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(54) Title: BENZODIOXAN ANALOGUES AS ALPHA2C ADRENERGIC RECEPTOR MODULATORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of benzodioxan analogues as modulators of the  $\alpha$ 2C adrenergic receptor, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more conditions associated with the  $\alpha$ 2C adrenergic receptors using such compounds or pharmaceutical compositions.

**Benzodioxan Analogues As Alpha2C Adrenergic Receptor Modulators****Related Applications**

5 This application claims benefit of U.S. provisional application Ser. No. 61/103,401, filed October 7, 2008, herein incorporated by reference.

**Field of the Invention**

The present invention relates to benzodioxan analogues useful as alpha-2C (or "a2C") adrenergic receptor modulators, methods for making these compounds, 10 pharmaceutical compositions containing the compounds, and methods of treatment and prevention using the compounds and compositions to treat disease states associated with the modulation of the alpha-2C receptor, such as congestion (including nasal), migraine, congestive heart failure, cardiac ischemia, glaucoma, stress-induced urinary incontinence, Alzheimer's disease, Parkinson's disease, 15 attention deficit hyperactivity disorder, pain and psychotic disorders (e.g., depression and schizophrenia).

**Background of the Invention**

The initial classification of adrenergic receptors into  $\alpha$ - and  $\beta$ -families was first 20 described by Ahlquist in 1948 (Ahlquist RP, "A Study of the Adrenergic Receptors," Am. J. Physiol. 153:586-600 (1948)). Functionally, the  $\alpha$ -adrenergic receptors were shown to be associated with most of the excitatory functions (vasoconstriction, stimulation of the uterus and pupil dilation).  $\beta$ -adrenergic receptors were implicated in vasodilation, bronchodilation and myocardial stimulation (Lands et al., "Differentiation 25 of Receptor Systems Activated by Sympathomimetic amines," Nature 214:597-598 (1967)). Since this early work,  $\alpha$ -adrenergic receptors have been subdivided into  $\alpha_1$  - and  $\alpha_2$ -adrenergic receptors. Cloning and expression of  $\alpha$ -adrenergic receptors have confirmed the presence of multiple subtypes of both  $\alpha_1$  -( $\alpha_{1A}$ ,  $\alpha_{1B}$ ,  $\alpha_{1D}$ ) and  $\alpha_2$ -( $\alpha_{2A}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$ ) adrenergic receptors (Michel et al., "Classification of  $\alpha_1$  -Adrenoceptor 30 Subtypes," Naunyn-Schmiedeberg's Arch. Pharmacol. 352:1-10 (1995); Macdonald et al., "Gene Targeting--Homing in on  $\alpha_2$ -Adrenoceptor-Subtype Function," TIPS, 18:211-219 (1997)).

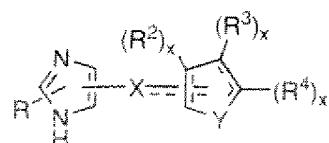
Current therapeutic uses of  $\alpha$ -2 adrenergic receptor drugs involve the ability of

those drugs to mediate many of the physiological actions of the endogenous catecholamines. There are many drugs that act on these receptors to control hypertension, intraocular pressure, eye reddening and nasal congestion and induce analgesia and anesthesia.

- 5        $\alpha_2$  adrenergic receptors can be found in the rostral ventrolateral medulla, and are known to respond to the neurotransmitter norepinephrine and the antihypertensive drug clonidine to decrease sympathetic outflow and reduce arterial blood pressure (Bousquet et al., "Role of the Ventral Surface of the Brain Stem in the Hypotensive Action of Clonidine," Eur. J. Pharmacol., 34:151-156 (1975); Bousquet et al.,  
10      "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Clonidine and other imidazolines also bind to imidazoline receptors (formerly called imidazoline-guanidinium receptive sites or IGRS) (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Some researchers have speculated that the central and peripheral effects of imidazolines as  
15      hypotensive agents may be related to imidazoline receptors (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995); Reis et al., "The Imidazoline Receptor: Pharmacology, Functions, Ligands, and Relevance to Biology and Medicine," Ann. N.Y. Acad. Sci., 763:1-703 (1995)).

Compounds having adrenergic activity are well-known in the art and are  
20      described in numerous patents and scientific publications. It is generally known that adrenergic activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having an adrenergic compound or compounds as the active ingredient  
25      are useful for treating, among other things, glaucoma, chronic pain, migraines, heart failure, and psychotic disorders (e.g., schizophrenia).

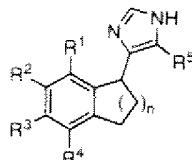
For example, published PCT application WO 02/076950 discloses compounds having  $\alpha_2$  agonist activity of the following general formula:



Other publications disclosing similar compounds includes WO 01/00586, WO 99/28300, US 6,841,684 B2 and US 2003/0023098 A1.

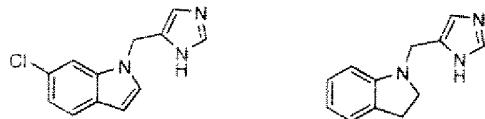
Another class of compounds having  $\alpha_2$ -agonist properties is disclosed in U.S. Patent No. 5,658,938, and has the following general formula:

5



wherein  $n=1-2$ ,  $R^1-R^3$  represent hydrogen, halogen hydroxy, alkyl or alkoxy, and  $R^5$  is hydrogen or alkyl.

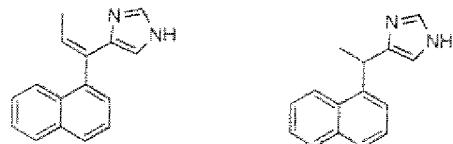
Another class of compounds reported to have affinity for  $\alpha_2$  receptors includes  
10 the following two compounds (Bagley et.al., *Med. Chem. Res.* 1994, **4**:346-364):



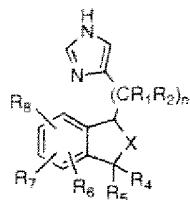
It is also known that compounds having adrenergic activity, such as  $\alpha_2A$   
agonists, may be associated with undesirable side effects. Examples of such side  
15 effects include hyper-and hypotension, sedation, locomotor activity, psychotic  
disorders (e.g., schizophrenia).

Another class of compounds reported to have affinity for  $\alpha_2$  receptors includes  
the following two compounds (Miller et.al., *J. Med. Chem.* 1994, **37**:2328-2333; *J. Med.*  
*Chem.* 1996, **39**:3001-3013; *J. Med. Chem.* 1997, **37**:3014-3024):

20

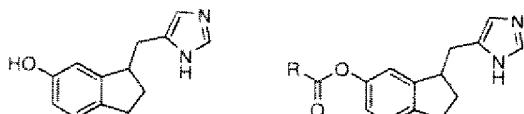


Another class of indane and tetrahydronaphthalene type compounds having  $\alpha_2$ -agonist properties is disclosed in PCT application WO 97/12874 and WO20040506356. This class has the following general formula:



wherein n = 0-1, X is 1 or 2 carbon units, R<sub>4</sub> is H, OH, alkyl, or alkoxy, R<sub>5</sub> may be taken together with R<sup>4</sup> to form a carbonyl, and R<sup>6</sup>-R<sup>8</sup> = H, OH, SH, alkyl, alkenyl, cycloalkyl, alkoxy, hydroxyalkyl, alkylthio, alkylthiol, halo, CF<sub>3</sub>, NO<sub>2</sub>, or alkylamino. This class

5 specifically includes MPV-2426 (fadolmidine) and its prodrug esters:



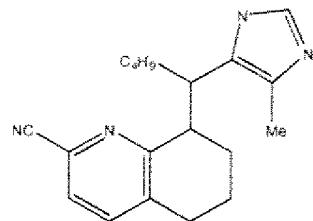
wherein R is optionally substituted lower alkyl, aryl, cycloalkyl, heteroaryl, lower alkylamino, and saturated 5- or 6-membered heterocyclic groups containing 1 or 2 N atoms.

10 Further, other classes of compounds that exhibit functional selectivity for the alpha 2C receptor have been discovered. Application USSN 11/508,458, filed August 23, 2006 and published as US 2007/0099872 A1, discloses indoline compounds that possess this activity and application USSN 11/508,467, filed on the same date and published as US 2007/0093477 A1, describes morpholine compounds that are  
15 functionally selective of the alpha 2C receptor. CIP applications of these applications have been filed; the Ser. Nos. are 11/705,673 and 11/705,683, both filed on February 13, 2009 and published as US 2008/039439 A1 and US 2008/0027100 A1 respectively.

Additional applications that have been filed by Schering-Plough and disclose  
20 alpha2C receptor agonists include applications WO 2008/100480 (PCT/US2008/001808); WO 2008/100459 (PCT/US2008/001770) and WO 2008/100456 (PCT/US2008/001765).

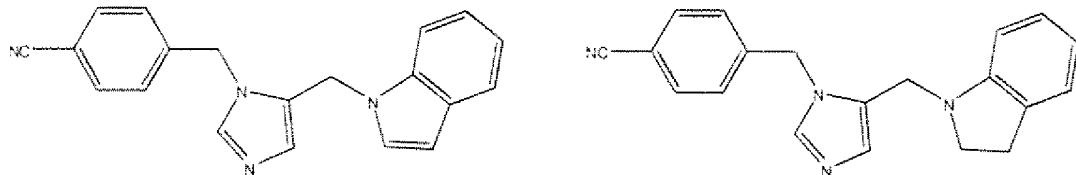
Allergan has three published patent applications that describe methylimidazole derivatives that are said to be useful in treating disease states such as glaucoma,  
25 ocular hypertension and congestion. These published applications are: WO 2008/086131 ("Naphthylimidazoles as Therapeutic agents"); WO 2008/088936 ("Quinolynylimidazoles as Therapeutic Agents") and WO 2008/088937

(“Quinolynylmethylimidazoles as Therapeutic Agents”). WO 2008/088936 discloses the following compound:



5 WO 2008/052907 to Hoffmann – La Roche describe substituted 2-imidazoles as modulators of the trace amine associated receptors.

