Title: ADRENERGIC RECEPTOR ANTAGONISTS

Abstract: The present invention relates to \( \alpha_1 \) and/or \( \alpha_2 \) adrenergic receptor antagonists, which can be used to treat a disease or disorder mediated through \( \alpha_1 \) and/or \( \alpha_2 \) adrenergic receptors. Compounds and pharmaceutical compositions disclosed herein can be used to treat benign prostatic hyperplasia (BPH) and related symptoms thereof. Further, such compounds can be used to treat lower urinary tract symptoms that may or may not be associated with BPH. The present invention also relates to processes to prepare the disclosed compounds, pharmaceutical compositions thereof, and methods of treating BPH or related symptoms thereof.
ADRENERGIC RECEPTOR ANTAGONISTS

Field of the Invention

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

Background of the Invention

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

The symptoms of BPH are a result of two pathological components affecting the prostate gland: a static component and a dynamic component. The static component is related to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of the urine from the bladder. The dynamic component is related to increased smooth muscle tone of the bladder neck and prostate itself and is regulated by $\alpha$-1 adrenergic receptor.

Currently, the most effective treatment for BPH is a surgical procedure known as transurethral resection of the prostate (TURP), which involves removing obstructing tissue (C. Chapple, Br. Med. Journal, 304:1198-1199 (1992)). TURP is directed both to the static and dynamic components of the BPH. However, TURP is associated with mortality (1%), adverse events, e.g., incontinence (2-4%), infection (5-10%), and impotence (5-10%). Therefore, noninvasive alternative treatments are highly desirable.
Some drug therapies address the static component of BPH. Administration of finasteride is one such therapy, which is indicated for the treatment of symptomatic BPH. This drug is a competitive inhibitor of the enzyme 5-α 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 5-α reductase, reduce the size of the prostate and improve urine flow through the prostatic urethra. Although finasteride is a potent 5-α reductase inhibitor that causes a marked decrease in serum and tissue concentrations of dihydrotestosterone, it is moderately effective in the treatment of symptomatic BPH. The effects of finasteride take 6-12 months to become evident and for many men the clinical development is minimal.

The dynamic component of BPH has been addressed by the use of adrenergic receptor blocking agents, which act by decreasing the smooth muscle tone within the prostate gland. A variety of α₁a AR antagonists, for example, terazosin, doxazosin, prazosin, alfuzosin and tamulosin, have been investigated for the treatment of symptomatic bladder outlet obstruction due to BPH. However, these drugs are associated with vascular side effects (e.g., postural hypertension, syncope, dizziness, headache etc.) due to lack of selectivity of action between prostatic and vascular α₁ adrenoceptors. There are several lines of evidence suggesting that selectivity for α₁a adrenoceptor over α₁b adrenoceptor will result in relative lack of vascular side effects, thus lead to better tolerability. Mice deficient in α₁b adrenoceptors show diminished blood pressure response to phenylephrine injection when compared to homozygous controls (decreased blood pressure response in mice deficient of α₁b adrenergic receptor. (Proc. Nat’l Acad. Sci. USA, 94:1589-11594 (1997)). In-vivo studies in healthy subjects comparison of α₁a/α₁d selective antagonists (e.g., tamsulosin) or α₁a selective antagonists (e.g., urapidil) with non selective antagonists (e.g., doxazosin, prazosin, or terazosin) under a variety of experimental conditions (e.g., involving the administration of exogenous agonist or release of endogenous agonist by cold stimulation) in several vascular beds including the skin circulation in finger tips, the dorsal hand vein, or with total peripheral resistance have been reported. (Eur. J. Clin. Pharmacol., 49:371-375 (1996); N. Schmiedeberg, Arch. Pharmacol., 354:557-561 (1996); Jpn. J. Pharmacol., 80:209-215 (1999); Br. J. Clin. Pharmacol., 47:67-74 (1999)). These studies reported that an antagonist with high affinity
for \( \alpha_{1A} \) or \( \alpha_{1D}/\alpha_{1D} \) receptors can cause some degree of vasodilation, although it is much lower than with non-subtype-selective \( \alpha_{1A} \) adrenoceptor antagonists. Further, there is increased vascular \( \alpha_{1B} \) adrenoceptor expression in elderly patients and thus \( \alpha_{1A}/\alpha_{1D} \)-selective agents with selectivity over \( \alpha_{1B} \) adrenoceptor subtype would be of particular importance in benign prostatic hyperplasia. Antagonism of both \( \alpha_{1A} \) adrenoceptor and \( \alpha_{1D} \) adrenoceptor is important to relieve lower urinary tract symptoms especially associated with BPH. Targeting \( \alpha_{1A} \) adrenoceptors with antagonists is important in relaxing prostate smooth muscle and relieving bladder outlet obstruction, whereas \( \alpha_{1D} \) adrenoceptor antagonism is important to target irritative symptoms.

Over the past decade, there has been an intensive search for selective \( \alpha_{1A} \) adrenoceptor antagonists for benign prostatic hyperplasia, which would avoid the cardiovascular side effects, associated with currently used drugs. Many selective antagonists have been described in the literature.

The synthesis of [Phenyl-4-piperazin-1]-3 alcoyl-3-3H-benzo- and thieno-triazine-1,2,3 ones-for their application in therapeutic fields are described in US patent No. 4,552,878, FR 2,551,753 and Eur J Med Chem, 22(4): 337-345 (1987) disclose benzotriazine-1,2,3-ones-4 that are said to have antidepressant activity. United States Patent No. 6,166,009 and PCT Publication No. WO 96/31498 discloses N-substituted azaheterocyclic carboxylic acids and esters thereof and their use for hyperalgesic and/or inflammatory conditions. United States Patent Application No. US 2003/0032801 and PCT Publication No. WO 02/089810 discloses chemosensitizing agents for treating multiple resistant strains of Plasmodium falciparum. Other reports describing selective \( \alpha_{1A} \) adrenoceptor antagonists are GB 1,280,941, WO 93/16073, US 5,185, 335, WO 01/49670, US 2003/0159706, WO 99/31058, WO 98/15548, WO 98/15546, WO 00/32193 all these patents are incorporated by reference herein in their entirety. Compounds described in US patent Nos. 6,083,950, 6,090,809, 6,410,735, 6,420,559, 6,420,366, US patent appl. 2002/0156085, WO 00/05206 and WO 02/44151 have been shown to have good a1-adrenergic blocking activity and selectivity.
Summary of the Invention

Provided are compounds having a structure of the Formula I

\[ \text{R}_1 \text{A} \text{X}_1 \text{R}_2 \text{R}_3 \]

\[ \text{Formula I} \]

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

\( \text{X}_1 \) can be N or CR\(_4\);

\( \text{R}_4 \) can be hydrogen, hydroxyl or alkyl;

\( \text{A} \) can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR\(_{10}\) or CHR\(_{10}\)R\(_{11}\);

\( \text{R}_{10} \) and \( \text{R}_{11} \) can independently be alkyl, COO-alkyl, aryl or heterocyclyl;

\( \text{R}_1, \text{R}_2 \) and \( \text{R}_3 \) independently in each occurrence can be hydrogen, halogen, C\(_{1-3}\) alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, \( \text{R}_6 \) or S(O)\(_2\)R\(_5\);

\( \text{R}_5 \) can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

\( \text{R}_2 \) and \( \text{R}_3 \) together with \( \text{X}_1 \) to which they are attached can form a ring of the form

\[ \xymatrix{ \text{X}_1 \\ \text{M}_1 \\
\text{W} \\
\text{M}_2 \\
\text{R}_6 } \]

which contains one or more additional heteroatom(s) selected from O, S or N;

\( \text{M}_1 \) and \( \text{M}_2 \) can independently be hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or \( \text{M}_1 \) and \( \text{M}_2 \) together can form a bridging group (C\(_{0-3}\));

\( \text{W} \) can be N, CH or COH;

\( \text{R}_6 \) can be
Y can be O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)₂R₅ or NH₂SO₃R₅;

L can be a linker; and

• can be a point of attachment.

Also provided are compounds selected from:

3-{3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one,

Methyl [4-{3-(4-oxy-1,2,3-benzotriazin-3(4H)-yl)propyl] piperazin-1-yl] (phenyl)acetate,

3-{3-[4-[2-(cyclopentloxy) phenyl]piperazin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one,

3-{3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one,

3-{3-[4-(2-cyclopentloxy)-5-fluorophenyl]piperazin-1-yl]-2-methylpropyl]-1,2,3-benzotriazin-4(3H)-one,

3-{3-[4-(2-ethoxyphenyl) piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one,

3-{2-methyl-3-[4-(2-proxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

3-{3-[4-[2-(cyclopentloxy) phenyl]piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one,

3-{3-[4-(2-isopropoxyphenyl) piperazin-1-yl]-2-methylpropyl]-1,2,3-benzotriazin-4(3H)-one,

3-[3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl]-1,2,3-benzotriazin-4(3H)-one,

3-[5-{4-(2-methoxyphenyl) piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-ethoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-propoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-isopropoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(cyclopentyl)-5-fluorophenyl]piperazin-1-yl} pentyl)-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[3-(2-methoxyphenyl) imidazolidin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-[5-(6,7-dimethoxy-3,4-dihydro isoquinolin-2(1H)-yl)pentyl]-1,2,3-benzotriazin-4(3H)-one,
3-(3-{4-[2-(cyclopentyl)-5-fluorophenyl]piperazin-1-yl] propyl)-1,2,3-benzotriazin-4(3H)-one,
3-(3-{4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-[5-(3,4-dihydroisoquinolin-2(1H)-yl)pentyl]-1,2,3-benzotriazin-4(3H)-one,
3-{3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]acetamide,
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]benzamide,
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl] tetrahydrofuran-2-carboxamide,

3-[3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one,

3-(3-[4-[2-(cyclopentyloxy) phenyl]piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one,

3-(2-hydroxy-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

3-(2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

3-(2-hydroxy-3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

3-(2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-fluoro-6-isopropoxy phenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-(cyclopentyloxy)-6-fluoro phenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

10-[3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl]-10H-phenoxazine,

10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

8-(2-methoxyphenyl)-3-[3-(10H-phenothiazin-10-yl)propyl]-3-azabicyclo [3.2.1]octan-8-ol,

10-[3-[4-(2-(cyclopentyloxy)phenyl)piperazin-1-yl]propyl]-10H-phenothiazine,
\[ N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H\text{-}phenothenazinet-10-carboxamide, \]
\[ 10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ 10-[3-[4-[2-(cyclopentoxy)-5-fluoro phenyl]piperazin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ 10-[3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H\text{-}phenothenazinet-10-carboxamide, \]
\[ N-[2-(2-methoxyphenoxyl)ethyl]-10H\text{-}phenothenazinet-10-carboxamide, \]
\[ 10-[3-[4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ 10-[3-[3-(2-ethoxyphenyl)imidazolidin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ 10-[3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]propyl]-10H\text{-}phenothenazine, \]
\[ 1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H\text{-}phenothenazinet-10-yl)propan-2-ol, \]

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

Also provided are compounds selected from:

\[ 3-[3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl]-1,2,3-benzotriaizin-4(3H)-one hydrochloride salt, \]
\[ Methyl \ [4-[3-(3-oxo-1,2,3-benzotriaizin-3(4H)-yl)propyl] piperazin-1-yl](phenyl)acetate hydrochloride salt, \]
\[ 3-(3-[4-[2-(cyclopentoxy) phenyl]piperazin-1-yl]propyl)-1,2,3-benzotriaizin-4(3H)-one hydrochloride salt, \]
\[ 3-[3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriaizin-4(3H)-one hydrochloride salt, \]
\[ 3-(3-[4-[2-(cyclopentoxy)-5-fluorophenyl]piperazin-1-yl]-2-methylpropyl)-1,2,3-benzotriaizin-4(3H)-one hydrochloride salt, \]
\[ 3-[3-[4-(2-ethoxyphenyl) piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriaizin-4(3H)-one hydrochloride salt, \]
3-[(2-methyl-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,
5  3-[3-[4-[2-(cyclopentyoxy) phenyl]piperazin-1-yl]-2-methyl propyl]-1,2,3-
6  benzotriazin-4(3H)-one hydrochloride salt,
10  3-[3-[4-(2-isopropoxyphenyl) piperazin-1-yl]-2-methylpropyl]-1,2,3-
11  benzotriazin-4(3H)-one hydrochloride salt,
15  3-[3-[3,4-dihydroisoquinolin-2(1H)-yl]propyl]-1,2,3-benzotriazin-4(3H)-one
16  hydrochloride salt,
20  3-[5-[4-(2-methoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one
21  hydrochloride salt,
25  3-[5-[4-(2-ethoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one
26  hydrochloride salt,
30  3-[5-[4-(2-propoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one
31  hydrochloride salt,
35  3-[5-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-
36  4(3H)-one hydrochloride salt,
40  3-[5-[4-[2-(cyclopentyoxy)-5-fluorophenyl]piperazin-1-yl]pentyl]-1,2,3-
41  benzotriazin-4(3H)-one hydrochloride salt,
45  3-[5-[4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-
46  4(3H)-one hydrochloride salt,
3-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[5-(3,4-dihydroisoquinolin-2(1H)-yl)penty1]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]acetamide hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]benzamide hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]tetrahydrofuran-2-carboxamide hydrochloride salt,

3-[3-[4-(5-fluoro-2-isoproxy phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-(3-[4-2-(cyclopentoxy) phenyl]piperazin-1-yl)-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-isoproxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-isoproxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
10- [3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
5  10- [3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
10- [3-[4-(2-fluoro-6-isopropoxy phenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
10- [3-[4-[2-(cyclopentloxy)-6-fluoro phenyl]piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
15  10- [3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
20  10- [3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
20- [3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
25  10- [3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
30  8-(2-methoxyphenyl)-3-[3-[10H-phenothiazin-10-yl]propyl]-3-azabicyclo[3.2.1]octan-8-ol hydrochloride salt,
30- [3-[4-[2-(cyclopentloxy)phenyl] piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
35  N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide hydrochloride salt,
40  10- [3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
40- [3-[4-[2-(cyclopentloxy)-5-fluoro phenyl]piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
45  10- [3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,
45- [3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine-10-carboxamide hydrochloride salt,
45  N-[2-(2-methoxyphenoxy)ethyl]-10H-phenoxazine-10-carboxamide hydrochloride salt,
10-[(3-[4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-10H-phenoxazine hydrochloride salt,

10-[(3-[2-ethoxyphenyl)imidazolidin-1-yl]propyl]-10H-phenothenazine hydrochloride salt,

10-[(4-[5-fluoro-2-propoxyphenyl]piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H-phenoxazin-10-yl)propan-2-ol hydrochloride salt.

