, s), 6.66-6.72 (1H, m), 6.86-6.96 (2H, m), 10.70 (1H, brs).

Mass (m/z): 382.3 (M^++1).

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt (Compound No. 24)

IR (KBr) cm^{-1}: 1744.3, 1690.9.

^1H NMR (300MHz, $CDCl_3$)δ: 3.38 (8H, m), 3.78 (3H, s), 4.35 (2H, s), 4.64 (2H, s), 6.76-6.79 (2H, m), 6.94-6.97 (1H, m), 10.70 (1H, brs).

Mass (m/z): 382.1 (M^++1).

Example 8 Pharmacological testing

Receptor Binding Assay

Receptor binding assays were performed using native α-1 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 rat submaxillary and liver respectively (Michel *et al., Br. J. Pharmacol.,* **98**:883-889 (1989)). The binding assays were performed according to U'Prichard *et al., Eur. J. Pharmacol.,* **50**:87-89 (1978) with minor modifications.

Submaxillary glands were isolated immediately after sacrifice. The liver was perfused with buffer (Tris HCl 50 mM, NaCl 100 mM, 10 mM EDTA pH 7.4). The tissues were homogenized in 10 volumes of buffer (Tris HCl 50 mM, NaCl 100 mM, EDTA 10 mM, pH 7.4). The homogenate was filtered through two layers of wet gauze and the filtrate was centrifuged at 500g for 10 min. The supernatant was subsequently centrifuged at 40,000g for 45 minutes. The pellet thus obtained was resuspended in an equivolume of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) and were stored at – 70 °C until the time of assay.

The membrane homogenates (150-250 μg protein) were incubated in 250 μL of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) at 24-25 °C for 1 hour. Non-specific binding was determined in the presence of 300 nM prazosin. The incubation was terminated by vaccum filtration over GF/B fiber filters. The filters were then washed with ice cold 50 mM Tris HCl buffer (pH 7.4). The filtermats 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 G pad prism software. The value of inhibition constant K_i was calculated from competitive binding studies by using the Cheng and Prusoff equation (Cheng and Prusoff, *Biochem. Pharmacol.*, **22**:3099-3108 (1973))

$$K_i = IC_{50} /(1+L/K_d)$$

where L is the concentration of [^{3}H] prazosin used in the particular experiment.

The K_i values for compounds described range as follows:

a) α_{1a} K_i (nM) for compounds described were between about 0.1 nM to about 1000 nM, for example between about 0.1 nM to about 100 nM, or for example between about 1.0 nM to about 28 nM.

b) α_{1b} K_i (nM) for compounds described were between about 1.9 nM to about 900 nM, for example between about 1.9 nM to about 631 nM, or for example about 1.9 nM to about 100 nM.

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.[1] 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 °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 K_d values were estimated by using the non-linear curve-fitting program using Graph pad prism software. The value of inhibition constant K_i was calculated from competitive binding studies by using Cheng and Prusoff equation (Cheng and Prusoff, *Biochem. Pharmacol.*, **22**:3099-3108 (1973)),

$$K_i = IC_{50} /(1+L/K_d)$$

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).

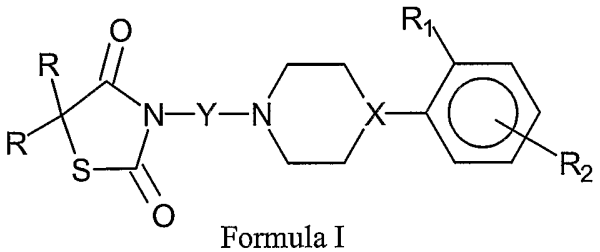
The results of the human recombinant assays of the compounds described are as follows:

a) The compounds described exhibited α_{1a} K_i (nM) values of between about 0.4 nM to about 7.8 nM, for example between about 0.4 nM to about 4 nM, and for example between about 0.4 nM to about 3.2 nM;

b) The compounds described exhibited α_{1b} K_i (nM) values of between about 0.8 nM to about 52 nM, for example, between about 0.8 nM to about 47 nM, and for example between about 0.8 nM to about 43 nM.

We Claim:

1. Compounds having the structure of Formula I,



Formula I

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

R is hydrogen, alkyl or aralkyl;

Y is $-CH_2-Z-CH_2$, wherein Z is $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, and wherein n is an integer of from 0 to 3, and R_3 is hydrogen, alkyl, aryl or aralkyl;

X is CH or nitrogen;

R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

with the proviso that when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and the proviso that when each R is hydrogen or when one R is hydrogen and the other R is alkyl, Z is a bond, $-CH_2-$ or $-CH_2CH_2-$, and R_1 is H, then R_2 cannot be 3-chloro or 3-alkyl.