US Patent 5,977,134 to Ciccarone *et al.* describe peptidomimetic 1,2,3,4-tetrahydroisoquinolines and homologous compounds which inhibit farnesyl-protein transferase (see, Summary of the Invention). Homologues includes 5-imidazolylmethyl indole or 5-imidazolylmethyl indoline derivatives, such as, for example the following compounds:



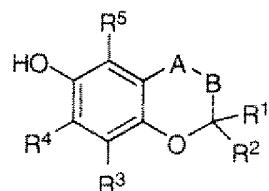
15 U.S. Patent 7,399,868 to Allegra describe 4-(heteroaryl-methyl and 4-substituted heteroyl – methyl)-imidazole -2-thimes that are said to act as agonists of the  $\alpha$ 2C receptor.

Compounds that act as antagonists of the alpha-2C receptor are also known in the art. Hoeglund *et al.* describe quinoline derivatives that are said to be potent and 20 selective alpha 2C antagonists and said to be useful in treating “certain psychiatric disorders such as depression and schizophrenia” (Hoeglund *et al.*, J. Med. Chem. 49:6351-6363 (2006)). WO 2001/64645 to Orion Corp. also describes quinoline derivatives that are alpha-2C receptor antagonists and indicates that these compounds are useful for the treatment of conditions of the peripheral or CNS system, including 25 treating depression, anxiety, post traumatic stress disorder, schizophrenia, Parkinson’s disease and other movement disorders, and dementias (e.g., Alzheimer’s disease).

WO 2003/082825, also to Orion Corp., indicates alpha-2C receptor antagonists have utility in treating symptoms of disorders and conditions with sensorimotor-gating deficits. Selliner *et al.*, indicate that acridin-9-yl-[4-(4-methylpiperazinal-1-yl)-phenyl]amine is a highly selective alpha-2C adrenergic receptor antagonist and may be useful in treating neuropsychiatric disorders (Selliner *et al.*, British J. Pharmacol. 150:391-402 (2007)).

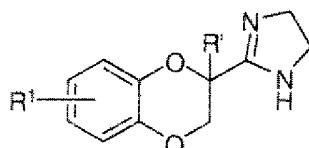
It is also known that compounds having adrenergic activity, such as α2A agonists, may be associated with undesirable side effects. Examples of such side effects include hyper- and hypotension, sedation, locomotor activity, and body temperature variations.

WO 2006/044556 to Gallileo Pharmaceuticals discloses dual lipoxygenase inhibitors of the formula:



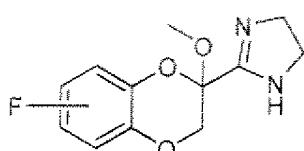
wherein A-B is -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>0-2-</sub> or -CH=CH-. These compounds are used to treat diabetes.

Gentili *et al.* disclose α<sub>2</sub> adreneroreceptors antagonists of the formula:



wherein R' is phenyl. Gentile *et al.*, J. Med. Chem 51:4289-4299 (2008).

US 6,610,725 to Pierre Fabre Medicament discloses fluorinated imidazoline benzodioxanes compounds such as the following:



This compound is said to possess α2 antagonistic activity.

U.S. Patent 6,673,337 describes and claims an ophthalmic composition comprising an alpha-2C agonist component and a solubility enhancing component

other than cyclodextrin. The patent does not specifically describe alpha-2C receptor agonists.

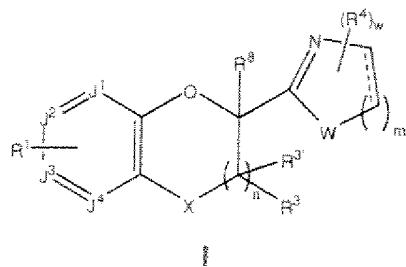
It has been discovered in accordance with the present invention that the inventive compounds act as modulators of the alpha-2C receptor (i.e., they can act 5 as alpha-2C receptor agonists or as alpha-2C receptor antagonists) and are useful in treating disorders modulated by the alpha-2C receptor.

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with  $\alpha$ 2C adrenergic receptors. Further, there is a need for alpha-2C receptor modulators that minimize adverse side effects, such as 10 those associated with the alpha-2A receptor subtype (*viz.*, blood pressure or sedation). It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

#### Summary of the Invention

15 In its many embodiments, the present invention provides a novel class of heterocyclic compounds that are modulators of the  $\alpha$ 2C adrenergic receptor, or metabolites, stereoisomers, salts, solvates or polymorphs thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one 20 or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more conditions associated with  $\alpha$ 2C receptors using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or metabolites, solvates, prodrugs or polymorphs of said compound, said 25 compound having the general structure shown in Formula



wherein:

$J^1$ ,  $J^2$ ,  $J^3$  and  $J^4$  are independently -N-, -N(O)-, or -C( $R^2$ )-;

X is -C( $R^6$ )( $R^6$ )-, -N( $R^6$ )-, -O- or -S-;

W is -N( $R^{14}$ )-, -O- or -S-;

— is a single or double bond, provided that there cannot be two continuous  
5 double bonds;

$R^1$  is a ring selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocyclil, heterocyclenyl, and heteroaryl, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3)  $R^{12}$ ;

$R^2$  is absent or independently selected from the group consisting of H,

10 halo, -CN, -NO<sub>2</sub>, -OH, -SF<sub>5</sub>, -OSF<sub>5</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -[C( $R^a$ )( $R^b$ )]<sub>q</sub>YR<sup>7</sup>, -

[C( $R^a$ )( $R^b$ )]<sub>q</sub>N( $R^7$ )YR<sup>7</sup>, -[C( $R^a$ )( $R^b$ )]<sub>q</sub>N( $R^7$ )CN, -[C( $R^a$ )( $R^b$ )]<sub>q</sub>OYR<sup>7</sup>, and -

(CH<sub>2</sub>)<sub>q</sub>ON=CR<sup>7</sup>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl,

cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclil, and

heterocyclalkyl groups optionally substituted with at least one (preferably 1 to 5,

15 more preferably 1 to 3)  $R^5$ ;

Y is selected from the group consisting of a bond, -C(=O)-, -C(=O)NR<sup>7</sup>-,  
-C(=O)O-, -C(=O)N( $R^9$ )-O-, -C(=NR<sup>7</sup>)-, -C(=NOR<sup>7</sup>)-, -C(=NR<sup>7</sup>)NR<sup>7</sup>-, -C(=NR<sup>7</sup>)NR<sup>7</sup>O-, -  
C(=N-CN)-, -S(O)<sub>p</sub>-, -SO<sub>2</sub>NR<sup>7</sup>-, and -C(=S)NR<sup>7</sup>-;

wherein  $R^a$  and  $R^b$  are independently selected from the group consisting

20 of H, alkyl, alkoxy, and halo, and

$R^c$  is H or alkyl;

$R^3$  is independently selected from the group consisting of H, -OH,

halo, -CN, -NO<sub>2</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup> and -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, and alkyl, alkoxy, alkenyl,

alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl,

25 heteroarylalkyl, heterocyclil, and heterocyclalkyl groups optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3)  $R^5$ ;

$R^3'$  is independently selected from the group consisting of H, -OH, halo, and

alkyl, and alkoxy; or

$R^3$  and  $R^3'$  may be taken together to form (=O), provided that when n >

30 1, there are no more than 1 (=O) groups;

$R^4$  is independently selected from the group consisting of H, -OH,

halo, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>7</sup>, -C(O)-OR<sup>7</sup>,

-C(O)-NR<sup>7</sup>, and (=O), and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) R<sup>6</sup>;

- 5 R<sup>5</sup> is independently selected from the group consisting of H, halo, -OH, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O) groups,
- 10 R<sup>6</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, and -C(O)-N(R<sup>7</sup>)R<sup>10</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O) groups, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;
- 15 R<sup>6</sup> is independently selected from the group consisting of H, -S(O)<sub>p</sub>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, -C(O)-N(R<sup>7</sup>)R<sup>10</sup> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O) groups substituents, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>; or
- 20 when X is -C(R<sup>6</sup>)(R<sup>6</sup>'), R<sup>6</sup> and R<sup>6</sup>' taken together can form (=O);
- 25 R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R<sup>12</sup>;

R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloenyl, cyclocycloenylalkyl, aryl, aryalkyl, heterocycl, heterocyclalkyl, heterocycenyl, heterocycloenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times

5 (preferably 1 to 5, more preferably 1 to 3) by R<sup>12</sup>; or

a) when a variable is -NR<sup>7</sup>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup> or -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>, R<sup>7</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached independently form a 3- to 8-membered heterocycl, heterocycenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms independently selected from the group consisting of O, N, -N(R<sup>9</sup>)- and S, wherein said rings are optionally substituted by 1 to 5 independently selected R<sup>12</sup> moieties and/or 1 or 2 (=O) groups, or

b) when a variable is -(CH<sub>2</sub>)<sub>q</sub>ON=CR<sup>7</sup>R<sup>7</sup>, R<sup>7</sup> and R<sup>7</sup> together with the carbon atom to which they are attached independently form a 3- to 8-membered cycloalkyl, cycloalkenyl, aryl, heterocycl, heterocycenyl or heteroaryl ring, wherein said heterocycl, heterocycenyl or heteroaryl rings have 1-3 heteroatoms which are independently selected from the group consisting of O, N, -N(R<sup>9</sup>)- and S, wherein said rings are optionally substituted by 1 to 5 independently selected R<sup>12</sup> moieties and/or 1 or 2 (=O) groups,

10 R<sup>8</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycl, and heterocyclalkyl groups optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) R<sup>5</sup>;

15 R<sup>9</sup> is independently selected from the group consisting of H, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, and -S(O)<sub>p</sub>-R<sup>10</sup> and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aryalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> substituents and/or 1 or 2 (=O) groups; and

20 R<sup>10</sup> is independently selected from the group constituting of H, and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1

to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> substituents and/or 1 or 2 (=O);

R<sup>11</sup> is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl,

- 5 heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent (preferably 1 to 5, more preferably 1 to 3) independently selected from the group consisting of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O) groups;

R<sup>11</sup> is independently selected from the group consisting of H, alkyl, alkoxy,

- 10 alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R<sup>12</sup> is independently selected from the group consisting of H, halo, -

OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, -C(O)-OR<sup>13</sup>, -C(O)-R<sup>13</sup>, -N(R<sup>13</sup>)-C(O)-R<sup>13</sup>, -N(R<sup>13</sup>)-C(O)<sub>2</sub>-R<sup>13</sup>, -C(O)-N(R<sup>11</sup>)<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -N(R<sup>11</sup>)-S(O)<sub>2</sub>-R<sup>11</sup>, -S(O)<sub>2</sub>-N(R<sup>11</sup>)<sub>2</sub> and -S(O)<sub>p</sub>R<sup>11</sup> and/or

- 15 1 or 2 (=O) groups, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least

- 20 once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyl, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O) groups, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyl when substituted are substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R<sup>11</sup>;

R<sup>13</sup> is independently H, alkyl, or aryl;

- 30 R<sup>14</sup> is selected from the group consisting of H, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, -C(O)-N(R<sup>7</sup>)(R<sup>7</sup>), and -S(O)<sub>p</sub>-R<sup>10</sup>, SO<sub>2</sub>-NR<sup>7</sup>R<sup>7</sup> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one

(preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> and/or 1 or 2 (=O) groups substituents, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;

q is independently an integer from 0-10;

5 n is 1 or 2;

m is an integer from 1-3;

p is independently an integer from 0-2; and

w is independently an integer from 0-6,

provided that when X is O and W is NH, m is 1 and n is 1, then R<sup>1</sup> cannot be phenyl.