In another aspect, provided are pharmaceutical compositions comprising therapeutically effective amounts of one or more compounds having the structure of the Formula I

$$R_1 \_X_1 \_R_2 \_R_3$$

Formula I

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

one or more pharmaceutically acceptable carriers, excipients or diluents, wherein:

$X_1$ can be N or CR$_2$;

$R_4$ can be hydrogen, hydroxyl or alkyl;

$A$ can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CH$_{10}$$R_{11}$;

$R_{10}$ and $R_{11}$ can independently be alkyl, COO-alkyl, aryl or heterocyclyl;

$R_1$, $R_2$ and $R_3$ independently in each occurrence can be hydrogen, halogen, C$_{1-3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R$_6$ or S(O)$_{0-2}$R$_5$;

$R_5$ can be alkyl, alkenyl, alknyl, aryl, cycloalkyl or heterocyclyl;

$R_2$ and $R_3$ together with $X_1$ to which they are attached can form a ring of the form
which contains one or more additional heteroatom(s) selected from O, S or N;

\[ M_1 \text{ and } M_2 \text{ can independently be hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or } M_1 \text{ and } M_2 \text{ together form a bridging group (C} \text{-} \text{C}\text{);} \]

\[ W \text{ can be N, CH or COH;} \]

\[ R_6 \text{ can be} \]

\[ Y \text{ can be } O, S, NR_2, C=O \text{ or a bond;} \]

\[ R_7, R_8 \text{ and } R_9 \text{ can independently be hydrogen, hydroxyl, amino, } S(O)O_2R_5 \text{ or } NHSO_2R_5; \]

\[ L \text{ can be a linker; and} \]

\[ \bullet \text{ can be a point of attachment.} \]

In another aspect, provided are methods for treating 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 having the structure of the Formula I

\[ R_1^1 \text{-} A \text{--} X_1 R_2 R_3 \]

Formula I

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, \( N \)-oxides or metabolites thereof, or a
pharmaceutical composition comprising a therapeutically effective amount of one or more compounds having the structure of the Formula I, wherein

\[ X_1 \text{ can be N or CR}_4; \]

\[ R_4 \text{ can be hydrogen, hydroxyl or alkyl;} \]

\[ A \text{ can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR}_{10} \text{ or } \text{CHR}_{10}R_{11}; \]

\[ R_{10} \text{ and } R_{11} \text{ can independently be alkyl, COO-alkyl, aryl or heterocyclyl;} \]

\[ R_1, R_2 \text{ and } R_3 \text{ independently in each occurrence can be hydrogen, halogen, C}_{1-3} \text{ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R}_6 \text{ or } S(O)_{1-2}R_5; \]

\[ R_5 \text{ can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;} \]

\[ R_2 \text{ and } R_3 \text{ together with } X_1 \text{ to which they are attached can form a ring of the form} \]

\[
\begin{array}{c}
\text{N} \\
\text{W} \\
\text{R}_6
\end{array}
\]

which contains one or more additional heteroatom(s) selected from O, S or N;

\[ M_1 \text{ and } M_2 \text{ can independently be hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or } M_1 \text{ and } M_2 \text{ together form a bridging group (C}_{0-3}); \]

\[ W \text{ can be N, CH or COH;} \]

\[ R_6 \text{ can be} \]

\[
\begin{array}{c}
\text{Y} \\
\text{I} \\
\text{I}
\end{array}
\]

or

\[
\begin{array}{c}
\text{R}_5 \\
\text{R}_6
\end{array}
\]
Y can be O, S, NR₂, C=O or a bond;
R₇, R₈ and R₉ can independently be hydrogen, hydroxyl, amino, S(O)ₓR₅ or NHSO₃R₅;
L can be a linker; and

• can be a point of attachment.

The methods can also include one or more of the following embodiments. For example, the disease or disorder can be benign prostatic hyperplasia or lower urinary tract symptoms. In another example, the compounds described herein can cause minimal fall or no fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

In another aspect, provided are methods for preparing compounds of Formula VI,

\[
\begin{array}{c}
\text{R} \rightarrow \text{L} \rightarrow \text{W} \\
\text{X}_1 \rightarrow \text{A} \rightarrow \text{R}_1 \\
\text{M}_1 \rightarrow \text{M}_2
\end{array}
\]

Formula VI

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides or metabolites thereof, comprising the steps of:

(a) reacting the compound of Formula II

\[
\begin{array}{c}
\text{R} \rightarrow \text{H}
\end{array}
\]

Formula II

with a compound of Formula III (wherein X₂ and X₃ are leaving groups)

\[
\begin{array}{c}
\text{X}_2 \rightarrow \text{L} \rightarrow \text{X}_3
\end{array}
\]

Formula III

to form a compound of Formula IV

\[
\begin{array}{c}
\text{R} \rightarrow \text{L} \rightarrow \text{X}_3
\end{array}
\]

Formula IV

(b) treating the compound of Formula IV with a compound of Formula V
to form a compound of Formula VI,

wherein,

$X_1$ can be N or CR$_4$;

R$_4$ can be hydrogen, hydroxyl or alkyl;

A can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CH$_{10}$R$_{11}$;

R$_{10}$ and R$_{11}$ can independently be alkyl, COO-alkyl, aryl or heterocyclyl;

R$_1$ can be hydrogen, halogen, C$_{1,3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy,

R$_6$ or S(O)$_{0,5}$R$_5$;

R$_5$ can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

R$_6$ can be

M$_1$ and M$_2$ can independently be hydrogen, halogen, hydroxyl, amino, nitro,

cyano, alkyl, alkoxy or acyl; or M$_1$ and M$_2$ together form a bridging group (C$_{0,3}$);

W can be N, CH or COH;

R can be
Y can be O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ can independently be hydrogen, hydroxyl, amino, S(O)ₓ₂R₅ or NHSO₂R₅; and

L can be a linker.

In another aspect, provided are methods for preparing compound of Formula IX,

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides or metabolites thereof, comprising the steps of:

(a) reacting the compound of Formula II

\[
\begin{align*}
R & \quad \text{II} \\
\text{Formula II}
\end{align*}
\]

with a compound of Formula VII (wherein X₃ is a leaving group)

\[
\begin{align*}
\text{O} & \quad \text{X₃} \\
\text{Formula VII}
\end{align*}
\]

to form a compound of Formula VIII
(b) treating the compound of Formula VIII with a compound of Formula V

\[
\begin{align*}
&\text{Formula VIII} \\
&\text{Formula V}
\end{align*}
\]

to form a compound of Formula IX,

5 wherein,

\[X_1 \text{ can be N or CR}_4;\]

\[R_4 \text{ can be hydrogen, hydroxyl or alkyl;}\]

\[A \text{ can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR}_{10} \text{ or } \text{CHR}_{10}R_{11};\]

\[R_{10} \text{ and } R_{11} \text{ can independently be alkyl, COO-alkyl, aryl or heterocyclyl;}\]
\[R_1 \text{ can be hydrogen, halogen, } C_{1-3} \text{ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, } R_6 \text{ or } S(O)_{2}R_5;\]

\[R_5 \text{ can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl; and}\]

\[R_6 \text{ can be}\]

\[\begin{align*}
&\text{or}
\end{align*}\]

\[M_1 \text{ and } M_2 \text{ can independently be hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or } M_1 \text{ and } M_2 \text{ together form a bridging group (C}_0\text{)};\]

\[W \text{ can be N, CH or COH;}\]
R can be

Y can be O, S, NR₂, C=O or a bond; and

R₇, R₈ and R₉ can independently be hydrogen, hydroxyl, amino, S(O)₂R₅ or NHSO₂R₅.

In yet another aspect, provided are methods for preparing compounds of Formula XIV,

pharmacologically acceptable salts, pharmacologically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides or metabolites thereof, comprising the steps of:

(a) reacting the compound of Formula V(a) with a compound of Formula X

(wherein X₅ is alkenyl or halogen)
to form a compound of Formula XI

(b) reducing the compound of Formula XI to form a compound of Formula XII

(c) reacting the compound of Formula XII with a compound of Formula XIII

to form a compound of Formula XIV,

wherein,

- $X_1$ can be N or CR$_3$;
- R$_4$ can be hydrogen, hydroxyl or alkyl;
- A can be aryl, aryloxy, heterocycl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CHR$_{10}$R$_{11}$;
- R$_{10}$ and R$_{11}$ can independently be alkyl, COO-alkyl, aryl or heterocycl;
- R$_1$ can be hydrogen, halogen, C$_{1-3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy,
- R$_6$ or S(O)$_{1-2}$R$_5$;
- R$_5$ can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocycl;
R₆ can be

or

M₁ and M₂ can independently be hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or M₁ and M₂ together form a bridging group (C₀.₃); and

Y can be O, S, NR₃, C=O or a bond;

In another aspect, provided are methods for preparing compounds of Formula XX,

pharmacetically acceptable salts, pharmacetically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides or metabolites thereof, comprising the steps of:

(a) reacting the compound of Formula X

\[
\begin{align*}
R₁ & \quad \text{--A--OH} \\
\text{Formula XV}
\end{align*}
\]

with a compound of Formula VII

\[
\begin{align*}
X₂ & \quad \text{(CH₂)_₃} \\
\text{Formula XVI}
\end{align*}
\]
to form a compound of Formula XVII

\[
\begin{align*}
&\text{R}_1
\end{align*}
\]

Formula XVII

(b) treating the compound of Formula XVII with a hydrazine hydrate to form a compound of Formula XVIII, and

\[
\begin{align*}
&\text{R}_1
\end{align*}
\]

Formula XVIII

(c) treating the compound of Formula XVIII with a compound of Formula XIX

\[
\begin{align*}
&\text{R}_1
\end{align*}
\]

Formula XIX

to form a compound of Formula XX,

wherein,

A can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR\textsubscript{10} or CHR\textsubscript{10}R\textsubscript{11};

R\textsubscript{10} and R\textsubscript{11} can independently be alkyl, COO-alkyl, aryl or heterocyclyl;

R\textsubscript{1} can be hydrogen, halogen, C\textsubscript{1-3} alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R\textsubscript{6} or S(O)\textsubscript{10-2}R\textsubscript{5};

R\textsubscript{5} can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

R\textsubscript{6} can be

\[
\begin{align*}
&\text{R}_1
\end{align*}
\]

or

\[
\begin{align*}
&\text{R}_1
\end{align*}
\]
Y can be O, S, NR₄, C=O or a bond; and
n can be an integer of from 0 to 5.

**Detailed Description of the Invention**

The present invention provides α₄ and/or α₄ adrenergic receptor antagonists, which can be used to treat benign prostatic hyperplasia (BPH) or related symptoms thereof, or lower urinary tract symptoms (LUTS) with or without BPH. The present invention also provides for processes for the synthesis of such compounds. Also provided herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxide of such compounds. Also provided are pharmaceutical compositions containing the described compounds and one or more pharmaceutically acceptable carriers, excipients or diluents, which can be used to treat BPH or related symptoms thereof or LUTS with or without BPH. 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.

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

\[
R_1^-A^+X_1R_2R_3
\]

**Formula I**

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

X₁ can be N or CR₄, wherein

R₄ can be hydrogen, hydroxyl or alkyl;
A can be aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOMCHR₁₀ or CHR₁₀R₁₁, wherein

R₁₀ and R₁₁ can be independently alkyl, COO-alkyl, aryl or heterocyclyl;

R₁, R₂ and R₃ independently in each occurrence can be hydrogen, halogen, C₁₋₃ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R₆ or S(O)₃R₆, wherein
R₅ can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocycl; and

R₂ and R₃ together with X₁ to which they are attached may also form a ring of the form

which may contain additional one or more heteroatom(s) selected from O, S or N, wherein

M₁ and M₂ can independently be hydrogen, halogen, hydroxyl, amino, nitro,
cyano, alkyl, alkoxy or acyl; or M₁ and M₂ together can form a bridging group (C₈₋₃);  

W can be N, CH or COH; and

R₆ can be

wherein

Y can be O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ can be independently hydrogen, hydroxyl, amino, S(O)₂R₅  
or NHSO₃R₅;

L can be a linker; and

• can be point of attachment.