2. The compound of claim 1, wherein:

R is hydrogen or aralkyl;

Z is $-CH_2-$ or -CO-;

R_1 is alkoxy, cycloalkoxy or haloalkoxy;

R_2 is halogen; and

X is nitrogen.

3. A compound selected from:

5,5-Dibenzyl-3-{3[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3{3{4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl}-propyl)-thiazolidine-2,4-dione,

3(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(2-Methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione,

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-ethoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione,

3-{5-[4-(5-Fluoro-2-propoxyphenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione or

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates

enantiomers, diastereomers, N-oxides, polymorphs or metabolites thereof.

4. A compound selected from:

5,5-Dibenzyl-3-{3[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

5-Benzyl-3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3{4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl}-propyl)-thiazolidine-2,4-dione hydrochloride salt,

3-(3-[4-(2-Cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-[2-(2,2,2-Trifluoroethoxy)-phenyl]-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(2-Methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(4-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-2-oxo-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(3-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-cyclopentyloxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(3-Fluoro-2-methoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{3-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-propyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{4-[4-(5-Fluoro-2-isopropoxyphenyl)-piperazin-1-yl]-butyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-methoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

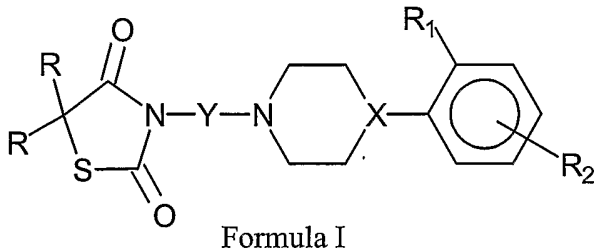
3-{5-[4-(5-Fluoro-2-isopropoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(2-Cyclopentyloxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt,

3-{5-[4-(5-Fluoro-2-propoxy-phenyl)-piperazin-1-yl]-pentyl}-thiazolidine-2,4-dione hydrochloride salt.

5. A pharmaceutical composition comprising therapeutically effective amounts of one or more compounds of claim 1 optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.

6. A method for treating a patient suffering from a disease or disorder mediated through alpha 1a or alpha 1d adrenergic receptors comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds having the structure of Formula I,



Formula I

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

R is hydrogen, alkyl or aralkyl;

Y is $-CH_2-Z-CH_2$, wherein Z is $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, and wherein n is an integer of from 0 to 3, and R_3 is hydrogen, alkyl, aryl or aralkyl;

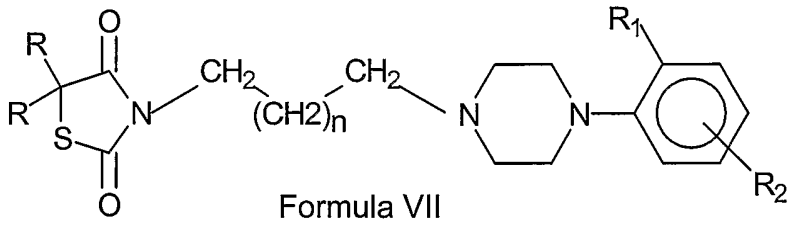
X is CH or nitrogen;

R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

with the proviso that when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and the proviso that when each R is hydrogen or when one R is hydrogen and the other R is alkyl, Z is a bond, $-CH_2-$ or $-CH_2CH_2-$, and R_1 is H, then R_2 cannot be 3-chloro or 3-alkyl.

7. The method of claim 6, wherein the disease or disorder is benign prostatic hyperplasia (BPH) or lower urinary tract symptoms (LUTS).