10 The compounds of Formula I can be useful as α2C adrenergic receptor modulators and can be useful in the treatment or prevention of one or more conditions associated with the α2C receptor by administering at least one compound of Formula I to a mammal in need of such treatment. Conditions that may be treated by modulating the α2C receptor include allergic rhinitis, congestion (including congestion associated 15 with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis, congestion caused by polyps, or caused by the common cold), pain (e.g., neuropathy, inflammation, arthritis, or diabetes), diarrhea, glaucoma, congestive heart failure, chronic heart failure, cardiac ischemia, manic disorders, depression, anxiety, 20 migraine, stress-induced urinary incontinence, neuronal damage from ischemia, schizophrenia, attention deficit hyperactivity disorder, symptoms of diabetes, post traumatic stress disorder, Parkinson's disease or a dementia (e.g., Alzheimer's disease).

Another embodiment of this invention is the treatment or prevention of one or 25 more conditions associated with the α2C receptor by administering at least one compound of Formula I to a mammal in need of such treatment by selectively modulating α2C adrenergic receptors in the mammal.

Another embodiment of this invention is the treatment or prevention of one or more conditions associated with the α2C receptor by administering an effective 30 amount at least one compound of Formula I to a mammal in need of such treatment without modifying blood pressure at the therapeutic dose.

Another embodiment of the present invention is a method for selectively modulating  $\alpha_2C$  adrenergic receptors in a cell in a mammal in need thereof, comprising contacting said cell with a therapeutically effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt, ester, prodrug or salt thereof.

Another embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof without modifying the blood pressure at therapeutic doses which comprises administering to the mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a selective agonist of the  $\alpha_2C$  receptor.

#### Detailed Description

In an embodiment, the present invention discloses certain spiroaminooxazoline derivatives, which are represented by structural Formula I, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

- 15 In another embodiment,  $J^1$ ,  $J^2$ , and  $J^3$  are each  $-C(R^2)-$ .
- 20 In another embodiment,  $J^2$ ,  $J^3$  and  $J^4$  are each  $-CH-$ .
- 25 In another embodiment,  $J^2$  and  $J^3$  are  $-CH-$  and  $J^1$  is  $-N-$ .
- 30 In another embodiment,  $J^2$  and  $J^3$  are  $-CH-$  and  $J^2$  is  $-N-$ .
- In another embodiment,  $J^1$ ,  $J^2$  and  $J^3$  are independently  $-C(R)^2-$  or  $-N-$ .
- In another embodiment,  $J^1$  and  $J^2$  are  $-CH-$  and  $J^3$  is  $-N-$ .
- In another embodiment,  $J^1$  and  $J^4$  are  $-CH-$  and  $J^3$  is  $-N-$ .
- In another embodiment,  $n$  is 1.
- In another embodiment,  $n$  is 2.
- In another embodiment,  $q$  is 0 or 1.
- In another embodiment,  $p$  is 1 or 2.
- In another embodiment,  $w$  is 1, 2 or 3.
- In another embodiment,  $X$  is  $-CH_2-$ .
- In another embodiment,  $X$  is  $-C(=O)-$ .
- In another embodiment,  $X$  is  $-NH-$ .
- In another embodiment,  $X$  is  $-O-$ .

In another embodiment, X is -S-.

In another embodiment, X is -N(R<sup>6</sup>).

In another embodiment, W is -NH-.

In another embodiment, W is -O-.

5 In another embodiment, W is -S-.

In one embodiment R<sup>1</sup> is optionally substituted (preferably 1 to 5 times) aryl (e.g., substituted phenyl) or optionally substituted (preferably 1 to 5 times) heteroaryl, wherein the optional substituents are, for example, any of the "ring system substituents" identified below. Examples of heteroaryl rings include pyridine,

10 pyrimidine, furan, pyrrole, thiophene, pyridazine, pyrazine, indolizine, oxazole, pyrazole, isoxazole, indole, isoindole, imidazole, indoline, benzofuran, benzothiophene, indazole, benzimidazole, benzthiazole, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, and naphthyridine. Preferred heteroaryl rings include pyridine, pyrimidine, furan, pyrrole, thiophene, pyridazine,

15 pyrazine, indole, indoline, benzofuran, benzothiophene, benzimidazole, and benzthiazole. More preferred heteroaryl rings include pyridine, pyrimidine, pyrazole, pyrazine, isoxazole, and oxazole. Preferred optional substituents include alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, haloalkoxy, aryl, and heteroaryl, wherein said aryl and heteroaryl are optionally substituted 1 to 5, preferably 1 to 3, times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and haloalkoxy.

20 In another embodiment R<sup>1</sup> is an optionally substituted (preferably 1 to 5 times) cycloalkyl or cycloalkenyl ring. Examples of rings include cyclopentane, cyclohexane and cyclohexene. Examples of substituents include any of the "ring system

25 substituents" identified below. Preferred optional substituents include alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, haloalkoxy, aryl, and heteroaryl, wherein said aryl and heteroaryl are optionally substituted 1 to 5, preferably 1 to 3, times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and haloalkoxy.

30 In another embodiment R<sup>1</sup> is an optionally substituted (preferably 1 to 5 times) heterocyclcyl or heterocyclenyl ring or cycloalkenyl ring. Examples of rings include morpholine, piperazine, 2-pyrrolidine and tetrahydrofuran. Examples of

substituents include any of the "ring system substituents" identified below. Preferred optional substituents include alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, haloalkoxy, aryl, and heteroaryl, wherein said aryl and heteroaryl are optionally substituted 1 to 5, preferably 1 to 3, times by alkyl,

- 5 haloalkyl, nitro, cyano, halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and haloalkoxy.

In another embodiment, R<sup>1</sup> is an optionally substituted pyridine ring.

In another embodiment, R<sup>1</sup> is an optionally substituted pyrimidine ring.

In another embodiment, R<sup>1</sup> is an optionally substituted pyrazine ring.

- 10 In another embodiment, R<sup>1</sup> is an optionally substituted oxazole ring.

In another embodiment, R<sup>1</sup> is an optionally substituted phenyl ring.

In another embodiment, R<sup>1</sup> is an optionally substituted naphthylene ring.

In another embodiment, R<sup>1</sup> is an optionally substituted isoxazole ring.

In another embodiment, R<sup>1</sup> is an optionally substituted pyrazole ring.

- 15 In another embodiment, R<sup>1</sup> is bonded to J<sup>1</sup>; J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -CH<sub>2</sub>-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>1</sup>; J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -NH-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>1</sup>; J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -O-.

- 20 In another embodiment, R<sup>1</sup> is bonded to J<sup>1</sup>; J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -S-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>4</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>3</sup> are -CH-; and X is -CH<sub>2</sub>-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>4</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>3</sup> are -CH-; and X is -NH-.

- 25 In another embodiment, R<sup>1</sup> is bonded to J<sup>4</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>3</sup> are -CH-; and X is -O-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>4</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>3</sup> are -CH-; and X is -S-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>2</sup>; J<sup>1</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -CH<sub>2</sub>-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>2</sup>; J<sup>1</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -

- 30 NH-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>2</sup>; J<sup>1</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -O-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>2</sup>; J<sup>1</sup>, J<sup>3</sup> and J<sup>4</sup> are -CH-; and X is -S-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>3</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>4</sup> are -CH-; and X is -CH<sub>2</sub>-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>3</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>4</sup> are -CH-; and X is -NH-.

5 In another embodiment, R<sup>1</sup> is bonded to J<sup>3</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>4</sup> are -CH-; and X is -O-.

In another embodiment, R<sup>1</sup> is bonded to J<sup>3</sup>; J<sup>1</sup>, J<sup>2</sup> and J<sup>4</sup> are -CH-; and X is -S-.

In another embodiment, R<sup>1</sup> is optionally substituted heteroaryl.

In another embodiment, m is 1 and n is 1.

In another embodiment, J<sup>2</sup>, J<sup>3</sup>, and J<sup>4</sup> are each -C(R<sup>2</sup>)- and R<sup>2</sup> is independently H or

10 halo.

In another embodiment, R<sup>3</sup> is H.

In another embodiment, R<sup>3</sup> is H, halo, -OH or alkoxy.

In another embodiment, R<sup>3</sup> is H or halo.

15 In another embodiment R<sup>4</sup> is H, -OH, halo, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, wherein R<sup>7</sup> and R<sup>7</sup> are independently H, alkyl, R<sup>12</sup>-aryl, and R<sup>12</sup>-cycloalkyl, alkyl, or haloalkyl

In another embodiment R<sup>8</sup> is H, alkoxy, or alkyl.

In another embodiment, n is 1, m is 1 and W is -O-.

In another embodiment, n is 1, m is 1 and W is -S-.