In another aspect, provided herein are compounds selected from:

3-[(3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,

Methyl [4-3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl] piperazin-1-yl](phenyl)acetate,

3-(3-[4-(cyclopentyloxy) phenyl]piperazin-1-yl)propyl]-1,2,3-benzotriazin-4(3H)-one,

3-[3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one,
3-(3-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl]-2-methylpropyl}-1,2,3-benzotriazin-4(3H)-one,
5 3-{3-[4-(2-ethoxyphenyl) piperazin-1-yl]-2-methyl propyl}-1,2,3-benzotriazin-4(3H)-one,
    3-[2-methyl-3-{4-(2-propoxy phenyl)piperazin-1-yl}propyl]-1,2,3-benzotriazin-4(3H)-one,
10 3-(3-{4-[2-(cyclopentyloxy) phenyl]piperazin-1-yl]-2-methyl propyl}-1,2,3-benzotriazin-4(3H)-one,
    3-[3-{4-(2-isopropoxyphenyl) piperazin-1-yl]2-methylpropyl} -1,2,3-benzotriazin-4(3H)-one,
15 3-[3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl]-1,2,3-benzotriazin-4(3H)-one,
    3-[5-{4-(2-methoxyphenyl) piperazin-1-yl}pentyl]-1,2,3-benzotriazin-4(3H)-one,
20 3-{5-[4-(2-ethoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriaizin-4(3H)-one,
    3-[5-{4-(2-propoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
25 3-[5-{4-(2-isopropoxyphenyl) piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
    3-[5-{4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]pentyl}-1,2,3-benzotriazin-4(3H)-one,
30 3-{5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl} penty}-1,2,3-benzotriazin-4(3H)-one,
    3-[5-{4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl}penty}-1,2,3-benzotriazin-4(3H)-one,
    3-[5-{3-(2-methoxyphenyl) imidazolidin-1-yl}penty}-1,2,3-benzotriazin-4(3H)-one,
35 3-[5-(6,7-dimethoxy-3,4-dihydro isoquinolin-2(1H)-yl)penty]-1,2,3-benzotriazin-4(3H)-one,
    3-(3-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl} propyl}-1,2,3-benzotriazin-4(3H)-one,
40 3-{5-[4-(2-fluoro-2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl]-1,2,3-benzotriazin-4(3H)-one,
    3-[5-{4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}pentyl]-1,2,3-benzotriazin-4(3H)-one,
45 3-[5-{4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}pentyl}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyI}-1,2,3-benzotriazin-4(3H)-one,
3-{15-[3,4-dihydroisoquinolin-2(1H)-yl]pentyI]-1,2,3-benzotriazin-4(3H)-one,
3-{3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3- 
benzotriazin-4(3H)-one,
N-{3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6- 
yl}acetamide,
N-{3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6- 
yl}benzamide,
N-{3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl} 
tetrahydrofuran-2-carboxamide,
3-{3-[4-[5-fluoro-2-isopropoxy phenyl]piperazin-1-yl]-2-hydroxypropyl]-1,2,3- 
benzotriazin-4(3H)-one,
3-(3-[4-[2-(cyclopentyl)oxy phenyl]piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-
4(3H)-one,
3-{2-hydroxy-3-[1-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)- 
one,
3-{2-hydroxy-3-(4-(methoxyphenyl)piperazin-1-yl)propyl]-1,2,3-benzotriazin-4(3H)-one,
3-{2-hydroxy-3-[4-(isopropoxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)- 
one,
3-{2-hydroxy-3-(4-(methoxy phenyl)piperazin-1-yl)propyl]-1,2,3-benzotriazin-4(3H)- 
one,
10-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine,
10-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine,
10-{3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine,
10-{3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine,
10-{3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine,
10-{3-[4-(2-fluoro-6-isopropoxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine,
10-(3-{4-[2-(cyclopentyl)oxy]-6-fluoro phenyl)piperazin-1-yl]propyl)-10H-phenoxazine,
10-{3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl}-10H-phenoxazine,
10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

8-(2-methoxyphenyl)-3-[3-(10H-phenothiazin-10-yl)propyl]-3-azabicyclo[3.2.1]octan-8-ol,

10-(3-[4-{2-(cyclopentyloxy)phenyl} piperazin-1-yl]propyl)-10H-phenothiazine,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide,

10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

10-(3-[4-[2-(cyclopentyloxy)-5-fluoro phenyl]piperazin-1-yl]propyl)-10H-phenothiazine,

10-[3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H-phenothiazine,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine-10-carboxamide,

N-[2-(2-methoxyphenoxy)ethyl]-10H-phenoxazine-10-carboxamide,

10-(3-[4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-10H-phenoxazine,

10-[3-[3-(2-ethoxyphenyl)imidazolidin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H-phenoxazin-10-yl)propan-2-ol,

A pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof.

In another aspect, provided herein are compounds selected from:

3-[3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

Methyl [4-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl] piperazin-1-yl](phenyl)acetate hydrochloride salt,

3-(3-[4-[2-(cyclopentyloxy) phenyl]piperazin-1-yl]propyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,
3-(3-[(4-[(2-cyclopentyl)oxy]-5-fluorophenyl]piperazin-1-yl]-2-methylpropyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(3-[4-(2-ethoxyphenyl)piperazin-1-yl]-2-methylpropyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(2-methyl-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-(3-[4-[(2-cyclopentyl)oxy]phenyl]piperazin-1-yl]-2-methylpropyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(3-[4-(2-isopropoxyphenyl)piperazin-1-yl]-2-methylpropyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(3-[3,4-dihydroisoquinolin-2(1H)-yl]propyl]-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl]-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[4-(2-ethoxyphenyl)piperazin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[4-(2-propoxyphenyl)piperazin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[4-(2-isopropoxyphenyl)piperazin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-(5-[4-[(2-cyclopentyl)oxy]-5-fluorophenyl]piperazin-1-yl) pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[3-(2-methoxyphenyl) imidazolidin-1-yl]pentyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-[(5-[(6,7-dimethoxy-3,4-dihydro isoquinolin-2(1H)-yl]pentyl]-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,

3-(3-[4-[(2-cyclopentyl)oxy]-5-fluorophenyl]piperazin-1-yl) propyl)-1,2,3-benzotrazin-4(3H)-one hydrochloride salt,
3-(3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-(5-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]pentyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[5-(3,4-dihydroisoquinolin-2(1H)-yl)pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[3-[4-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]acetamide hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]benzamide hydrochloride salt,

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]tetrahydrofuran-2-carboxamide hydrochloride salt,

3-[3-[4-(5-fluoro-2-isoproxy phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[3-[4-[2-(cyclopentoxy) phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-isoproxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-fluoro-6-isopropoxy phenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-cyclopentyloxy)-6-fluoro phenyl]piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,

10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

8-(2-methoxyphenyl)-3-[3-(10H-phenothiazin-10-yl)propyl]-3-azabicyclo[3.2.1]octan-8-ol hydrochloride salt,

10-[3-[4-(2-cyclopentyloxy)phenyl] piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carbox amide hydrochloride salt,

10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

10-[3-[4-(2-ethoxyphenyl)-5-fluoro phenyl]piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

10-[3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine-10-carboxamide hydrochloride salt,

N-[2-(2-methoxyphenoxy)ethyl]-10H-phenoxazine-10-carboxamide hydrochloride salt,

10-[3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt,
10-{{3-(2-ethoxyphenyl)imidazolidin-1-yl}propyl}-10H-phenothiazine hydrochloride salt,

10-{{3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl}propyl}-10H-phenoxazine hydrochloride salt, or

1-{4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl}-3-(10H-phenoxazin-10-yl)propan-2-ol hydrochloride salt.

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

In another aspect, provided herein are methods for treating a disease or disorder mediated through \( \cap_{\alpha} \) and/or \( \cap_{\beta} \) adrenergic receptors, comprising administering to a patient in need thereof therapeutically effective amounts of one or more compounds or compositions described herein.

In another aspect, provided herein are methods for treating benign prostatic hyperplasia (BPH) and related symptoms, 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 or compositions described herein. In an embodiment, compounds described herein cause minimal decrease or no decrease in blood pressure at dosages effective to alleviate benign prostatic hyperplasia. 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).

In another aspect, provided herein are methods for treating 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 described herein in combination with one or more agents selected from bladder selective muscarinic receptor antagonist, testosterone 5 alpha-reductase inhibitor, endothelin antagonists, melanocortin receptor agonist, cGMP elevators, HMG-CoA reductase inhibitors, e.g., statins, 5-HT antagonists or combination thereof.

In yet another aspect, provided are processes for preparing compounds described herein.
The compounds of this invention are potent adrenergic receptor antagonists. Compounds described herein have good selectivity for $\alpha_{1a}$ vs $\alpha_{1b}$. Alpha 1a adrenergic receptors are involved in relieving the obstructive symptoms whereas $\alpha_{1d}$ adrenoreceptor antagonism is associated with alleviation of irritative symptoms. The relatively low affinity at the $\alpha_{1b}$ adrenergic receptor limits the cardiovascular side effects, for example, orthostatic hypotension. The present invention therefore provides pharmaceutical compositions for treatment of a disease or disorder mediated through $\alpha_{1a}$ adrenoceptors. Compounds and compositions described herein can be administered orally, parenterally, subcutaneously, transdermally or topically or any other suitable route.

The term “alkyl” refers to straight or branched saturated hydrocarbon having one to six carbon atom(s). Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl and butyl, and the like.

The term “alkenyl or alkynyl” stands for unsaturated hydrocarbon having two to six carbon atoms. One or more hydrogen of said alkenyl or alkynyl can be replaced by halogen. Examples of alkenyl and alkynyl include, but are not limited to, ethylene, propylene, ethynyl, propynyl, and the like.

The term “cycloalkyl” refers to saturated carbocyclic ring having three to seven carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl and cyclopentyl, and the like.

The term “cycloalkenyl refers to unsaturated carbocyclic ring having three to seven carbon atoms. Examples of cycloalkenyl include, but are not limited to, cyclopropenyl and cyclobutenyl, and the like.

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

The term “aryl” stands for an aromatic radical having 6 to 14 carbon atoms.

Examples of aryl include, but are not limited to, phenyl, napthyl, anthryl and biphenyl, and the like.

The term “aralkyl” stands for an aryl radical having 7 to 14 carbon atoms, which is bonded to an alkylene chain. Examples of aralkyl include, but are not limited to, benzyl, napthylmethyl, phenethyl and phenylpropyl, and the like.
The term “heterocyclyl” refers to non-aromatic or aromatic ring system having one or more heteroatom(s) wherein the said hetero atom(s) is/ are selected from the group comprising of nitrogen, sulphur and oxygen and the ring system includes mono, bi or tricyclic. Examples of heterocycles include, but not limited to, azetidinyl, benzimidazolyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, dihydroimidazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, indolanyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoaxazolidinyl, isoaxazolyl, morpholinyl, napthyridinyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrroldinyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, thiazolyl, and thienyl, and the like.

The said heterocyclyl may be fused with an aryl or heterocyclyl ring. Examples include, but not limited to, 1, 2, 3, 4-tetrahydro-quinoline, 1, 2, 3, 4-tetrahydro-isoquinoline, and the like.

The said alkyl, aryl, heterocyclyl and cycloalkyl may optionally be substituted with one or more substituent(s) independently selected from halogen, hydroxy, nitro, mercapto, cyano, alkyl, haloalkyl, cycloalkyl, cycloalkenyl, alkoxy, haloalkoxy, thioalkyl, cycloalkoxy, −NR_{11}R_{12}, −CONR_{11}R_{12}, −COOR_{12}, −CONH_{12}, −OCOR_{12}, −COR_{12}, −NHSO_{2}R_{12} and −SO_{2}NHR_{12} wherein R_{11} and R_{12} are independently selected from hydrogen or alkyl.

The term “alkoxy” herein refers to OR_{a} wherein R_{a} can be alkyl, alkenyl or alkynyl.

The term “cycloalkoxy” herein refers to OR_{b} wherein R_{b} can be cycloalkyl.

The term 'linker' refers to CON(R_{b})_{2}, CS(R_{b})_{2}, [wherein R_{b} can be selected from: hydrogen, alkylene, alkenylene], alkylene chain of from one to six carbon atoms, which may be saturated or unsaturated or may comprise a ring. The chain may be interrupted at any point by one or more heteroatom(s) selected from N, S, and O and may be substituted with 'substituent(s)' as mentioned above.

The term "leaving group" refers to any group that leaves the molecule during substitution, elimination and addition-elimination reactions. Illustrative examples of
suitable leaving groups include, but are not limited to -F, -Cl, -Br, alkyl chlorides, alkyl bromides, alkyl iodides, alkyl sulfonates, alkyl benzenesulfonates, alkyl p-toluenesulfonates, alkylbenzenesulfonates, alkyl p-toluenesulfonates, alkyl methanesulfonates, triflate or nay group having a bisulfate, methyl sulfate or sulfonate ion.