8. A process of preparing compounds of Formula VII:



Formula VII

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides, polymorphs or metabolites thereof, wherein

R is hydrogen, alkyl or aralkyl;

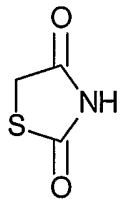
Y is $-CH_2-Z-CH_2$, wherein Z is $-(CH_2)_n-$, $-CHOR_3$, $-NR_3$, -CO- or -CS-, and wherein n is an integer of from 0 to 3, and R_3 is hydrogen, alkyl, aryl or aralkyl;

X is CH or nitrogen;

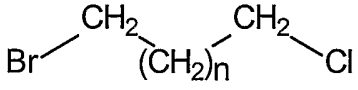
R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl;

the method comprising the steps of:

(a) reacting 2,4-thiazolidinone of Formula II with a compound of Formula III

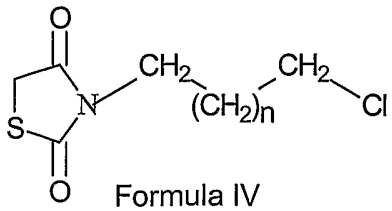


Formula I



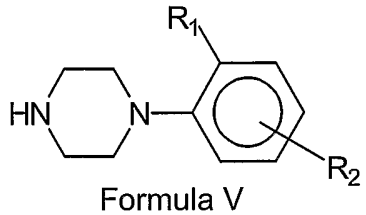
Formula III

to form a compound of Formula IV,



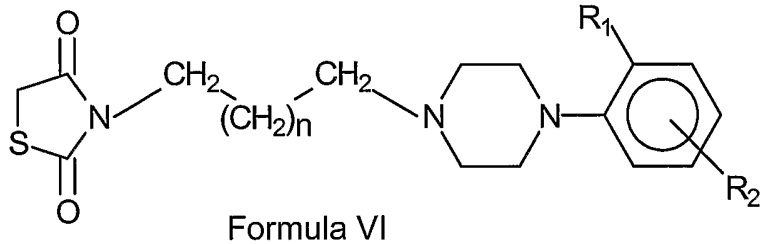
Formula IV

(b) treating the compound of Formula IV with a compound of Formula V



Formula V

to form a compound of Formula VI, wherein R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl; and

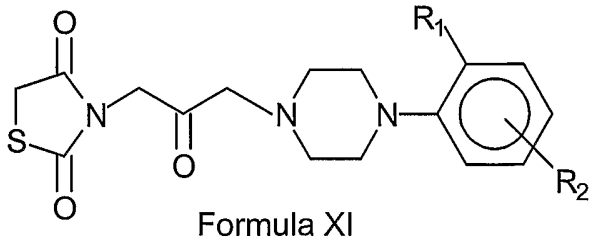


Formula VI

(c) treating the compound of Formula VI with a compound of Formula RX (wherein X is halogen) to form a compound of Formula VII, wherein R is alkyl or aralkyl.

10. The process of claim 9, wherein when each R is hydrogen or lower alkyl, R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and when each R is hydrogen and Z is a bond, then R_2 cannot be 3-chloro.

11. A process of preparing a compound having the structure of Formula XI,



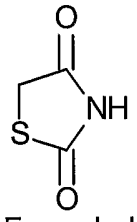
Formula XI

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

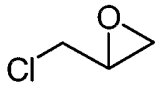
R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl,

which method comprises:

(a) reacting 2,4-thiazolidinedione of Formula II with epichlorohydrin of Formula VIII

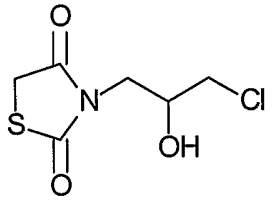


Formula II



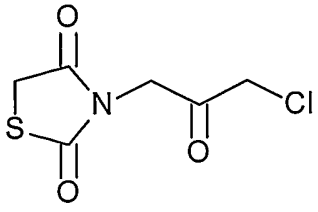
Formula VIII

to form 3-(3-chloro-2-hydroxy propyl)-thiazolidine-2,4-dione of Formula IX



Formula IX

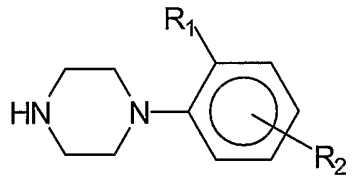
(b) oxidizing the compound of Formula IX to form 3-(3-chloro-2-oxo-propyl)-thiazolidine-2,4-dione of Formula X, and



IV

Formula X

(c) treating the compound of Formula X with a compound of Formula V



Formula V

to form a compound of Formula XI, wherein R_1 and R_2 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, haloalkoxy, halogen, aryl, aralkyl, heterocycle or (heterocycle)alkyl.

12. The process of claim 11, wherein when R_1 is alkoxy and Z is CH_2, then R_2 cannot be hydrogen; and when Z is a bond, then R_2 cannot be 3-chloro.