In another embodiment, n is 1, m is 1 and W is -NH-.

20 In another embodiment R<sup>14</sup> is H, optionally substituted alkyl, optionally substituted cycloalkyl (e.g., cyclopropyl, cyclopentyl, or cyclohexyl) or, optionally substituted aryl (e.g., phenyl), wherein the optional substituents are halo, hydroxyl, amino, alkyl amino, dialkyl amino, nitro, or cyano.

In another embodiment R<sup>14</sup> is H or alkyl.

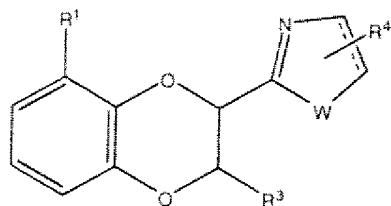
25 In another embodiment, R<sup>2</sup> is H, halo or alkyl.

In another embodiment, ----- is a single bond.

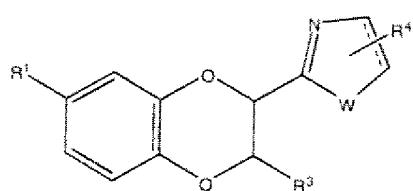
In another embodiment, ----- is a double bond.

In another embodiment, X is -O-, W is -NH-, and ----- is a single bond.

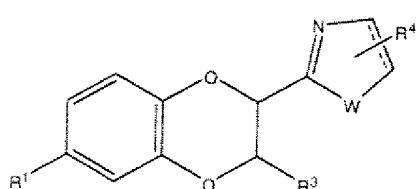
30 In another embodiment, the present invention discloses compounds which are represented by structural formulae II-V or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various definitions are those described above for Formula I:



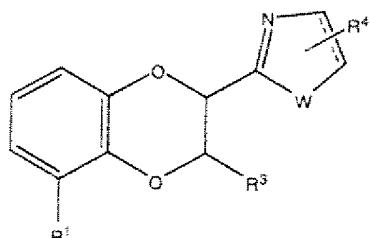
Formula II



Formula III



Formula IV



Formula V

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An embodiment of Formulae II-V is those compounds wherein:

- R<sup>1</sup> is optionally substituted aryl, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted pyridyl, optionally substituted pyrimidyl,
- 15      optionally substituted furanyl, optionally substituted thiophenyl, optionally substituted quinolinyl, optionally substituted indolyl, optionally substituted pyrrolyl, and optionally substituted pyrrolidinyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, optionally substituted isoxazolyl, optionally substituted imidazole, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted tetrazolyl, optionally substituted imidazopyrimidinyl, optionally substituted thiazolyl,
- 20      optionally substituted isothiazolyl, optionally substituted indazolyl, optionally substituted benzofuranyl, optionally substituted benzothiophenyl, optionally substituted isoquinolyl, optionally substituted benzimidazolyl, optionally substituted benzthiazolyl, optionally substituted quinoxalinyl, wherein said groups may be optionally substituted
- 25      1 to 3 times with substituents selected from the group consisting of alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, -C(O)-amino; -C(O)-alkylamino, -C(O)-dialkylamino, -C(O)-OH, -C(O)-O-alkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said

aryl and heteroaryl are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxy; and R<sup>4</sup> is H or alkyl (e.g., methyl or ethyl), alkoxy (e.g., methoxy or ethoxy), halo, -CN, -OH, NO<sub>2</sub>, amino, alkylamino or dialkylamino.

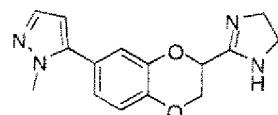
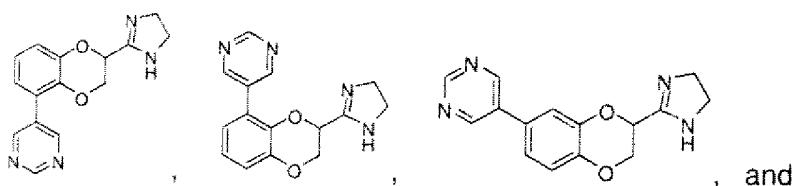
- 5 or a pharmaceutically acceptable ester, salt or solvate thereof.

Another embodiment of compounds of Formulae II-V, \_\_\_\_\_ is a single bond.

Another embodiment of compounds of Formulae II-V, W is -NH-, R<sup>3</sup> is H, R<sup>4</sup> is H or alkyl and \_\_\_\_\_ is a single bond.

A group of compounds falling within Formula I are those shown below:

10



In another embodiment the compound of Formula I or its pharmaceutically accept salt, solvate or ester thereof is present in its isolated and purified form.

15

One embodiment of the present invention is compounds that act as agonists of the α2C receptor. Alpha-2C receptor agonists can be used in the treatment or prevention of allergic rhinitis, congestion (including, but not limited to nasal congestion), migraine, congestive heart failure, chronic heart failure, cardiac ischemia, glaucoma, stress-induced urinary incontinence, attention deficit hyperactivity disorder,

20

neuronal damage from ischemia and psychotic disorders. Further, alpha-2C receptor agonists can be useful in the treatment of pain (both chronic and acute), such as pain that is caused by inflammation, neuropathy, arthritis (including osteo and rheumatoid arthritis), diabetes (e.g., diabetes mellitus or diabetes insipidus) or pain of an unknown origin. Examples of neuropathic pain may include but not limited to; diabetic

25

neuropathy, neuralgia of any etiology (e.g. post-herpetic, trigeminal), chemotherapy-induced neuropathy, HIV, lower back pain of neuropathic origin (e.g. sciatica), traumatic peripheral nerve injury of any etiology, central pain (e.g. post-stroke, thalamic, spinal nerve injury). Other pain that can be treated is nociceptive pain and

pain that is visceral in origin or pain that is secondary to inflammation or nerve damage in other diseases or diseases of unknown origin. Further, alpha-2C receptor agonists can be useful in the treatment of symptoms of diabetes. Examples of symptoms of diabetes may include but are not limited to: hyperglycemia, hypertriglyceridemia,

- 5 increased levels of blood insulin and hyperlipidemia.

A compound is defined to be an agonist of the alpha-2c receptor if the compound's efficacy at the  $\alpha$ 2C receptor is  $\geq 30\% E_{max}$  (GTP $\gamma$ S assay).

A further embodiment of the present invention are that act selectively, and preferably even specifically, as agonists of the  $\alpha$ 2C or the  $\alpha$ 2B/ $\alpha$ 2C (hereinafter

- 10 referred to as  $\alpha$ 2C or  $\alpha$ 2B/ $\alpha$ 2C) receptor subtypes in preference over the  $\alpha$ 2A receptor subtype and that act functionally selectively as agonists of the  $\alpha$ 2C or the  $\alpha$ 2B/ $\alpha$ 2C receptor subtype in preference over the  $\alpha$ 2A receptor subtype possess desirable therapeutic properties associated with adrenergic receptors but without having one or more undesirable side effects such as changes in blood pressure or sedation. For the 15 purposes of the present invention, a compound is defined to be a specific or at least functionally selective agonist of the  $\alpha$ 2C receptor subtype over the  $\alpha$ 2A receptor subtype if the compound's efficacy at the  $\alpha$ 2C receptor is  $\geq 30\% E_{max}$  (GTP $\gamma$ S assay) and its efficacy at the  $\alpha$ 2A receptor is  $\leq 35\% E_{max}$ , (GTP $\gamma$ S assay).

In another embodiment of the present invention the compound acts as an 20 antagonist of the alpha-2C receptor. Alpha-2C receptor antagonists can be used in the treatment or prevention of disease states such as depression, schizophrenia, post traumatic stress disorder, Parkinson's disease, dementias (e.g., Alzheimer's disease and neuropathic disorders.

A compound is defined to be an antagonist of the alpha-2C receptor if the 25 compounds's efficacy at the  $\alpha$ 2C receptor is  $< 30\% E_{max}$  (GTP $\gamma$ S assay) and the binding inhibition of at the  $\alpha$ 2C receptor ( $K_i$ ) is  $< 500$  nM, preferably  $< 200$  nM, and most preferably  $< 20$  nM. In a further embodiment of the present invention, the  $\alpha$ 2C receptor subtype antagonists possess desirable therapeutic properties associated with the  $\alpha$ 2C adrenergic receptor but without having one or more undesirable side effects 30 associated with  $\alpha$ 2A agonism. For the purposes of this invention, compounds that act as antagonists at the  $\alpha$ 2C receptor subtype preferably do not possess an efficacy at the  $\alpha$ 2A receptor of  $35\% E_{max}$  or more (GTP $\gamma$ S assay).

Alternatively, the present invention provides for a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the  $\alpha_{2c}$  receptor or the  $\alpha_{2C}/\alpha_B$  adrenergic receptor.

A further embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the  $\alpha_{2C}$  receptor or the  $\alpha_{2C}/\alpha_B$  adrenergic receptor, wherein the selective agonist of the  $\alpha_{2c}$  receptor or the  $\alpha_{2C}/\alpha_B$  adrenergic receptor has an efficacy that is greater than or equal to 30%  $E_{max}$  when assayed in the GTP $\gamma$ S assay and its efficacy at the  $\alpha_{2A}$  receptor is  $\leq 35\%$   $E_{max}$  (GTP $\gamma$ S assay).

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

“Patient” includes both human and animals.

“Mammal” means humans and other mammalian animals.

“alpha-2C modulator” or “ $\alpha_{2C}$  modulator” means that a compound has affinity for (or binds to) the  $\alpha_{2C}$  receptor which provokes a biological response (*i.e.*, either an agonistic or antagonistic response).

“alpha-2C receptor agonist” or “ $\alpha_{2C}$  receptor agonist” is a compound that has affinity for the  $\alpha_{2C}$  receptor and elicits a biological response that mimics the response observed by the endogenous ligand (*e.g.*, neurotransmitter) that binds to the same receptor.

“alpha-2C receptor antagonist” or “ $\alpha_{2C}$  receptor antagonist” is a compound that has affinity for the  $\alpha_{2C}$  receptor and elicits a biological response that blocks or dampens the response observed by the endogenous ligand (*e.g.*, neurotransmitter) that binds to the same receptor.