The term “polymorphs” includes all crystalline form as well as amorphous form for compounds described herein and as such are intended to be included 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 includes hydrochlorides, sulfates, phosphates, tartrates, 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.

Scheme I

\[
\begin{align*}
R\quad & H + X_2\quad & L\quad & X_3 \rightarrow R\quad & L\quad & X_3 \\
\text{Formula II} \quad & \quad \text{Formula III} \quad & \quad \text{Formula IV}
\end{align*}
\]

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, and IV.

Compounds of Formula VI can be prepared according to Scheme I. Thus, compounds of Formula II can be reacted with compounds of Formula III (wherein \(X_2\) and \(X_3\) are leaving groups) to form compounds of Formula IV. Compounds of Formula IV can be treated with compounds of Formula V to form compounds of Formula VI (wherein \(L, R_7, R_8, R_9, W, M_1, M_2, X_1, A, Y\) and \(R_1\) are the same as defined earlier). Compounds of Formula VI can be further converted into their pharmaceutically acceptable salts using the methods well known to one of ordinary skill in art.
Compounds of Formula II can be reacted in one or more solvents, for example, polar protic (e.g., methanol, ethanol or isopropanol), polar aprotic solvents (e.g., acetone, dimethylformamide, acetonitrile, dimethylsulfoxide or hexamethylyphosphoric acid triamide) or mixtures thereof.

Compounds of Formula II can also be reacted in the presence of one or more bases, for example, inorganic bases (e.g., sodium carbonate, cesium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydride, lithium hydroxide, sodium metal or mixtures thereof), organic bases (e.g., triethylamine, pyridine, tributylamine, diisopropylethylamine, sodium-t-butoxide, 4-(N-dimethylamino)pyridine, lithium diisopropylamine, potassium-t-butoxide, n-butyllithium or dry liquid ammonia or mixtures thereof) or mixtures thereof.

Compounds of Formula IV can be treated in one or more solvents, for example, polar protic solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof), polar aprotic solvents (e.g., methylethylketone, acetone, dimethylformamide, dimethylacetamide, dimethylsulfoxide or mixtures thereof) or mixtures thereof.

Compounds of Formula IV can also be treated in the presence of one or more bases, for example, inorganic bases (e.g., ammonium hydroxide, hydrazine, sodium carbonate, cesium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or mixtures thereof), organic bases (e.g., triethylamine, pyridine, tributylamine, diisopropylethylamine or 4-(N-dimethylamino)pyridine or mixtures thereof) or mixtures thereof.
Compounds of Formula IX can be prepared according to Scheme II. Thus, compounds of Formula II can be reacted with compounds of Formula VII (wherein \( X_3 \) is a leaving group) to form compounds of Formula VIII. Compounds of Formula VIII can be treated with compounds of Formula V to form compounds of Formula IX (wherein \( R_7, R_8, R_9, W, M_1, M_2, X_1, A, Y \) and \( R_4 \) are the same as defined earlier). Compounds of Formula IX can be further converted into their pharmaceutically acceptable salts using the methods well known to one of ordinary skill in art.

Compounds of Formula II can be reacted in one or more solvents, for example, polar protic solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof), polar aprotic solvents (e.g., methylethyl ketone, acetone, dimethylformamide, dimethylsulfoxide, acetonitrile or mixtures thereof) or mixtures thereof.

Compounds of Formula II can be reacted in the presence of one or more inorganic bases, for example, sodium carbonate, cesium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate or mixtures thereof.

Compounds of Formula VIII can be treated in one or more solvents, for example, polar protic solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof), polar
aprotic (e.g., dimethylsulfoxide, acetonitrile, dimethylformamide or mixtures thereof) or mixtures thereof.

Compounds of Formula VIII can be treated in the presence of one or more organic bases, for example, triethylamine, pyridine, tributylamine, diisopropylethylamine, 4-(N-dimethylamino)pyridine or mixtures thereof.

Scheme III

Compounds of Formula XIV can be prepared according to Scheme III. Thus, compounds of Formula V(a) can be reacted with compounds of Formula X (wherein \( X_3 \) is alkenyl or halogen and \( n \) is an integer of from 0 to 3) to form compounds of Formula XI.

Compounds of Formula XI can be reduced to form compounds of Formula XII.

Compounds of Formula XII can be treated with compounds of Formula XIII (wherein \( X_3 \) is a leaving group) to form compounds of Formula XIV (wherein \( Y, M_1, M_2, X_1, A \) and \( R_1 \) are the same as defined earlier). Compounds of Formula XIV can be further converted into their pharmaceutically acceptable salts using the methods well known to one of ordinary skill in art.

Compounds of Formula V(a) can be reacted in one or more solvents, for example, polar protic solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof), polar aprotic solvents (e.g., methylethylketone, acetone, dimethylformamide or mixtures thereof) or mixtures thereof.
Compounds of Formula V(a) can also be reacted in the presence of one or more bases, for example, inorganic bases (e.g., ammonium hydroxide, hydrazine, sodium carbonate, cesium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or mixtures thereof), organic bases (e.g., triethylamine, diisopropylamine, pyridine, tributylamine or mixtures thereof) or mixtures thereof.

Compounds of Formula XI can be reduced in the presence of one or more reducing agents, for example, raney nickel/hydrogen, palladium-carbon/hydrogen, platinum/hydrogen and ammonia in one or more polar protic solvents (e.g., methanol, ethanol, propanol, isopropanol, water or mixtures thereof), or mixtures thereof.

Compounds of Formula XII can be reacted in one or more solvents, for example, chlorinated solvents (e.g., chloroform, dichloromethane, dichloroethane or mixtures thereof), aprotic polar solvents (e.g., dimethylformamide, acetonitrile, dimethylsulfoxide or mixtures thereof), protic polar solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof) or mixtures thereof.

Compounds of Formula XII can also be reacted in the presence of one or more activating and coupling reagents, for example, pyridinium salts, phosphonium salts, uranium salts, active esters or carbodimides or mixtures thereof. Compounds of Formula XII can also be reacted in presence of one or more bases, for example, 4-dialkylaminopyridines, Hunig's base, 4-alkylmorpholine, triethylamine, 1-methylimidazole, 4-(1-pyrrolidino)pyridine or mixtures thereof.
Compounds of Formula XX can be prepared according to Scheme IV. Thus, compounds of Formula XV can be reacted with compounds of Formula XVI (wherein X₂ is a leaving group) to form compounds of Formula XVII. Compounds of Formula XVII can be reacted with hydrazine hydrate to form compounds of Formula XVIII. Compounds of Formula XVIII can be finally treated with compounds of Formula XIX (wherein X₃, is a leaving group) to form compounds of Formula XX (wherein Y, A and R₁ are the same as defined earlier and n is an integer of from 1 to 5). Compounds of Formula XX can be further converted into their pharmaceutically acceptable salts using the methods well known to one of ordinary skill in art.

Compounds of Formula XV can be reacted in one or more polar aprotic solvents, for example, methylethylketone, acetone, dimethylformamide or mixtures thereof.

Compounds of Formula XV can also be reacted in the presence of one or more bases, for example, inorganic bases (e.g., potassium carbonate, sodium hydrogen carbonate, sodium hydride, sodium carbonate, sodium acetate, sodium thiosulphate or mixtures thereof), organic bases (e.g., pyridine, triethylamine, diisopropylethylamine or mixtures thereof) or mixtures thereof.

Compounds of Formula XVII can be reacted in one or more solvents, for example, polar protic solvents (e.g., methanol, ethanol isopropanol or mixtures thereof), polar aprotic solvents (e.g., dimethylsulfoxide, acetonitrile or mixtures thereof) or mixtures thereof.

Compounds of Formula XVIII can be treated in one or more solvents, for example, chlorinated solvents (e.g., chloroform, dichloromethane, dichloroethane or mixtures thereof), aprotic polar solvents (e.g., dimethylformamide, acetonitrile, dimethylsulfoxide or mixtures thereof), protic polar solvents (e.g., methanol, ethanol, isopropanol or mixtures thereof) or mixtures thereof.

Compounds of Formula XVIII can be treated in the presence of activating and coupling reagents, for example, pyridinium salts, phosphonium salts, uranium salts, active esters or carbodiimides or mixtures thereof, and in the presence of one or more organic bases, for example, 4-dialkylaminopyridines, Hunig’s base, 4-alkylmorpholine, triethylamine, 1-methylimidazole, 4-(1-pyrrolidino)pyridine or mixtures thereof.
In the above schemes, where the base, solvents, etc., are indicated, other bases, solvents, etc., known to those skilled in the art may be used. Similarly, reaction temperatures and durations may be adjusted accordingly.

Compounds of the present invention include, for example:

3-[3-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-y]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 1) and its hydrochloride salt (Compound No. 2),

Methyl [4-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl]propyl] piperazin-1-yl](phenyl)acetate (Compound No. 3) and its hydrochloride salt (Compound No. 4),

3-[3-[4-[2-(cyclopentoxy) phenyl]piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 5) and its hydrochloride salt (Compound No. 6),

3-[3-[4-[5-fluoro-2-isopropoxy phenyl]piperazin-1-yl]2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 7) and its hydrochloride salt (Compound No. 8),

3-[3-[4-[2-(cyclopentoxy)-5-fluorophenyl]piperazin-1-yl]2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 9) and its hydrochloride salt (Compound No. 10),

3-[3-[4-(2-ethoxyphenyl) piperazin-1-yl]2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 11) and its hydrochloride salt (Compound No. 12),

3-[2-methyl-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 13) and its hydrochloride salt (Compound No. 14),

3-[3-[4-[2-(cyclopentoxy) phenyl]piperazin-1-yl]2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 15) and its hydrochloride salt (Compound No. 16),

3-[3-[4-(2-isopropoxyphenyl) piperazin-1-yl]2-methylpropyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 17) and its hydrochloride salt (Compound No. 18),

3-[3-(3,4-dihydroisoquinolin-2(1H)-yl]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 19) and its hydrochloride salt (Compound No. 20),

3-[5-[4-(2-methoxyphenyl) piperazin-1-y]pentyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 21) and its hydrochloride salt (Compound No. 22),

3-[5-[4-(2-ethoxyphenyl) piperazin-1-y]pentyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 23) and its hydrochloride salt (Compound No. 24),

3-[5-[4-(2-propoxyphenyl) piperazin-1-y]pentyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 25) and its hydrochloride salt (Compound No. 26),

3-[5-[4-(2-isopropoxyphenyl) piperazin-1-y]pentyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 27) and its hydrochloride salt (Compound No. 28),
3-[5-4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 29) and its hydrochloride salt (Compound No. 30),

3-[5-{4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl} penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 31) and its hydrochloride salt (Compound No. 32),

3-[5-{4-[5-fluoro-2-methoxy phenyl]piperazin-1-yl]penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 33) and its hydrochloride salt (Compound No. 34),

3-[5-{3-[2-methoxyphenyl] imidazolidin-1-yl} penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 35) and its hydrochloride salt (Compound No. 36),

3-[5-{6,7-dimethoxy-3,4-dihydro isquinolin-2(1H)-yl]penty1}-1,2,3-benzotriazin-4(3H)-one (Compound No. 37) and its hydrochloride salt (Compound No. 38),

3-{3-[4-[2-(cyclopentyloxy)-5-fluorophenyl]piperazin-1-yl] propyl}-1,2,3-benzotriazin-4(3H)-one (Compound No. 39) and its hydrochloride salt (Compound No. 40),

3-[3-[4-[fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 41) and its hydrochloride salt (Compound No. 42),

3-[5-[4-[fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 43) and its hydrochloride salt (Compound No. 44),

3-[5-{4-[5-fluoro-2-propoxyphenyl] piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one (Compound No. 45) and its hydrochloride salt (Compound No. 46),

3-[5-{4-[2-ethoxy-5-fluorophenyl]piperazin-1-yl]penty1]-1,2,3-benzotriazin-4(3H)-one (Compound No. 47) and its hydrochloride salt (Compound No. 48),

3-[5-{3,4-dihydroisquinolin-2(1H)-yl]penty1}-1,2,3-benzotriazin-4(3H)-one (Compound No. 49) and its hydrochloride salt (Compound No. 50),

3-[3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one (Compound No. 51) and its hydrochloride salt (Compound No. 52),

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl]propyl]-3-azabicyclo[3.1.0]hex-6-y1]acetamide (Compound No. 53) and its hydrochloride salt (Compound No. 54),

N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl]propyl]-3-azabicyclo[3.1.0]hex-6-y1]benzamide (Compound No. 55) and its hydrochloride salt (Compound No. 56).
$N\{3\{3\{4\{oxo\-1,2,3\-benzotriazin-3(4H\)-yl\}propyl\}-3\azabicyclo[3.1.0]hex-6-yl\}$
tetrahydro- furan-2-carboxamide (Compound No. 57) and its hydrochloride salt
(Compound No. 58),

5 $3\{3\{4\{5\-fluoro-2\-isopropoxy phenyl\}piperazin-1-yl\}-2\-hydroxypropyl\}-1,2,3\-
benzotriazin-4(3H\)-one (Compound No. 59) and its hydrochloride salt (Compound No.
60),

3\{3\{4\{2\{(cyclopentyl)oxy\} phenyl\}piperazin-1-yl\}-2\-hydroxypropyl\}-1,2,3\-
benzotriazin-4(3H\)-one (Compound No. 61) and its hydrochloride salt (Compound No. 62),