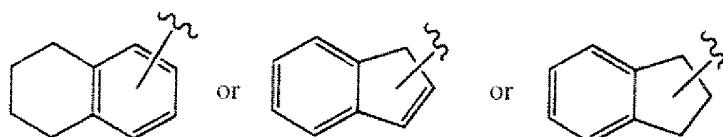
“Congestion” refers to all type of congestion including, but not limited to, congestion associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute

rhinosinusitis, or chronic rhinosinusitis or when the congestion is caused by polyps or is associated with the common cold.

- "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred 5 alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" 10 means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.
- 15 "Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl 20 or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and -S(alkyl). Non-limiting 25 examples of suitable alkenyl groups include ethenyl, propenyl, n-but enyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.
- "Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 30 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to

about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each 5 substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is an aryl ring, comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally 10 substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. Non-limiting examples of aryl multicyclic ring systems include:

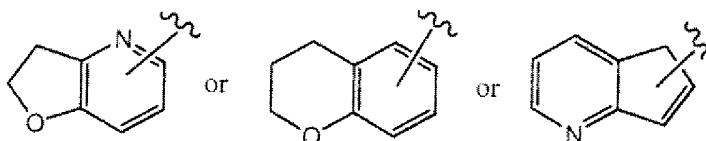


"Heteroaryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is aromatic, comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The 20 "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable 25 heteroaryls include pyridyl, pyrazinyl, furanyl, thieryl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl,

pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindoyl, 1,2,4-triazinyl, benzothiazolyl and the like.

Non-limiting examples of heteroaryl multicyclic ring systems include:

5



"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and

10 naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

15 "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms.

Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable  
20 monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Halogen" and "Halo" mean fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

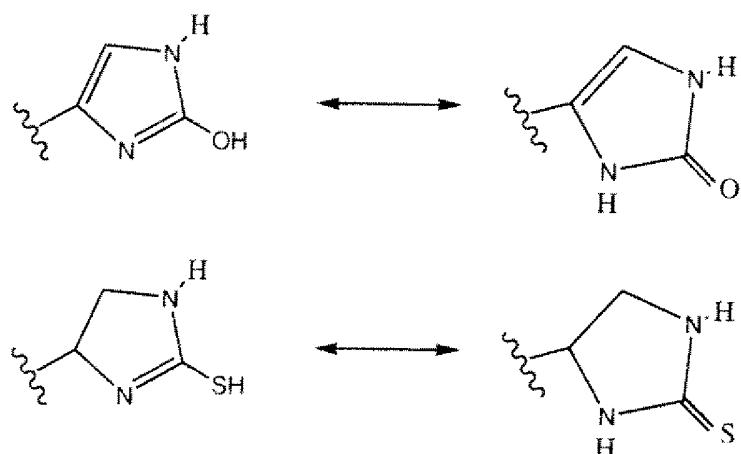
25 "Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl,  $Y_1Y_2N\text{-}$ ,  $Y_1Y_2N\text{-alkyl-}$ ,  $Y_1Y_2NC(O)\text{-}$  and  $Y_1Y_2NSO_2\text{-}$ , wherein  $Y_1$  and  $Y_2$  may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

- 5 "Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred  
10 heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected moieties are also considered part of this invention. The heterocyclyl  
15 can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl,  
20 thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and the like.

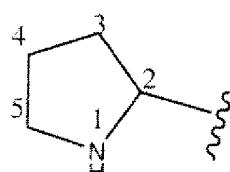
Compounds of Formula I and salts, esters, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention. Non-  
25 limiting examples of tautomeric forms that are part of this invention are as follows:

25



It should be noted that in saturated heterocycl containing systems of this invention, there are no hydroxyl, amino, or thiol groups on carbon atoms adjacent to a N, O or S atom. Thus, for example, in the ring:

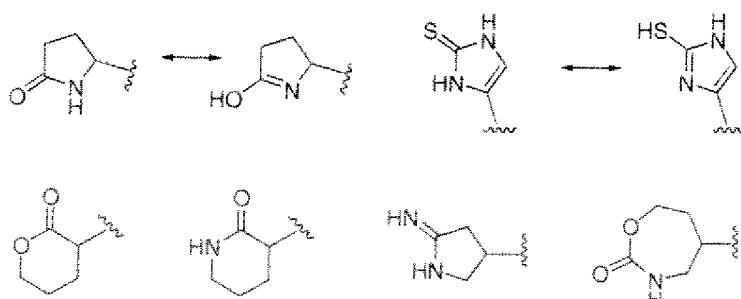
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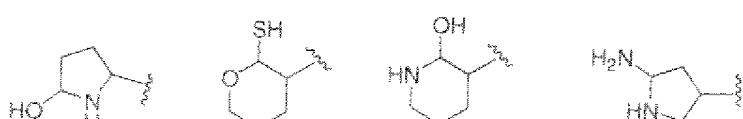
there is no -OH attached directly to carbons marked 2 and 5. It should also be noted that this definition does not preclude (=O), (=S), or (=N) substitutions, or their tautomeric forms, on C atoms adjacent to a N, O or S. Thus, for example, in the above ring, (=O) substitution on carbon 5, or its imino ether tautomer is allowed.

10

Non-limiting examples which illustrate the present invention are as follows:



The following non-limiting examples serve to illustrate radicals not contemplated by the present invention:



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"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

5 "Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

10 "Heterocyclalkyl" means a heterocycl-alkyl group in which the heterocycl and the alkyl are as previously described. Preferred heterocyclalkyls contain a lower alkyl group. Non-limiting examples of suitable heterocyclalkyl groups include piperidylmethyl, piperidylethyl, pyrrolidylmethyl, morpholinylpropyl, piperazinylethyl, azindylmethyl, azetidylethyl, oxiranylpropyl and the like. The bond to the parent moiety is through the alkyl group.

15 "Heterocyclenyl" (or "heterocycloalkenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, 20 wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridyl, 1,4,5,6-tetrahydropyrimidyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 25 2-pyrazolinyl, 2-oxazolinyl, 2-thiazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic

oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

- "Heterocyclenylalkyl" means a heterocyclenyl-alkyl group in which the heterocyclenyl and the alkyl are as previously described.
- "Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.
- "Acyl" means an organic acid group in which the -OH of the carboxyl group is replaced by some other substituent. Suitable non-limiting examples include H-C(O)-, alkyl-C(O)-, cycloalkyl-C(O)-, heterocyclyl-C(O)-, and heteroaryl-C(O)- groups in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.
- "Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.
- "Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.
- "Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.
- "Aralkyloxy" or "arylaikyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.
- "Heteroarylalkoxy" means a heteroarylalkyl-O-group in which the heteroarylalkyl group is as previously described.
- "Heterocyclalkoxy" means a heterocyclalkyl-O group in which the heterocyclalkyl group is as previously described.

"Heterocyclenylalkoxy" means a heterocyclenylalkyl-O group in which the heterocyclenylalkyl group is as previously described.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and 5 ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as 10 previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

15 "Aryloxy carbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxy carbonyl groups include phenoxy carbonyl and naphthoxy carbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a 20 suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O<sub>2</sub>)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

25 "Arylsulfonyl" means an aryl-S(O<sub>2</sub>)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents 30 and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently

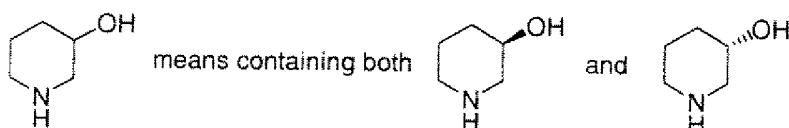
robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

It is noted that carbons of Formula I can be replaced with 1-3 silicon atoms, provided all valency requirements are satisfied.

5 The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

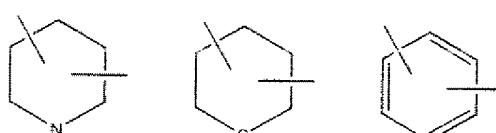
The straight line —— as a bond generally indicates a mixture of, or either of, the possible isomers, non-limiting example(s) include, containing (R)- and (S)- stereochemistry. For example,

10



A dashed line (----) represents an optional bond.

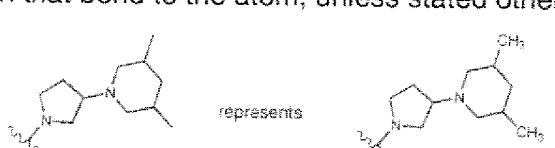
Lines drawn into the ring systems, such as, for example:



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indicate that the indicated line (bond) may be attached to any of the substitutable ring atoms, non-limiting examples include carbon, nitrogen and sulfur ring atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom to satisfy the valences.

25

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site

when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

5 When any variable (e.g., aryl, heterocycle, R<sup>2</sup>, etc.) occurs more than one time in any constituent or formula, its definition on each occurrence is independent of its definition at every other occurrence.

Unless defined otherwise, all definitions for the variables follow the convention that the group to the right forms the point of attachment to the molecule; i.e., if a  
10 definition is arylalkyl, this means that the alkyl portion of the definition is attached to the molecule.

Further, all divalent variables are attached from left to right. For example when R<sup>2</sup> is -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)YR<sup>7</sup> and Y is -C(=O)-, -C(=O)O- or -C(=O)NR<sup>7</sup>, then R<sup>2</sup> forms the group -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)-C(=O)-R<sup>7</sup>, -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)-C(=O)O-R<sup>7</sup>, or -  
15 [C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)-C(=O)N(R<sup>7</sup>)(R<sup>7</sup>).

In this application, unless otherwise indicated, whenever there is a structural formula provided, such as those of Formulae I to V, this formula is intended to encompass all forms of a compound such as, for example, any solvates, hydrates, stereoisomers, tautomers, etc.

20 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also  
25 contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S.  
30 Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

- For example, if a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>12</sub>)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxy carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>2</sub>-C<sub>3</sub>)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl, N,N-di (C<sub>1</sub>-C<sub>2</sub>)alkylcarbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl and piperidino-, pyrrolidino- or morpholino(C<sub>2</sub>-C<sub>3</sub>)alkyl, and the like.

Similarly, if a compound of of Formula I contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxymethyl, 1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl, 1-methyl-1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyloxymethyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonylaminomethyl, succinoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, α-amino(C<sub>1</sub>-C<sub>4</sub>)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)<sub>2</sub>, -P(O)(O(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub> or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of of Formula I incorporates -NH- functional group, such as in a primary or secondary amine or in a nitrogen-containing heterocycle, such as imidazole or piperazine ring, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, -C(OH)C(O)OY<sup>1</sup> wherein Y<sup>1</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl or benzyl, -C(OY<sup>2</sup>)Y<sup>3</sup> wherein Y<sup>2</sup> is (C<sub>1</sub>-C<sub>4</sub>) alkyl and Y<sup>3</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl or mono-N- or di-N,N-(C<sub>1</sub>-C<sub>6</sub>)alkyl, and the like.

$C_6$ alkylaminoalkyl,  $-C(Y^4)Y^5$  wherein  $Y^4$  is H or methyl and  $Y^5$  is mono-N- or di-N,N- $(C_1-C_6)$ alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and  
5 the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules  
10 are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of illustrative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is  $H_2O$ .

One or more compounds of the invention may optionally be converted to a  
15 solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et*  
20 *al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the  
25 presence of the solvent (or water) in the crystals as a solvate (or hydrate).

Metabolic conjugates, such as glucuronides and sulfates which can undergo reversible conversion to the compounds of of Formula I are contemplated in the present invention.

"Effective amount" or "therapeutically effective amount" is meant to describe an  
30 amount of compound or a composition of the present invention effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The terms "purified", "in purified form" or "in isolated and purified form," as used herein, for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and

5 purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

10 "Capsule" is meant to describe a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and  
15 preservatives.

"Tablet" is meant to describe a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

20 "Oral gels" is meant to describe to the active ingredients dispersed or solubilized in a hydrophilic semi-solid matrix.

"Powders for constitution" refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

25 "Diluent" refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60%  
30 by weight, even more preferably from about 12 to about 60%.

"Disintegrants" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include

starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline 5 celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

"Binders" refers to substances that bind or "glue" powders together and make 10 them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; 15 cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

20 "Lubricant" is meant to describe a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, 25 sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, 30 more preferably from about 0.3 to about 1.5% by weight.

"Glidents" means materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents

include silicon dioxide and talc. The amount of glidant in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

“Coloring agents” refers to excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

“Bioavailability” refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control. Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term “salt(s)”, as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions (“inner salts”) may be formed and are included within the term “salt(s)” as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of Formula I or may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates,

camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons or sulfurs on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. For example, if a compound of Formula I incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are

embraced within the scope of the invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula I may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as <sup>2</sup>H, <sup>3</sup>H, <sup>13</sup>C, <sup>14</sup>C, <sup>15</sup>N, <sup>18</sup>O, <sup>17</sup>O, <sup>31</sup>P, <sup>32</sup>P, <sup>35</sup>S, <sup>18</sup>F, and <sup>36</sup>Cl, respectively.

Certain isotopically-labelled compounds of Formula I (e.g., those labeled with <sup>3</sup>H and <sup>14</sup>C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., <sup>3</sup>H) and carbon-14 (i.e., <sup>14</sup>C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such

as deuterium (i.e.,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be useful as  $\alpha_2\text{C}$  adrenoreceptor agonists.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula I. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more therapeutic agents such as, for example, glucocorticosteroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium,  $\text{H}_1$  receptor antagonists, 5-HT<sub>1</sub> agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists,  $\beta$ -blockers,  $\beta$ -agonists (including both long and short acting), leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, natriuretic peptides, pain management/analgesic agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

Suitable steroids include prednisolone, fluticasone (including all ester such as the propionate or furoate esters), triamcinolone, beclomethasone, mometasone (including any ester form such as mometasone furoate), budasamine, ciclesonide betamethasone, dexamethasone, prednisone, flunisolide, and cortisone.

Suitable PDE-4 inhibitors include roflumilast, theophylline, rolipram, piclamilast, cilomilast and CDP-840.

Suitable antimuscarinic agents include ipratropium bromide and tiatropium bromide.

Suitable  $\text{H}_1$  antagonists include astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine,

cyproheptadine, carboxamine, descarboethoxyloratidine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratidine, levocabastine, meclizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, 5 noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

Suitable anti-inflammatory agents include aspirin, diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin.

10 Suitable aldosterone antagonists include spironolactone.

Suitable ionotropic agents include digitalis.

Suitable angiotensin II receptor agonists include irbesartan and losartan.

Suitable diuretics include spironolactone, methyclothiazide, bumetanide, torsemide, hydroflumethiazide, trichlormethiazide, hydrochlorothiazide, triamterene, 15 ethacrynic acid, methyclothiazide, hydrochlorothiazide, benzthiazide, hydrochlorothiazide, quinethazone, hydrochlorothiazide, chlorthalidone, furosemide, indapamide, hydrochlorothiazide, triamterene, trichlormethiazide, hydrochlorothiazide, amiloride HCl, amiloride HCl, metolazone, trichlormethiazide, bendroflumethiazide, hydrochlorothiazide, polythiazide, hydroflumethiazide, chlorthalidone, and metolazone.

20 Suitable pain management/analgesic agents include Celecoxib, amitriptyline, ibuprofen, naproxen, gabapentin, tramadol, rofecoxib, oxycodone HCl, acetaminophenoxycodeine HCl, carbamazepine, amitriptyline, diclofenac, diclofenac, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, meloxicam, nabumetone, naproxen, 25 oxaprozin, piroxicam, sulindac, tolmetin sodium, valdecoxib, diclofenac/ misoprostol, oxycontin, vicodin, darvocet, percocet, morphine sulfate, dilaudid, stadol, stadol NS, acetaminophen with codeine, acetaminophen with codeine #4, Lidoderm® patches, ziconotide, duloxetine, roboxetine, gabapentin and pregabalin.

30 Suitable β-blockers include acebutolol, atenolol, atenolol/chlorthalidone, betaxolol, bisoprolol fumarate, bisoprolol/HCTZ, labetolol, metoprolol tartrate, nadolol, pindolol, propranolol, propranolol/HCTZ, sotalol, and timolol.

Suitable β-agonists include dobutamine, ritodrine, salbutamol, levalbuterol,

metaproteranol, formoterol, fenoterol, bambuterol, brocaterol, clenbuterol, terbutaline, tulobuterol, epinephrine, isoprenalin, and hexoprenalin.

Suitable leucotriene antagonists include levamisole.

Suitable anti-migraine agents include rovatriptan succinate, naratriptan HCl, 5 rizatriptan benzoate, sumatriptan succinate, zolmitriptan, almotriptan malate, methysergide maleate, dihydroergotamine mesylate, ergotamine tartrate, ergotamine tartrate/caffeine, Fioricet®, Fiorninal®, Depakene®, and Depakote®.

Suitable anti-anxiety and anti-depressant agents include amitriptyline HCl, 10 bupropion HCl, citalopram hydrobromide, clomipramine HCl, desipramine, fluoxetine, fluvoxamine maleate, maprotiline HCl, mirtazapine, nefazodone HCl, nortriptyline, paroxetine HCl, protriptyline HCl, sertraline HCl, doxepin, and trimipramine maleate.

Suitable angiotensin converting enzyme inhibitors include Captopril, enalapril, enalapril/HCTZ, lisinopril, lisinopril/HCTZ, and Aceon®.

The pharmacological properties of the compounds of this invention may be 15 confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate 20 of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, 25 cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's 30 Pharmaceutical Sciences*, 18<sup>th</sup> Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. When preparing a liquid preparation, the inclusion of one or more solubility enhancing components is excluded. Solubility enhancing components are described, for example, in U.S. 6,673,337 in column 2, line 50 to column 3, line 17 and in column 6, 5 line 49 to line 31; US 6,673,337 is expressly incorporated by reference. Specific solubility enhancing agents that are excluded in the liquid form preparations include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelloses, hydroxypropylmethyl celluloses derivative of these compounds, and cyclodextrins. As an example of liquid form preparations according to the invention may be mentioned 10 water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions or suspensions for intranasal administration.

An aspect of this invention is that the pharmaceutical composition is in a solid dosage form comprising a compound of Formula I or a pharmaceutical acceptable 15 salt, ester, solvate or prodrug thereof and a least one pharmaceutically acceptable carrier, adjuvant or vehicle.

Another aspect of this invention is a liquid, aqueous pharmaceutical composition comprising a compound of Formula I or a pharmaceutical acceptable salt, ester, solvate or prodrug thereof and a least one pharmaceutically acceptable 20 carrier, adjuvant or vehicle provided that the adjuvant is not a solubility enhancing component, such as those described in US 6,673,337 (discussed above).

Another aspect of this invention is a liquid, aqueous pharmaceutical composition comprising a compound of Formula I or a pharmaceutical acceptable salt, ester, solvate or prodrug thereof and a least one pharmaceutically acceptable 25 carrier, adjuvant or vehicle wherein if a solubility enhancement component is present it is cyclodextrin.

Another aspect of this invention is a pharmaceutical formulation that is a nasal spray wherein the pH is equal to or less than about 6.5, more preferably between about 6.1 to 6.2.

30 Another aspect of this invention the formulation is a nasal spray wherein the adjuvants include a suspending agent (e.g., AVICEL (such as AVICIL RC-581, RC-591 and CL-611), which are microcrystalline cellulose and carboxymethylcellulose

sodium; hydroxypropylmethyl cellulose; methyl cellulose; polyvinyl alcohol; or CARBOPOL) and a humectant (e.g., glycerin, propylene glycol; polyethylene glycol; povidone; or dextrose).

Liquid form preparations include solutions, suspensions and emulsions. As an 5 example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions or suspensions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in 10 powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

15 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.  
20 Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

25 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements 30 of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For

convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one therapeutic agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

In general, the compounds in the invention may be produced by a variety of processes known to those skilled in the art and by known processes analogous thereto.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art. The practitioner is not limited to these methods.

One skilled in the art will recognize that one route will be optimized depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of steps has to be controlled to avoid functional group incompatibility.