10 $3\{2\-hydroxy-3\{4\{2\-propoxy phenyl\}piperazin-1-yl\}propyl\}-1,2,3\-benzotriazin-4(3H\)-
one (Compound No. 63) and its hydrochloride salt (Compound No. 64),

15 $3\{2\-hydroxy-3\{4\{2\-methoxy phenyl\}piperazin-1-yl\}propyl\}-1,2,3\-benzotriazin-4(3H\)-
one (Compound No. 65) and its hydrochloride salt (Compound No. 66),

20 $3\{2\-hydroxy-3\{4\{2\-isopropoxyphenyl\}piperazin-1-yl\}propyl\}-1,2,3\-benzotriazin-4(3H\)-
one (Compound No. 67) and its hydrochloride salt (Compound No. 68),

25 $3\{2\-hydroxy-3\{4\{2\-methoxy phenyl\}piperazin-1-yl\}propyl\}-1,2,3\-benzotriazin-4(3H\)-
one (Compound No. 69) and its hydrochloride salt (Compound No. 70),

$10\{3\{4\{2\-methoxyphenyl\}piperazin-1-yl\}propyl\}-10H\-phenoixazine$ (Compound No. 71)
and its hydrochloride salt (Compound No. 72),

$10\{3\{4\{2\-ethoxyphenyl\}piperazin-1-yl\}propyl\}-10H\-phenoixazine$ (Compound No. 73)
and its hydrochloride salt (Compound No. 74),

30 $10\{3\{4\{2\-propoxyphenyl\}piperazin-1-yl\}propyl\}-10H\-phenoixazine$ (Compound No. 75)
and its hydrochloride salt (Compound No. 76),

35 $10\{3\{4\{2\-isopropoxy phenyl\} piperazin-1-yl\}propyl\}-10H\-phenoixazine$ (Compound No.
77) and its hydrochloride salt (Compound No. 78),

$10\{3\{4\{2\-fluoro-6\-methoxy phenyl\} piperazin-1-yl\}propyl\}-10H\-phenoixazine$
(Compound No. 79) and its hydrochloride salt (Compound No. 80),

$10\{3\{4\{2\-fluoro-6\-isopropoxy phenyl\} piperazin-1-yl\}propyl\}-10H\-phenoixazine$
(Compound No. 81) and its hydrochloride salt (Compound No. 82),

40 $10\{3\{4\{2\{(cyclopentyl)oxy\} 6\-fluoro phenyl\} piperazin-1-yl\}propyl\}-10H\-phenoixazine$
(Compound No. 83) and its hydrochloride salt (Compound No. 84),

45 $10\{3\{2\-methoxyphenyl\} imidazolidin-1-yl\}propyl\}-10H\-phenoixazine$ (Compound No.
85) and its hydrochloride salt (Compound No. 86),
10-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 87) and its hydrochloride salt (Compound No. 88),

10-{3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 89) and its hydrochloride salt (Compound No. 90),

10-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 91) and its hydrochloride salt (Compound No. 92),

8-(2-methoxyphenyl)-3-{3-(10H-phenothiazin-10-yl)propyl}-3-azabicyclo[3.2.1]octan-8-ol (Compound No. 93) and its hydrochloride salt (Compound No. 94),

10-{3-[4-(2-cyclopentoxyphenyl) piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 95) and its hydrochloride salt (Compound No. 96),

N-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine-10-carbox amide (Compound No. 97) and its hydrochloride salt (Compound No. 98),

10-{3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 99) and its hydrochloride salt (Compound No. 100),

10-{3-[4-(2-cyclopentoxy)-5-fluoro phenyl]piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 101) and its hydrochloride salt (Compound No. 102),

10-{3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl}-10H-phenothiazine (Compound No. 103) and its hydrochloride salt (Compound No. 104),

N-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine-10-carboxamide (Compound No. 105) and its hydrochloride salt (Compound No. 106),

N-{2-(2-methoxyphenoxy)ethyl}-10H-phenoxazine-10-carboxamide (Compound No. 107) and its hydrochloride salt (Compound No. 108),

10-{3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl}-10H-phenoxazine (Compound No. 109) and its hydrochloride salt (Compound No. 110),

10-{3-[3-(2-ethoxyphenyl)imidazolidin-1-yl]propyl}-10H-phenothiazine (Compound No. 111) and its hydrochloride salt (Compound No. 112),

10-{3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine (Compound No. 113) and its hydrochloride salt (Compound No. 114),

1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H-phenoxazin-10-yl)propan-2-ol (Compound No. 115) and its hydrochloride salt (Compound No. 116),

pharmacologically acceptable salts, esters, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs or pharmaceutically acceptable solvates thereof.
Compounds described herein may be administered with or without an excipient. The present invention also provides compositions, which may be prepared by admixture of one or more compounds with apposite excipients and other assisting agents, if required, for oral, sublingual, parenteral, topical, rectal or transdermal administration.

The solid compositions include, but are not limited to, tablets, capsules, microcapsules, powders, granules, pills, wafers, dragees, catchets, caplets, suppositories or pastilles.

Tablets, capsules, or pills can be 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, flavoring agents, sweeteners, preservatives or mixtures thereof.

Tablets may be sugar coated, enteric coated or film coated by standard techniques well known in the art. 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 inert solid diluents, for example, sodium carbonate, calcium carbonate, lactose, starch, calcium phosphate, sodium phosphate or mixtures thereof; disintegrants, for example, sodium starch glycolate, croscarmellose sodium or mixtures thereof; or mixtures thereof.

Dispersible powders and granules suitable for reconstitution to form a stable suspension by addition of water are provided with one or more active ingredients (i.e., compounds described herein and any additional active ingredient) with one or more dispersing agents and one or more suspending agents. Additional excipients, for example, coloring agents, flavoring agents and sweetening agents may also be added.

Suppositories for rectal administration may include carbon dioxide releasing laxative suppositories. Dosage forms for topical or transdermal administration of one or more compounds described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, spot-on or patches. The active compound can be admixed under sterile condition with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required.
Liquid form preparations for oral administration include, for example, pharmaceutically acceptable emulsions, microemulsions, solutions, aqueous or oily suspensions, syrups, sprays or elixirs.

For liquid form preparations, active ingredients can be mixed with water or other solvent, solubilizing agents, cosolvents, 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, groundnut, corn, germ, olive, castor and sesame oil), glycerol, and fatty acid esters of sorbitan and mixture thereof; suspending agents, for example, sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose or carboxymethylcellulose and preservatives, for example, methyl or propyl p-hydroxybenzoate and sorbic acid. The spray composition can contains suitable propellants.

Injectable preparations, for example, sterile aqueous or non-aqueous injections, injectable depot forms, aqueous suspensions or emulsions may be formulated according to the art using parenterally dispersing or wetting and suspending agent. Among the acceptable vehicles and solvents that may be employed include, for example, water for injection, Ringer’s solution and isotonic sodium chloride. Ophthalmic formulations, eardrops, eye ointments, powders and solutions are also provided herein.

Pharmaceutical preparations can be in unit dosage form. In such form, preparations can be subdivided into unit doses containing appropriate quantities of the active ingredient(s). Unit dosage forms can be packaged preparations, the package containing discrete capsules, powders, in vials or ampoules, and ointments capsule, sachet, tablet, gel, cream itself or it can be the appropriate number of any of these packaged forms.

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

General Procedure

Preparation of a compound of Formula V

a) Preparation of 8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol

5 Step 1: Preparation of 3-benzyl-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol

A solution of 2-methoxy phenyl magnesium bromide (1.3 equiv.) in
tetrahydrofuran was added to a solution of 3-benzyl-3-azabicyclo[3.2.1]octan-8-one (1.0
equiv.) in tetrahydrofuran at about 25-30°C under nitrogen atmosphere. The reaction
mixture was stirred for about 12 hours at the same temperature and quenched by addition
of saturated ammonium chloride solution. The tetrahydrofuran layer was separated and
the aqueous layer was extracted with ethyl acetate. The combined organic layer was
concentrated to form 3-benzyl-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol.
Yield: 76%

Step 2: Preparation of 8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol

A solution of 3-benzyl-8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol and
palladium-carbon (10% by weight) in methanol was hydrogenated at about 25-30°C and
under 50 psi pressure for about 5 hours. The reaction mixture was filtered through a bed
of celite and concentrated to form 8-(2-methoxyphenyl)-3-azabicyclo[3.2.1]octan-8-ol.
Yield: 90%

1,4-(2-methoxyphenyl)piperidin-4-ol was prepared similarly.

b) Preparation of Methyl phenyl(piperazin-1-yl)acetate

A solution of methyl ester of (S)-phenyl glycine (1.0 equiv.), bis-(2-chloroethyl)
amine hydrochloride (2.0 equiv.) and triethylamine (3.0 equiv.) in n-butanol was heated at
about 120-130°C for about 16 hours. The reaction mixture was concentrated under
vacuum. The residue was basified with 10% sodium hydroxide solution and extracted
with dichloromethane. The dichloromethane layer was washed with water, dried and
concentrated. The residue was purified by silica gel column chromatography using
methanol and dichloromethane mixture as eluent to form Methyl phenyl(piperazin-1-yl)acetate. Yield: 43%
c) Preparation of 1-(2-methoxyphenyl)imidazolidine

Step 1: Preparation of N-(2-methoxyphenyl)ethane-1,2-diamine

A solution of α-anisidine (1.0 equiv.), bromoethyl amine hydrobromide (1.5 equiv.) and potassium carbonate (0.5 equiv.) in water was refluxed for about 24 hours. The reaction mixture was cooled to about 25-30°C then basified with 20% sodium hydroxide solution followed by extraction with ethyl acetate. The organic layer was washed with water and brine solution. The organic layer was then dried and concentrated to form a crude product which was purified on silica gel column using mixture of methanol and dichloromethane as eluent. Yield: 25%

Step 2: Preparation of 1-(2-methoxyphenyl)imidazolidin-2-one

A solution of N-(2-methoxyphenyl)ethane-1,2-diamine (1.0 equiv.) and N,N’-carbonyldiimidazole (1.5 equiv.) in dry tetrahydrofuran was stirred at about 25-30°C for about 24 hours. The reaction mixture was concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate and the organic layer was washed with water and brine solution. The organic layer was then dried and concentrated to form a crude product, which was purified by silica gel column chromatography using ethyl acetate in hexane as solvent to yield the title compound. Yield: 75%.

Step 3: Preparation of 1-(2-methoxyphenyl)imidazolidine

Borane-dimethylsulfide complex (2.0 equiv.) was added dropwise to a solution of 1-(2-methoxyphenyl)imidazolidin-2-one (1.0 equiv.) in toluene at about -20°C under nitrogen and the reaction mixture was refluxed for about 18 hours. The reaction mixture was cooled to about -20°C and 10% sodium bicarbonate solution was added dropwise. The reaction mixture was refluxed for about 2 hours. The reaction mixture was cooled and the organic layer was then separated. Aqueous layer was extracted with ethyl acetate. The organic layer was concentrated to form 1-(2-methoxyphenyl)imidazolidine. Yield: 90%.

The following compound was prepared similarly:

1-(2-ethoxyphenyl)imidazolidine

d) Preparation of N-3-azabicyclo[3.1.0]hex-6-ylacetamide
N-3-benzylazabicyclo[3.1.0]hex-6-ylacetamide (1.0 equiv.) was taken in methanol, palladium-carbon (10% dry, 1 equiv.) was added to it and the reaction was subjected to hydrogenation in the Parr apparatus under about 50 psi pressure for about 6 hours. The reaction mixture was then filtered through a bed of celite and the bed washed well with methanol. The filtrate was concentrated to form N-3-azabicyclo[3.1.0]hex-6-ylacetamide as a reddish brown oil.

e) Preparation of N-3-azabicyclo[3.1.0]hex-6-yltetrahydrofuran-2-carboxamide

N-3-azabicyclo[3.1.0]hex-6-ylacetamide was taken in a mixture of ethanol and 5N sodium hydroxide solution (2:1) and refluxed overnight. The reaction mixture was then cooled and the solvent was removed. The resulting product was diluted with water and extracted with dichloromethane. The solvent was then removed to afford the crude product as white solid, which was purified on silica gel column.