The prepared compounds may be analyzed for their composition and purity as well as characterized by standard analytical techniques such as, for example, elemental analysis, NMR, mass spectroscopy and IR spectra.

One skilled in the art will recognize that reagents and solvents actually used may be selected from several reagents and solvents well known in the art to be

effective equivalents. Hence, when a specific solvent or reagent is mentioned, it is meant to be an illustrative example of the conditions desirable for that particular reaction scheme and in the preparations and examples described below.

- Where NMR data are presented,  $^1\text{H}$  spectra were obtained on either a Varian  
5 VXR-400 (400 MHz,  $^1\text{H}$ ), Varian Gemini-300 (300 MHz), Varian Mercury VX-400  
(400MHz), or Bruker-Biospin AV-500 (500MHz), and chemical shifts are reported as  
ppm with number of protons and multiplicities indicated parenthetically. Where LC/MS  
data are presented, analyses was performed using an Applied Biosystems API-100  
mass spectrometer and C18 column, 10-95%  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (with 0.05% TFA) gradient.  
10 The observed parent ion is given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

- Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; t-Bu = *tert*-butyl; Ph = phenyl, and Ac  
= acetyl  
15  $\mu\text{l}$  = microliters  
AcOEt or EtOAc = ethyl acetate  
AcOH or HOAc = acetic acid  
ACN = acetonitrile  
aq = aqueous  
20 atm = atmosphere  
Boc = *tert*-butoxycarbonyl  
BINAP = 2,2'-bis(diphenylphosphino)-1,1'-bisnaphthyl  
cat = catalyst or catalytic  
Cbz = benzoxycarbonyl  
25 DEAD = diethylazodicarboxylate  
DCM or  $\text{CH}_2\text{Cl}_2$  dichloromethane:  
DMAP = 4-Dimethylaminopyridine  
DIPEA = diisopropylethylamine  
DME = 1,2-dimethoxyethane  
30 DMF = dimethylformamide  
DMS = dimethylsulfide  
DMSO = dimethyl sulfoxide

Dppf = 1,1'-bis(diphenylphosphino)ferrocene

EDCI or DEC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

g = grams

h = hour

5 HOBT = 1-hydroxybenzotriazole

LAH = lithium aluminum hydride

LCMS = liquid chromatography mass spectrometry

min = minute

mg = milligrams

10 mL = milliliters

mmol = millimoles

mCPBA = m-chloroperbenzoic acid

MeOH: methanol

MS = mass spectrometry

15 NBS = n-bromosuccimide

NMO =N-methylmorpholine N-oxide

NMR = nuclear magnetic resonance spectroscopy

PG = protecting group

Pyr = pyridine

20 *rac* or ( $\pm$ ) = racemic mixture or enantiomers

RT or rt = room temperature (ambient, about 25 °C)

sat = saturated

SM = starting material

TBSCl = t-butyldimethylsilyl chloride

25 TBS = t-butyldimethyl silyl

TEA = triethylamine (Et<sub>3</sub>N)

TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxyl

TFA = trifluoroacetic acid

TPAP = tetrapropylammonium perruthenate

30 THF = tetrahydrofuran

TLC = thin layer chromatography

TMS = trimethylsilyl

Tos or Ts = p-toluenesulfonyl (tosyl)

Tol = toluene

TosMIC = Toluenesulfonylmethyl isocyanide

Tr = triphenylmethyl

5

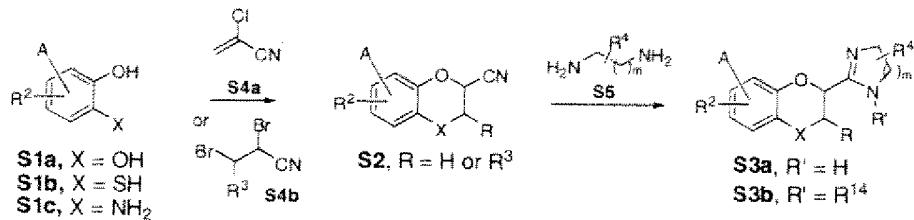
### EXAMPLES

The compounds of this invention can be prepared through the general approach outlined in the following schemes. These schemes are being provided to illustrate the present invention. While the schemes depict J<sup>1</sup>-J<sup>4</sup> as -CH-, wherein the hydrogen may be replaced by A or R<sup>2</sup>, this is for exemplary purposes only and one of ordinary skill in the art would be able to prepare compounds containing the other definitions for J<sup>1</sup>-J<sup>4</sup> by modifying these schemes using other procedures known to one in the art. To assist in one in this endeavor the ordinary practitioner would have full knowledge of literature sources such as *Chemical Abstracts*, *Beilstein*, etc.

Scheme 1 shows an approach in which a substituted catechol **S1a**, o-mercaptophenol **S1b**, or o-aminophenol **S1c** is converted to nitrile **S2** by reaction with 2-chloroacrylonitrile **S4a** (or similar reagent such as **S4b**) and a base (such as K<sub>2</sub>CO<sub>3</sub>). Compound **S2** is further reacted with diamine **S5** (optionally substituted) under a variety of conditions such as heat, acid (HCl-MeOH, pTsOH or the like) or base (NaOMe or the like). The resulting imidazoline **S3a** may be further alkylated or acylated with an electrophile to provide **S3b**.

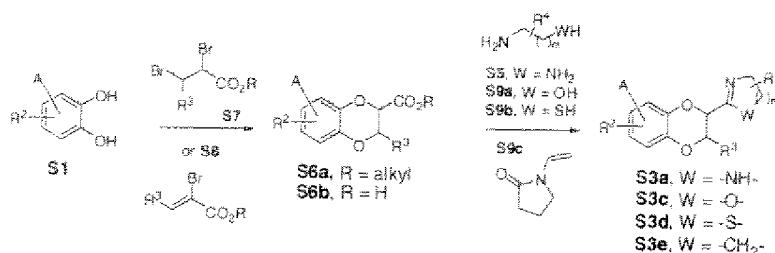
The biaryl coupling transformation (A = halogen or activated alcohol to A = the various definitions of R<sup>1</sup>, such as aryl, cycloalkenyl, heterocyclenyl, or heteroaryl) occurs via a metal catalyzed or metal-facilitated process (such as Stille coupling, Suzuki coupling, Negishi coupling or nucleophilic substitution reaction) with an appropriately substituted aryl or heteroaryl partner. Installation of the biaryl group may be done at various stages in the sequence.

The functionalized R<sup>2</sup> groups may exist in the starting material **S1** or its precursor. Alternatively, **S1** or its precursor may be functionalized with R<sup>2</sup> groups at various stages in the sequence.

SCHEME 1

Scheme 2 shows an approach in which a substituted catechol **S1** is converted  
 5 to ester **S6a** by reaction with either a 2,3-dibromopropionate **S7** or 2-bromoacrylate **S8**  
 (or similar reagent) and a base (such as KOH or  $\text{K}_2\text{CO}_3$ ). In various embodiments,  
**S6a** is converted to the following heterocycles:

- an imidazoline **S3a**, by reaction with diamine **S5** (optionally substituted) in the presence of  $\text{AlMe}_3$ ; or
  - 10 -a pyrrolidine **S3e**, by reaction with NaH and N-vinylpyrrolidinone **S9c**.
- Alternatively, ester **S6a** is saponified to acid **S6b** by a standard method (such as treatment with HCl, NaOH, LiOH or other method known in the literature). In various embodiments, **S6b** is converted to the following heterocycles:
- an oxazoline **S3c**, by sequential treatment with amino alcohol **S9a** (optionally substituted),  $\text{SOCl}_2$ , and then TEA; or
  - 15 -a thiazoline **S3b**, by sequential treatment with amino thiol **S9b** (optionally substituted), TEA, and  $\text{Ph}_3\text{P}$ .

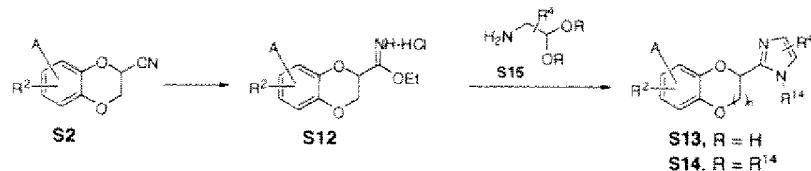
SCHEME 2

20

Scheme 3 shows an approach in which nitrile **S2** is treated with HCl and EtOH (or other alcohol). The resulting imidate **S12** is then sequentially treated with: an acetal or ketal (**S15**, optionally substituted), HCl, and then NaOH to provided

imidazole **S13**. Compound **S14** is obtained by the alkylation or acylation of **S13** with an appropriate electrophile and strong base (such NaH, NaHMDS etc.).

### SCHEME 3

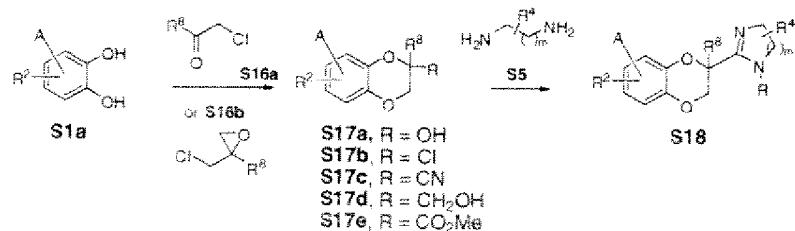


5 Scheme 4 shows an approach in which catechol **S1a** is treated with substituted  
 ketone **S16a** and NaOH. The resulting ketal **S17a** is then sequentially treated with HCl  
 (to give the chloride **S17b**) and then a cyanide source (such as TMSCN, NaCN etc) to  
 provided the nitrile **S17c**. Conversion to to **S18** is accomplished as described  
 previously.

10 Alternatively, catechol **S1a** is treated with epoxide **S16b** and NaOH. The resulting methylene alcohol **S17d** can be converted to the nitrile **S17c** by a four step sequence (oxidation with KMnO<sub>4</sub> to the acid, conversion to the acid chloride with SOCl<sub>2</sub>, amidation with NH<sub>3</sub>, and dehydration with P<sub>2</sub>O<sub>5</sub>)

Alternatively, the methylene alcohol **S17d** is oxidized to the acid and converted to the methyl ester **S17e**. Conversion to **S18** is accomplished as described previously.