The following compound was prepared similarly:

N-3-azabicyclo[3.1.0]hex-6-ylbenzamide

f) Preparation of 1-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]iperazinnes

Trifluoroethanol (1 equiv.) was taken in dichloromethane, cooled to about 5-10°C and stirred for about 15 minutes. Triethylamine was added to this mixture and again stirred for about 10 minutes. Methanesulphonylchloride (1.5 equiv.) in dichloromethane was the added dropwise to the solvent mixture. The reaction mixture was then allowed to come to room temperature and stirred overnight at this temperature. The reaction mixture was poured into 5% sodium bicarbonate solution and stirred for about 15 minutes. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane. The organic extract was dried, concentrated to afford the product in 90 % yield. To a suspension of sodium hydride (1 equiv.) in hexamethylphosphoronic triamide, cooled to about 0°C, 4-fluoro-2-nitro phenol was added portionwise and the reaction mixture was stirred for about 30 minutes. The above product (1.2 equiv.) was then added portionwise, the reaction mixture was allowed to come to room temperature and then heated at about 140 °C for about 24 hours. The reaction mixture was cooled, poured into chilled water and extracted with ethyl acetate to form a product in 38 % yield. The above product was dissolved in methanol, 10 % dry palladium-carbon was added and
hydrogenated in Parr apparatus under about 50-60 psi pressure. The reaction mixture was filtered through a bed of celite, the bed washed well with methanol, filtrate concentrated to afford the product in 94 % yield. Equimolar quantities of the above compound and Bis-(2-chloroethyl)amine hydrochloride were heated in a mixture of 1,2-dichlorobenzene and n-hexanol (10:1) for about 42 hours at about 160°C. The reaction mixture was cooled to about 40°C poured into hexane, filtered to form 1-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]iperazines. Yield: 85%

The following compounds were prepared similarly:

1-[2-(cyclopentyloxy)phenyl]iperazines, 1-[2-(cyclopentyloxy)-5-fluorophenyl]iperazines, 1-(5-fluoro-2-isopropoxyphenyl)iperazines, 1-(2-isopropoxyphenyl)iperazines, 1-(2-ethoxyphenyl)iperazines, 1-(2-propoxyphenyl)iperazines, 1-(2-methoxyphenyl)iperazines, 1-(5-fluoro-2-methoxyphenyl)iperazines, 1-(2-ethoxy-5-fluorophenyl)iperazines, 1-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]iperazines, 1-(2-fluoro-6-isopropoxyphenyl)iperazines, 1-(2-fluoro-6-methoxyphenyl)iperazines

The following examples illustrate the invention but do not limit it any way.

Example 1:

Preparation of 3-[3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt (Compound No. 2)

Step 1: Preparation of 3-(3-bromopropyl)-1,2,3-benzotriazin-4(3H)-one

A solution of 1, 2, 3-benzotriazin-4(3H)-one (commercially available, 1.0 equiv.), 1,3-dibromopropane (commercially available, 6.0 equiv.) and potassium carbonate (2.0 equiv.) in acetone was stirred at about 25-30°C for about 24 hours. The solvent was removed under vacuum and the residue was taken in water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water. The aqueous layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel column using mixture of ethyl acetate and hexane as eluent to form 3-(3-bromopropyl)-1,2,3-benzotriazin-4(3H)-one. Yield: 70%.
Step 2: Preparation of 3-{3-[4-hydroxy-4-(2-methoxy phenyl) piperidin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one

A solution of 3-(3-bromopropyl)-1, 2, 3-benzotriazin-4(3H)-one (1.0 equiv.), 4-(2-methoxyphenyl)piperidin-4-ol (prepared as described in *Chem. Pharm. Bull.* 48(12), 1978, (2000) 1.2 equiv.), potassium carbonate (3.0 equiv.) and potassium iodide (10 mole %) in methyl ethyl ketone was refluxed for about 12 hours. The reaction mixture was concentrated under vacuum. The residue was taken in water, extracted with ethyl acetate and the organic layer was washed with water. The aqueous layer was dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography using mixture of methanol and dichloromethane as eluent.

Step 3: Preparation of 3-{3-[4-hydroxy-4-(2-methoxy phenyl) piperidin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt

An equimolar quantity of isopropanol and hydrochloric acid was added to 3-{3-[4-hydroxy-4-(2-methoxy phenyl) piperidin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one. A solid precipitated and was then filtered. Mass (m/z): 395 (M⁺+1); IR (cm⁻¹): 1672.5.

The following compounds were prepared similarly.

Compound No. 4: Methyl[4-{3-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]propyl} piperazin-1-yl] (phenyl)acetate hydrochloride salt, Mass (m/z): 422 (M⁺+1); IR (cm⁻¹): 1742, 1684, hygroscopic;

Compound No. 6: 3-(3-[4-{2-(cyclopentoxy) phenyl}piperazin-1-yl]propyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 434 (M⁺+1); IR (cm⁻¹): 1685, hygroscopic;

Compound No. 8: 3-[3-{4-[5-fluoro-2-isopropoxy phenyl}piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 440 (M⁺+1), hygroscopic;

Compound No. 10: 3-{3-[4-{2-(cyclopentoxy)-5-fluorophenyl}piperazin-1-yl]-2-methylpropyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 466 (M⁺+1), hygroscopic;

Compound No. 12: 3-{3-[4-(2-ethoxyphenyl) piperazin-1-yl]-2-methyl propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 408 (M⁺+1); IR (cm⁻¹): 1636, hygroscopic;
Compound No. 14: 3-[2-methyl-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 422 (M^+1); IR (cm^-1): 2933, 1684, hygroscopic;

Compound No. 16: 3-[3-[4-(2-cyclopentoxy) phenyl]piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotiazin-4 (3H)-one hydrochloride salt, Mass (m/z): 448 (M^+1); IR (cm^-1): 1686, hygroscopic;

Compound No. 18: 3-[3-[4-(2-isopropoxyphenyl) piperazin-1-yl]-2-methylpropyl] -1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 422 (M^+1); IR (cm^-1): 1685, hygroscopic;

Compound No. 20: 3-[3-(3,4-dihydroisquinolin-2(1H)-yl)propyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 321 (M^+1), hygroscopic;

Compound No. 22: 3-[5-[4-(2-methoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 408 (M^+1); IR (cm^-1): 1683, hygroscopic;

Compound No. 24: 3-[5-[4-(2-ethoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 422 (M^+1); IR (cm^-1): 1685, hygroscopic;

Compound No. 26: 3-[5-[4-(2-propoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 436 (M^+1); IR (cm^-1): 1685, hygroscopic;

Compound No. 28: 3-[5-[4-(2-isopropoxyphenyl) piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 436 (M^+1), hygroscopic;

Compound No. 30: 3-[5-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 454 (M^+1); IR (cm^-1): 1687, hygroscopic;

Compound No. 32: 3-[5-[4-(2-cyclopentoxy)-5-fluorophenyl]piperazin-1-yl] pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 480 (M^+1), hygroscopic;

Compound No. 34: 3-[5-[4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 426 (M^+1), hygroscopic;

Compound No. 36: 3-[5-[3-(2-methoxyphenyl) imidazolidin-1-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 396 (M^+2); IR (cm^-1): 1685, hygroscopic;

Compound No. 38: 3-[5-[6,7-dimethoxy-3,4-dihydro isquinolin-2(1H)-yl]pentyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 409 (M^+1); IR (cm^-1): 1681, hygroscopic;

Compound No. 40: 3-[3-[4-(2-cyclopentoxy)-5-fluorophenyl]piperazin-1-yl] propyl]-1,2,3-benzotiazin-4(3H)-one hydrochloride salt, Mass (m/z): 452 (M^+1); IR (cm^-1): 1684, hygroscopic;
Compound No. 42: 3-[3-[4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass: m/z 466 (M^+1), hygroscopic;

Compound No. 44: 3-[5-[4-[5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 494.2 (M^+1), M.P.: 137-138°C;

Compound No. 46: 3-[5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 454.3 (M^+1), M.P.: 122°-123°C;

Compound No. 48: 3-[5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 440.3 (M^+1), M.P.: 161-162°C;

Compound No. 50: 3-[5-(3,4-dihydroisoquinolin-2(1H)-yl)penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 349.3 (M^+1), M.P.: 134-135°C;

Compound No. 52: 3-[3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 421 (M^+1) ; IR (cm⁻¹): 1678, hygroscopic;

Compound No. 54: N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0] hex-6-yl] acetamide hydrochloride salt, Mass (m/z): 328 (M^+1) ; IR (cm⁻¹): 1680, hygroscopic;

Compound No. 56: N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0] hex-6-yl] benzamide hydrochloride salt, Mass (m/z): 408 (M^+NH₄⁺); IR (cm⁻¹): 1685, hygroscopic;

Compound No. 58: N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl] tetrahydrofuran-2-carboxamide hydrochloride salt, Mass (m/z): 384 (M^+1) ; IR (cm⁻¹): 1690, 1647, hygroscopic;

Example 2:

Preparation of 3-[3-[4-(5-fluoro-2-isoproxy phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt (Compound No. 60)

Step 1: Preparation of 3-(oxiran-2-ylmethyl)-1,2,3-benzotriazin-4(3H)-one

A solution of 1,2,3-benzotriazin-4(3H)-one (commercially available, 1.0 equiv.), 2-chloromethyl-oxirane (4.0 equiv.) and potassium carbonate (4.0 equiv.) in methyl ethyl ketone was refluxed for about 16 hours. The reaction mixture was concentrated under vacuum; the residue was taken in water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was purified by silica
gel column chromatography using mixture of ethyl acetate and hexane as eluent to form 3-(oxiran-2-ylmethyl)-1,2,3-benzotriazin-4(3H)-one. Yield: 75%

Step 2: Preparation of 3-[3-[4-(5-fluoro-2-isoproxyphenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one

A solution of 3-(oxiran-2-ylmethyl)-1,2,3-benzotriazin-4(3H)-one (1.0 equiv.), 1-(5-fluoro-2-isoproxyphenyl)piperazine (commercially available, 1.0 equiv.) and triethylamine (1.5 equiv.) in ethanol was refluxed for about 16 hours. The reaction mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography using mixture of methanol and dichloromethane as eluent to form 3-[3-[4-(5-fluoro-2-isoproxyphenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one. Yield: 95%

Step 3: Preparation of 3-[3-[4-(5-fluoro-2-isoproxyphenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to 3-[3-[4-(5-fluoro-2-isoproxyphenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one.

A solid precipitated and was then filtered. Mass (m/z): 442 (M⁺+1) ; IR (cm⁻¹): 2924, 1679, hygroscopic.

The following compounds were prepared similarly,

Compound No. 62: 3-[3-[4-[2-(cyclopentyl)oxy]phenyl]piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 450 (M⁺+1) ; IR (cm⁻¹): 2362, 1662, hygroscopic;

Compound No. 64: 3-[2-hydroxy-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 424 (M⁺+1) ; IR (cm⁻¹): 2924, 2684, hygroscopic;

Compound No. 66: 3-[2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 410 (M⁺+1) ; IR (cm⁻¹): 2924, 1666, hygroscopic;

Compound No. 68: 3-[2-hydroxy-3-[4-(2-isoproxyphenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 424 (M⁺+1) ; IR (cm⁻¹): 2925, 1678, hygroscopic;
Compound No. 70: 3-(2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride salt, Mass (m/z): 396 (M^+1); IR (cm⁻¹): 2368, 1675, hygroscopic;

General Procedure

Preparation of 10-(3-chloropropyl)-10H-phenoxazine

A dry two-necked 250 ml round bottom flask containing about 75 ml of dry liquid ammonia and fitted with a stirring bar ammonia condenser and calcium chloride guard tube was charged with phenoxazine (3.5 g). Initially few sodium pieces were added carefully then Ferric chloride in catalytic amount was added. This was followed by further addition of sodium pieces, after stirring for about 1 hour, bromochloropropane was added drop wise. The reaction mixture was then allowed to come to room temperature slowly overnight. To the residue, water was added and extracted with ether. Ether extract was washed with water, and brine, dried over anhydrous sodium sulfate, concentrated *in vacuo* to form 10-(3-chloropropyl)-10H-phenoxazine Yield: 4.7 g

Preparation of 10-(3-chloropropyl)-10H-phenothiazine

In a 100 ml dry round bottom flask fitted with a stirring bar was placed phenothiazine (5.0 g) and dimethylformamide in cold condition, to this was added sodium hydride portionwise, then the reaction mixture was stirred overnight at room temperature. To this 1-bromo-3-chloropropane was added drop wise and stirred for about 12 hours at room temperature. The reaction mixture was then quenched with saturated ammonium chloride solution. The solvent was then evaporated under vacuum, the residue was partitioned between water and ethyl acetate. Ethyl acetate extract was washed with brine solution and concentrated under vacuum. The residue was purified by column chromatography. Yield: 2.3 g

Example 3:

Preparation of 10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt (Compound No. 72)

Step 1: Preparation of 10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine
A solution of 10-(3-chloropropyl)-10H-phenoxazine (1.0 equiv.), 1-(2-ethoxyphenyl)-piperazine (1.2 equiv.), potassium carbonate (3.0 equiv.) and potassium iodide (10 mole %) in methyl ethyl ketone was refluxed for about 12 hours. The reaction mixture was concentrated under vacuum. The residue was taken in water, extracted with ethyl acetate and the organic layer was washed with water. The aqueous layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel column chromatography using mixture of methanol and dichloromethane as eluent.

Step 2: Preparation of 10-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to 10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine. A solid precipitated and was then filtered. Mass (m/z): 416 (M^+1); IR (cm\(^{-1}\)): 3424, 1490; M.P.: 220-225°C;

The following compounds were prepared similarly

Compound No. 74: 10-[[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 430 (M^+1); IR (cm\(^{-1}\)): 2411, 1491, hygroscopic;

Compound No. 76: 10-[[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 444 (M^+1); IR (cm\(^{-1}\)): 1491, 1270, hygroscopic;

Compound No. 78: 10-[[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 444 (M^+1); IR (cm\(^{-1}\)): 3396, 1491, hygroscopic;

Compound No. 80: 10-[[3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 434 (M^+1); IR (cm\(^{-1}\)): 3396, 1491, hygroscopic;

Compound No. 82: 10-[[3-[4-(2-fluoro-6-isopropanoyl phenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 462 (M^+1); IR (cm\(^{-1}\)): 3382, 1492, hygroscopic;

Compound No. 84: 10-[[3-[4-(2-cyclopentyl oxy)-6-fluoro phenyl)piperazin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 488 (M^+1); IR (cm\(^{-1}\)): 2447, 1491, hygroscopic;

Compound No. 86: 10-[[3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl]-10H-phenoxazine hydrochloride salt, Mass (m/z): 404 (M^+1), hygroscopic;

Example 4:
Preparation of 10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt (Compound No. 88)

Step 1: Preparation of 10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine

The titled compound was prepared according to the procedure as described in Example 3 using 10-(3-chloropropyl)-10H-phenothiazine in place of 10-(3-chloropropyl)-10H-phenoxazine.

Step 2: Preparation of 10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to 10-[3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine. A solid precipitated and was then filtered. Mass (m/z): 445 (M⁺+1); IR (cm⁻¹): 3421, 1461, M.P: 196-198°C

The following compounds were prepared similarly:

Compound No. 90: 10-[3-[4-(2-isopropoxy phenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 459 (M⁺+1); IR (cm⁻¹): 3422, 1462, hygroscopic;

Compound No. 92: 10-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 432 (M⁺+1); IR (cm⁻¹): 3437, 1460, M.P: 190-195 °C;

Compound No. 94: 8-(2-methoxyphenyl)-3-[3-(10H-phenothiazin-10-yl)propyl]-3-azabicyclo [3.2.1]octan-8-ol hydrochloride salt, Mass (m/z): 472 (M⁺+1); IR (cm⁻¹): 2934, 1657, M.P:189-190°C;

Compound No. 96: 10-(3-[4-[2-(cyclopentyl oxy)phenyl] piperazin-1-yl]propyl)-10H-phenothiazine hydrochloride salt, Mass (m/z): 559 (M⁺+1), M.P: 210-212°C;

Compound No. 100: 10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 460 (M⁺+1); IR (cm⁻¹): 3439, 1459, M.P: 185-190°C;

Compound No. 102: 10-(3-[4-[2-(cyclopentloxy)-5-fluoro phenyl]piperazin-1-yl]propyl)-10H-phenothiazine hydrochloride salt, Mass (m/z): 503 (M⁺+1); IR (cm⁻¹): 3445, 1460, hygroscopic;

Compound No. 104: 10-[3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 478 (M⁺+1); IR (cm⁻¹): 3450, 1459, hygroscopic;
Compound No. 110: 10-(3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl)propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 502 (M^+1); IR (cm^-1): 3413, 2936, M.P.: 90-95 °C;

Compound No. 112: 10-[3-[3-(2-ethoxyphenyl)imidazolidin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 420 (M^+3); IR (cm^-1): 3399, 2922, M.P.: 80-85 °C;

Compound No. 114: 10-[3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine hydrochloride salt, Mass (m/z): 462 (M^+1); IR (cm^-1): 3409, 2935, M.P.: 164-165 °C;

Compound No. 116: 1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H-phenoxazin-10-yl)propan-2-ol hydrochloride salt hydrochloride salt, Mass (m/z): 450 (M^+1), M.P.: 223-225 °C;

Example 5:

Preparation of N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide hydrochloride salt (Compound No. 98)

Step 1: Preparation of N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide

In a dry 10 ml round bottom flask fitted with a stirring bar and guard tube, was placed, 3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-amine, dichloromethane, 4-dimethylamino- pyridine and triethylamine, the resulting solution was cooled in an ice cold bath. To it was added 10H-phenothiazine-10-carbonyl chloride in portions. The reaction mixture was then stirred at room temperature for about 18 hours. The reaction mixture was quenched with saturated sodium carbonate solution. The aqueous layer was extracted in dichloromethane. The combined dichloromethane layer was washed with water and saturated brine solution, then was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

Step 2: Preparation of N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide hydrochloride salt

An equimolar quantity of isopropyl alcohol and hydrochloric acid was added to N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide
A solid precipitated and was then filtered. Mass (m/z): 475 (M+1) ; IR (cm⁻¹): 1674, 2927, M.P: 189.7-190.9°C

The following compounds were prepared similarly:

Compound No. 106: N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine-10-carboxamide hydrochloride salt, Mass (m/z): 458 (M+1) ; IR (cm⁻¹): 1258, 1455, M.P: 204-206 °C;

Compound No. 108: N-[2-(2-methoxybenzoyl)ethyl]-10H-phenoxazine-10-carboxamide hydrochloride salt, Mass (m/z): 376 (M+1), hygroscopic

**Pharmacological testing**

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 α₁a and α₁b adrenoceptor subtypes was evaluated by studying their ability to displace specific [³H] 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% CO₂ at 37°C in DMEM medium supplemented with 10% heat inactivated fetal calf serum, 1mM glutamine, 100U/ml penicillin and 0.1mg/ml streptomycin. Selection pressure was maintained by regular addition of puromycin (3μg/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 polytron homogenizer. The homogenate was centrifuged at 40,000g for 20min 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 α₁-adrenoceptors was performed using [³H] 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 °C for 1 hour. Non-specific binding was determined in the presence of 10μM 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, 1973, 22:3099-3108), $Ki = IC_{50}/(1+L/Kd)$ where L is the concentration of $[^{3}H]$ prazosin used in the particular experiment.


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

a) The compounds described herein exhibited $\alpha_{1a}$ Ki (nM) values of between about 0.5 nM to about 2500 nM, between about 0.5 nM to about 166 nM, between about 0.5 nM to about 89 nM, and even between about 0.5 nM to about 70 nM.

b) The compounds described herein exhibited $\alpha_{1b}$ Ki (nM) values of between about 5 nM to about 1333 nM, between about 5 nM to about 759 nM, and even between about 5 nM to about 100 nM.
We claim:

1. A compound having the structure of the Formula I

\[
\begin{array}{c}
R_1 - A - X_1 R_2 R_3 \\
\text{Formula I}
\end{array}
\]

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

\(X_1\) is N or CR4;

\(R_4\) is hydrogen, hydroxyl or alkyl;

\(A\) is aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR10 or CHR10R11;

\(R_{10}\) and \(R_{11}\) are independently alkyl, COO-alkyl, aryl or heterocyclyl;

\(R_1, R_2\) and \(R_3\) independently in each occurrence are hydrogen, halogen, C1-3 alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, \(R_6\) or \(S(O)_{n \geq 2} R_5\);

\(R_5\) is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

\(R_2\) and \(R_3\) together with \(X_1\) to which they are attached also form a ring of the form

\[
\begin{array}{c}
\text{M}_1 \\
\text{N}_1 \\
\text{W} \\
\text{M}_2 \\
\text{R}_6
\end{array}
\]

which contains one or more additional heteroatom(s) selected from O, S or N;

\(\text{M}_1\) and \(\text{M}_2\) are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or \(\text{M}_1\) and \(\text{M}_2\) together form a bridging group (C0.3);

\(W\) is N, CH or COH;
R₆ is

Y is O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)₃,
S₂R₅ or NHSO₂R₅;

L is a linker; and

• is a point of attachment.

2. A compound selected from:

3-{3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl}-1,2,3-benzotriazin-
4(3H)-one,

Methyl [4-{3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl] piperazin-1-
yl}(phenyl)acetate,

3-{3-[4-{2-(cyclopentoxy)phenyl]piperazin-1-yl}propyl]-1,2,3-benzotriazin-
4(3H)-one,

3-{3-[4-{5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-methyl propyl]-1,2,3-
benzotriazin-4(3H)-one,

3-{3-{4-{2-(cyclopentoxy)-5-fluorophenyl)piperazin-1-yl]-2-methylpropyl}-
1,2,3-
benzotriazin-4(3H)-one,

3-{3-{4-{2-ethoxyphenyl} piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-
4(3H)- one,

3-{2-methyl-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl]-1,2,3-benzotriazin-
4(3H)-one,

3-{3-{4-{2-(cyclopentoxy) phenyl]piperazin-1-yl]-2-methyl propyl]-1,2,3-
benzotriazin-4 (3H)-one,

3-{3-[4-{2-isopropoxyphenyl} piperazin-1-yl]-2-methylpropyl] -1,2,3-
benzotriazin- 4(3H)-one,

3-{3-[3,4-dihydroisoquinolin-2(1H)-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-methoxyphenyl) piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-ethoxyphenyl) piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-propoxyphenyl) piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-isopropoxyphenyl) piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-cyclohexyl)-5-fluorophenyl]piperazin-1-yl} penty1)-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-methoxy phenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[3-(2-methoxyphenyl) imidazolidin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-[5-(6,7-dimethoxy-3,4-dihydro isoquinolin-2(1H)-yl)penty1]-1,2,3-benzotriazin-4(3H)-one,
3-(3-[4-(2-cyclohexyl)-5-fluorophenyl]piperazin-1-yl) propyl)-1,2,3-benzotriazin-4(3H)-one,
3-(3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-1,2,3-benzotriazin-4(3H)-one,
3-(5-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]penty1)-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]penty1}-1,2,3-benzotriazin-4(3H)-one,
3-{5-[3-(4-dihydroisoquinolin-2(1H)-yl)penty1]-1,2,3-benzotriazin-4(3H)-one,
3-[3-[8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl]propyl]-1,2,3-benzotriazin-4(3H)-one,
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]acetamide,
\[ N\text{-}[3\{-[3\{-4\text{-oxo-1,2,3-benzotriazin}-3(4H)\text{-yl}]propyl\}]-3\text{-azabicyclo}[3.1.0]hex-6-yl} \text{benzamide,} \]

\[ N\text{-}[3\{-[3\{-4\text{-oxo-1,2,3-benzotriazin}-3(4H)\text{-yl}]propyl\}]-3\text{-azabicyclo}[3.1.0]hex-6-yl} \text{tetrahydrofuran-2-carboxamide,} \]

\[ 3\{-[3\{-4\{-5\text{-fluoro-2-propoxy phenyl}\}piperazin-1-yl\}]-2\text{-hydroxypropyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 3\{-[3\{-4\{-2\{-cyclopentyl-oxy\} phenyl\}piperazin-1-yl\}]-2\text{-hydroxypropyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 3\{-[2\text{-hydroxy-3}\{-4\{-2\{-prooxy phenyl\}piperazin-1-yl\}propyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 3\{-[2\text{-hydroxy-3}\{-4\{-2\{-methoxy phenyl\}piperazin-1-yl\}propyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 3\{-[2\text{-hydroxy-3}\{-4\{-2\{-isopropoxyphenyl\}piperazin-1-yl\}propyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 3\{-[2\text{-hydroxy-3}\{-4\{-2\{-methoxy phenyl\}piperazin-1-yl\}propyl\}]-1,2,3-benzotriazin-4(3H)\text{-one,} \]

\[ 10\{-[3\{-4\{-2\{-methoxyphenyl\}piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-methoxyphenyl\}piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-prooxyphenyl\}piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-isopropoxy phenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-fluoro-6\{-methoxy phenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-fluoro-6\{-isopropoxy phenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-cyclopentyl-oxy\} -6\{-fluoro phenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-3\{-2\{-methoxyphenyl\} imidazolidin-1-yl\}propyl\}]-10H\text{-phenoxazine,} \]

\[ 10\{-[3\{-4\{-2\{-ethoxyphenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenothiazine,} \]

\[ 10\{-[3\{-4\{-2\{-isopropoxy phenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenothiazine,} \]

\[ 10\{-[3\{-4\{-2\{-methoxyphenyl\} piperazin-1-yl\}propyl\}]-10H\text{-phenothiazine,} \]

\[ 8\{-2\{-methoxyphenyl\}\{-3\{-10H\{-phenothiazin-10-yl\}propyl\}]-3\text{-azabicyclo} \]

\[ 3.2.1]octan-8\{-ol, \]
10-(3-[4-[2-(cyclopentyloxy)phenyl]piperazin-1-yl]propyl)-10H-phenothiazine,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine-10-carboxamide,

10-[3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenothiazine,

10-(3-[4-[2-(cyclopentyloxy)-5-fluoro phenyl]piperazin-1-yl]propyl)-10H-phenothiazine,

10-[3-[4-(5-fluoro-2-isopropoxyphenyl) piperazin-1-yl]propyl]-10H-phenothiazine,

N-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine-10-carboxamide,

N-[2-(2-methoxyphenoxy)ethyl]-10H-phenoxazine-10-carboxamide,

10-(3-[4-[5-floro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-10H-phenoxazine,

10-[3-[3-(2-ethoxyphenyl)imidazolidin-1-yl]propyl]-10H-phenothiazine,

10-[3-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]propyl]-10H-phenoxazine,

1-[4-(5-fluoro-2-methoxyphenyl) piperazin-1-yl]-3-(10H-phenoxazin-10-yl)propan-2-ol,

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, prodrugs, stereoisomers, tautomeric forms, N-oxides and metabolites thereof.
3. A compound selected from:

3-{3-[4-hydroxy-4-(2-methoxy phenyl)piperidin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

Methyl 4-{3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl] piperazin-1-yl}(phenyl)acetate hydrochloride salt,

3-{3-[4-{2-(cyclopentyoxy) phenyl}piperazin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{3-[4-{5-fluoro-2-isopropoxy phenyl}piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{3-[4-{2-(cyclopentyoxy)-5-fluorophenyl}piperazin-1-yl]-2-methylpropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{3-[4-{2-ethoxyphenyl} piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{2-methyl-3-[4-{2-propoxy phenyl}piperazin-1-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{3-[4-{2-(cyclopentyoxy) phenyl}piperazin-1-yl]-2-methyl propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{3-[4-{2-isopropoxyphenyl} piperazin-1-yl]-2-methylpropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-[3-[3,4-dihydroisoquinolin-2(1H)-yl]propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-{2-methoxyphenyl} piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-{2-ethoxyphenyl} piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-{2-propoxyphenyl} piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-{2-isopropoxyphenyl} piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{5-[4-{5-fluoro-2-isopropoxy phenyl}piperazin-1-yl]penty]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,
3-(5-[4-(3-fluorobenzyl)-5-methyl-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-[4-(4-fluoro-2-methoxy phenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-[3-(2-methoxyphenyl) imidazolidin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-(6,7-dimethoxy-3,4-dihydro isoquinolin-2(1H)-yl)pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-(3-[4-(2-cyclopentyl)-5-fluorophenyl]piperazin-1-yl) propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-(3-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl) propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-(5-[4-(5-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-[4-(5-fluoro-2-propoxyphenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-[4-(2-ethoxy-5-fluorophenyl)piperazin-1-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[5-[3,4-dihydroisoquinolin-2(1H)-yl]pentyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-[3-(8-hydroxy-8-(2-methoxy phenyl)-3-azabicyclo[3.2.1]oct-3-yl)propyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]acetamide hydrochloride salt,  
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]benzamide hydrochloride salt,  
N-[3-[3-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)propyl]-3-azabicyclo[3.1.0]hex-6-yl]tetrahydrofuran-2-carboxamide hydrochloride salt,  
3-[3-[4-(5-fluoro-2-isopropoxy phenyl)piperazin-1-yl]-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,  
3-(3-[4-(2-cyclopentyl)-5-fluorophenyl]piperazin-1-yl)-2-hydroxypropyl]-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,
3-{2-hydroxy-3-[4-(2-propoxy phenyl)piperazin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{2-hydroxy-3-[4-(2-methoxy phenyl)piperazin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

3-{2-hydroxy-3-[4-(2-isoproxyphenyl)piperazin-1-yl]propyl}-1,2,3-benzotriazin-4(3H)-one hydrochloride salt,

10-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-propoxyphenyl)piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-isoproxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-fluoro-6-methoxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-fluoro-6-isoproxy phenyl) piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-cyclopentyloxy)-6-fluoro phenyl]piperazin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[3-(2-methoxyphenyl) imidazolidin-1-yl]propyl}-10H-phenoxazine hydrochloride salt,

10-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine hydrochloride salt,

10-{3-[4-(2-isoproxy phenyl) piperazin-1-yl]propyl}-10H-phenothiazine hydrochloride salt,

10-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-10H-phenothiazine hydrochloride salt,

8-(2-methoxyphenyl)-3-[3-(10H-phenothiazin-10-yl)propyl]-3-azabicyclo[3.2.1]octan-8-ol hydrochloride salt,

10-{3-[4-(2-cyclopentyloxy)phenyl] piperazin-1-yl]propyl}-10H-phenothiazine hydrochloride salt,
4. A pharmaceutical composition comprising a therapeutically effective amount of
one or more compounds having the structure of the Formula I

\[ R_1^-A \rightarrow X_1 R_2 R_3 \]

Formula I

wherein:

- \( R_1 \) is a pharmaceutically acceptable salt, pharmaceutically acceptable solvate,
- polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof,
- together with one or more pharmaceutically acceptable carriers, excipients or
diluents, wherein:

\( X_1 \) is N or CR₄;
R₄ is hydrogen, hydroxyl or alkyl;

A is aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR₁₀ or CHR₁₀R₁₁;

R₁₀ and R₁₁ are independently alkyl, COO-alkyl, aryl or heterocyclyl;

R₁, R₂ and R₃ independently in each occurrence are hydrogen, halogen, C₁₋₃ alkyl,
alkoxy, alkyl, nitro, cyano, cycloalkoxy, R₆ or S(O)ₓR₅;

R₅ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

R₂ and R₃ together with X₁ to which they are attached also form a ring of the form

which contains one or more additional heteroatom(s) selected from O, S or N;

M₁ and M₂ are independently hydrogen, halogen, hydroxyl, amino, nitro,
cyano, alkyl, alkoxy or acyl; or M₁ and M₂ together form a bridging group
(C₀₋₃);

W is N, CH or COH;

R₆ is

Y is O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)ₓR₅;

₂R₅ or NH.SO₂R₅;

L is a linker; and

• is a point of attachment.
5. A method for treating 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 compound having the structure of the Formula I

$$R_1 - A - X_1 R_2 R_3$$

Formula I

a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof, or a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds having the structure of the Formula I, wherein

$X_1$ is N or CR$_4$;

$R_4$ is hydrogen, hydroxyl or alkyl;

$A$ is aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CHR$_{10}$R$_{11}$;

$R_{10}$ and $R_{11}$ are independently alkyl, COO-alkyl, aryl or heterocyclyl;

$R_1$, $R_2$ and $R_3$ independently in each occurrence are hydrogen, halogen, C$_{1-3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R$_6$ or S(O)$_{0-2}$R$_5$;

$R_5$ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

$R_2$ and $R_3$ together with $X_1$ to which they are attached also form a ring of the form

$$\begin{array}{c}
\text{M}_1 \\
\text{X}_1 \\
\text{M}_2 \\
\text{W} \\
\text{R}_6
\end{array}$$

which contains one or more additional heteroatom(s) selected from O, S or N;

$M_1$ and $M_2$ are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or $M_1$ and $M_2$ together form a bridging group (C$_{0-3}$);

$W$ is N, CH or COH;
24 R₆ is

Y is O, S, NR₄, C=O or a bond;

R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)₂

₂R₅ or NHSO₂R₅;

L is a linker; and

* is a point of attachment.

6. The method according to claim 5, wherein a disease or disorder is benign prostatic hyperplasia or lower urinary tract symptoms.

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

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

\[
\begin{align*}
R & \longrightarrow W \\
X & \longrightarrow A \\
M₁ & \longrightarrow R₁ \\
M₂ & \longrightarrow X₁
\end{align*}
\]

Formula VI

a pharmaceutically acceptable salt, pharmaceutically acceptable solvate,

polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof,

comprising the steps of:

(a) reacting the compound of Formula II

\[
\begin{align*}
R & \longrightarrow H \\
\text{Formula II}
\end{align*}
\]

with a compound of Formula III (wherein X₂ and X₃ are leaving groups)
X₂ — L — X₃
Formula III

to form a compound of Formula IV

R — L — X₃
Formula IV

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

![Diagram]

M₁ and M₂ are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or M₁ and M₂ together form a bridging group (C₀₃);

W is N, CH or COH;
28 R is

or

29 Y is O, S, NR₄, C=O or a bond;

30 R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)ₓR₅ or NHSO₃R₅; and

33 L is a linker.

9. A method for preparing a compound of Formula IX,

\[
\begin{array}{c}
R \quad \text{OH} \\
\text{Formula IX}
\end{array}
\]

a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof, comprising the steps of:

(a) reacting the compound of Formula II

\[
\begin{array}{c}
R \quad \text{H} \\
\text{Formula II}
\end{array}
\]

with a compound of Formula VII (wherein X₃ is a leaving group)

\[
\begin{array}{c}
\text{X}_3 \\
\text{Formula VII}
\end{array}
\]

9 to form a compound of Formula VIII
(b) treating the compound of Formula VIII with a compound of Formula V

to form a compound of Formula IX,

wherein,

\( X_1 \) is N or CR₄;

\( R_4 \) is hydrogen, hydroxyl or alkyl;

\( A \) is aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR₁₀ or CHR₁₀R₁₁;

\( R_{10} \) and \( R_{11} \) are independently alkyl, COO-alkyl, aryl or heterocyclyl;

\( R_1 \) is hydrogen, halogen, C₁-₃ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, \( R_6 \) or S(O)₀₋₂R₅;

\( R₅ \) is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl; and

\( R₆ \) is

\[ \text{or} \]

\( M_1 \) and \( M_2 \) are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or \( M_1 \) and \( M_2 \) together form a bridging group (C₀₋₃);

\( W \) is N, CH or COH;
R is

Y is O, S, NR₄, C=O or a bond; and

R₇, R₈ and R₉ are independently hydrogen, hydroxyl, amino, S(O)₂R₅ or NHSO₂R₅.

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

\[
\text{Formula XIV}
\]

a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite thereof, comprising the steps of:

(a) reacting the compound of Formula V(a) with a compound of Formula X (wherein X₅ is alkenyl or halogen)

\[
\text{Formula V(a)}
\]

(Formula V, wherein W=N)

\[
\text{Formula X}
\]

\[
\text{Formula XI}
\]


(b) reducing the compound of Formula XI to form a compound of Formula XII

(c) reacting the compound of Formula XII with a compound of Formula XIII

to form a compound of Formula XIV,

wherein,

$X_1$ is $N$ or $CR_4$;

$R_4$ is hydrogen, hydroxyl or alkyl;

$A$ is aryl, aryloxy, heterocycl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CHR$_{10}$R$_{11}$;

$R_{10}$ and $R_{11}$ are independently alkyl, COO-alkyl, aryl or heterocycl;

$R_1$ is hydrogen, halogen, C$_{1-3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, $R_6$ or S(O)$_{0-2}$R$_5$;

$R_5$ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocycl;

$R_6$ is

$M_1$ and $M_2$ are independently hydrogen, halogen, hydroxyl, amino, nitro, cyano, alkyl, alkoxy or acyl; or $M_1$ and $M_2$ together form a bridging group (C$_{0-3}$); and

$Y$ is O, S, NR$_4$, C=O or a bond;
11. A method for preparing a compound of Formula XX,

![Formula XX]

2 a pharmaceutically acceptable salt, pharmaceutically acceptable solvate,
3 polymorph, prodrug, stereoisomer, tautomeric form, N-oxide or metabolite
4 thereof, comprising the steps of:
5 (a) reacting the compound of Formula X

![Formula XV]

6 with a compound of Formula VII

![Formula XVI]

7 to form a compound of Formula XVII

![Formula XVII]

8 (b) treating the compound of Formula XVII with a hydrazine hydrate to form a
9 compound of Formula XVIII, and
10
11
12
13
14
treating the compound of Formula XVIII with a compound of Formula XIX
to form a compound of Formula XX,

wherein,

A is aryl, aryloxy, heterocyclyl, alkyl, alkoxy, cycloalkyl, NHCOR$_{10}$ or CHR$_{10}$R$_{11}$;

R$_{10}$ and R$_{11}$ are independently alkyl, COO-alkyl, aryl or heterocyclyl;

R$_1$ is hydrogen, halogen, C$_{1-3}$ alkyl, alkoxy, alkyl, nitro, cyano, cycloalkoxy, R$_6$ or S(O)$_{0-2}$R$_5$;

R$_5$ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or heterocyclyl;

R$_6$ is

Y is O, S, NR$_4$, C=O or a bond; and

n is an integer of from 0 to 5.
### INTERNATIONAL SEARCH REPORT

**PCT/IB2006/051392**

#### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC.

#### B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic databases consulted during the International search (name of database and, where practical, search terms used)

EPO-Internal, EMBASE, BEILSTEIN Data, WPI Data

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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**X** Further documents are listed in the continuation of Box C.

**X** See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

**"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**"** document member of the same patent family

Date of the actual completion of the international search

18 September 2006

Date of mailing of the international search report

06/10/2006

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer

SAHAGUN KRAUSE, H
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<td>X</td>
<td>CALIENDO G ET AL: &quot;Synthesis of new 1,2,3-benzotriazin-4-one-arylpiperazine derivatives as 5-HT(1A) serotonin receptor ligands&quot; BIOORGANIC AND MEDICINAL CHEMISTRY 2000 UNITED KINGDOM, vol. 8, no. 3, 2000, pages 533-538, XP002396680 ISSN: 0968-0896 pages 534-535, paragraph 2; tables 1-3</td>
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<td>WO 02/44151 A (RANBAXY LABORATORIES LIMITED; ANAND, NITYA; JAIN, SANJAY; SINHA, NEELI) 6 June 2002 (2002-06-06) Claim 1 and examples in pages 16-17, Tables I-III (page 21)</td>
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<td>GB 1 280 941 A (CASSELLA FARBWERKE MAINKUR AKTIENGESELLSCHAFT) 12 July 1972 (1972-07-12) page 4, column 2, line 105 - page 6 page 1, column 2, line 65 - page 2, column 1, line 7</td>
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<td>X</td>
<td>CALIENDO G ET AL: &quot;Synthesis by microwave irradiation and binding properties of novel 5-HT1A receptor ligands&quot; EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 36, no. 11-12, November 2001 (2001-11), pages 873-886, XP004400908 ISSN: 0223-5234 page 877 - page 879; tables 1,2</td>
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|                 |                 | IT 1031004 B            | 30-04-1979      |
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