**SCHEME 4**



In another embodiment (Scheme 5), nitrile **S2** is reacted with an electrophile and appropriate base to provide **S17c** (with R<sup>3</sup> substitution) which may be converted to **S18** as described previously.

### SCHEME 5

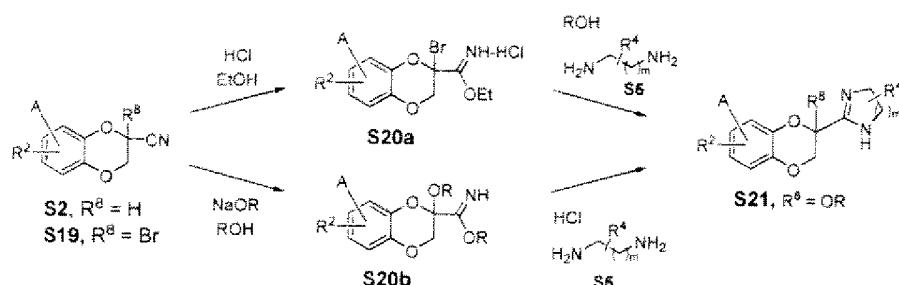


In another embodiment (Scheme 6), nitrile **S2** is brominated with NBS/CCl<sub>4</sub> to provide **S19** which is then converted to **S20a** by treatment with HCl-EtOH.

Subsequent reaction with an alcohol ROH and diamine **S5** provides **S21**.

Alternatively, **S19** is treated with the sodium salt of an appropriate alcohol, NaOR, and an alcohol ROH to provide **S20b**, which is then converted to **S21** (by treatment with HCl and diamine **S5**).

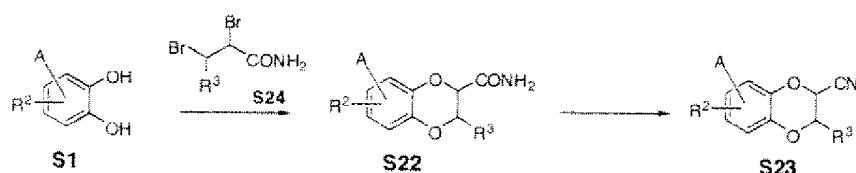
SCHEME 6



In another embodiment (Scheme 7), nitrile **S1** treated with 2,3-

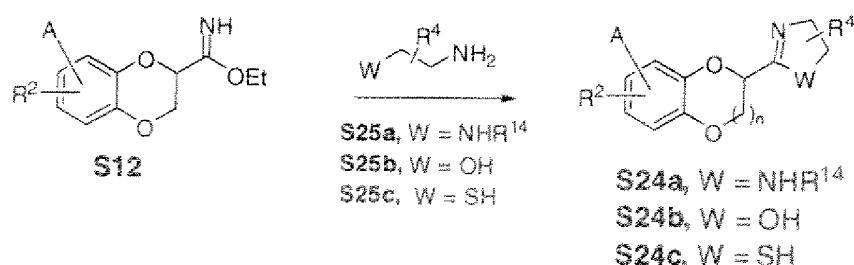
dibromopropionamide (optionally substituted with R<sup>3</sup>) and K<sub>2</sub>CO<sub>3</sub> to provide the carboxamide **S22**. Compound **S22** is then dehydrated with trifluoroacetic anhydride and pyridine to give nitrile **S23**, which is further elaborated as previously described.

SCHEME 7



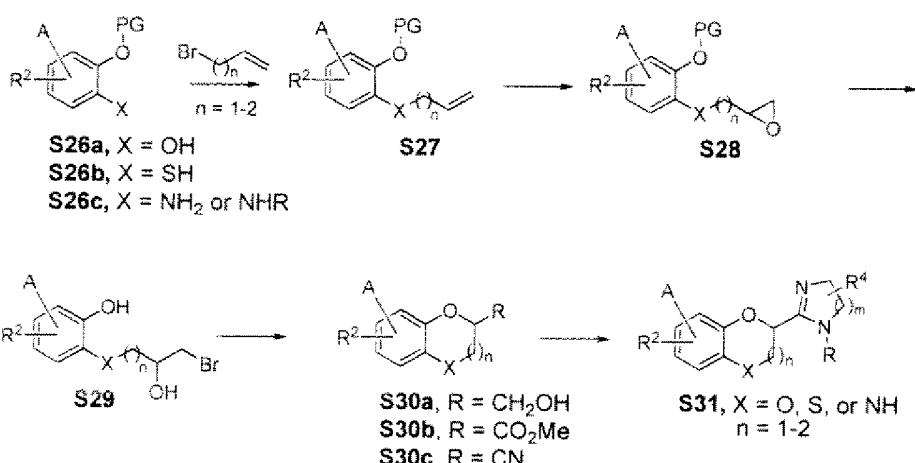
Scheme 8 shows an approach in which the imidate **S12** is condensed with diamine **S25a** (optionally substituted), aminoalcohol **S25b** (optionally substituted), or aminothiol **S25c** (optionally substituted) to give the corresponding imidazoline **S24a**, oxazoline **S24b**, or thiazoline **S24c**.

SCHEME 8



In another embodiment (Scheme 9), an appropriately protected (PG = Me, MOM or the like) and substituted 2-methoxyphenol (**S26a**), 2-methoxythiophenol (**S26b**) or 2-methoxyaniline (**S26c**) is alkylated with allyl bromide or homoallyl bromide to provide **S27** which is oxidized with mCPBA (or other related oxidant). Treatment of 5 resulting epoxide **S28** with HBr causes concomitant epoxide opening and phenol deprotection. The resulting phenol **S29** is reacted NaOH to provide the cyclized methylene alcohol **S30a** (R = CH<sub>2</sub>OH). This compound is converted to **S31** through the methyl ester (**S30b**) or nitrile (**S30c**) as previously described.

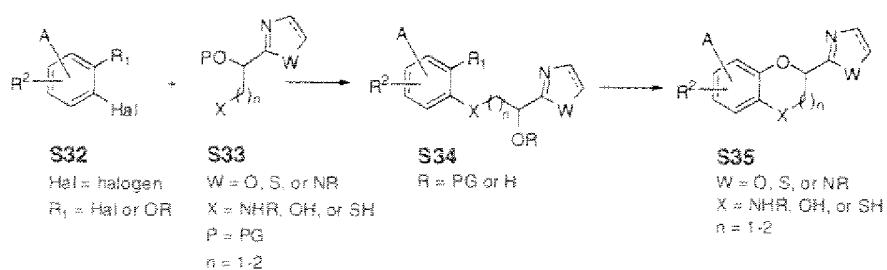
SCHEME 9



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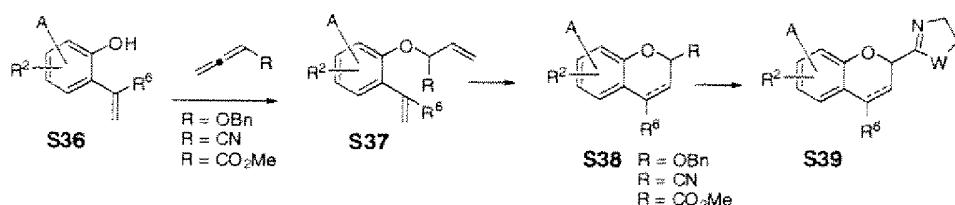
In another embodiment (Scheme 10), an electronically poor compound **S32** (R<sub>1</sub> = OH or halogen; substituted with an electron-withdrawing group such as nitro) is reacted with **S33** in a nucleophilic aromatic substitution reaction (with an appropriate base and/or heat) to provide **S34**, which is then deprotected (R = PG to R = H). 15 When R<sub>1</sub> is halogen, a second nucleophilic displacement occurs to provide **S35**. When R<sub>1</sub> is OH, a displacement occurs through activation of the benzylic alcohol (Mitsunobu or other related conditions).

SCHEME 10



In another embodiment (Scheme 11), the vinyl phenol **S36** is subjected to a Pd catalyzed reaction with an appropriately substituted allene (R = O<sub>Bn</sub>, CN, CO<sub>2</sub>Me, or other group) to provide **S37**. A subsequent metathesis reaction affects cyclization to **S38**. When R = O<sub>Bn</sub>, the benzloxy group is displaced with a cyanide source and 5 Lewis acid (such as TMSCN and BF<sub>3</sub>-OEt<sub>2</sub>) to provide R = CN. The nitrile or ester in **S38** is then further elaborated into **S39** as previously described. The double bond in **S38** or **S39** is optionally reduced to a single bond (by hydrogenation or other method).

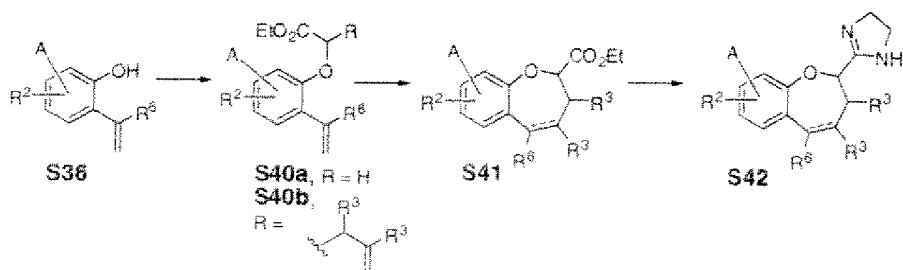
SCHEME 11



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In another embodiment (Scheme 12), the vinyl phenol **S36** is sequentially alkylated with BrCH<sub>2</sub>CO<sub>2</sub>E<sub>t</sub> and then an allyl bromide (optionally substituted). The resulting diene **S40b** undergoes a metathesis reaction to affect cyclization to **S41** (wherein R<sup>3</sup> substituents are independently defined as described in Formula I). 15 Further elaboration of the ester occurs as previously described. The double bond in **S41** or **S42** is optionally reduced to a single bond (by hydrogenation or other method).

SCHEME 12



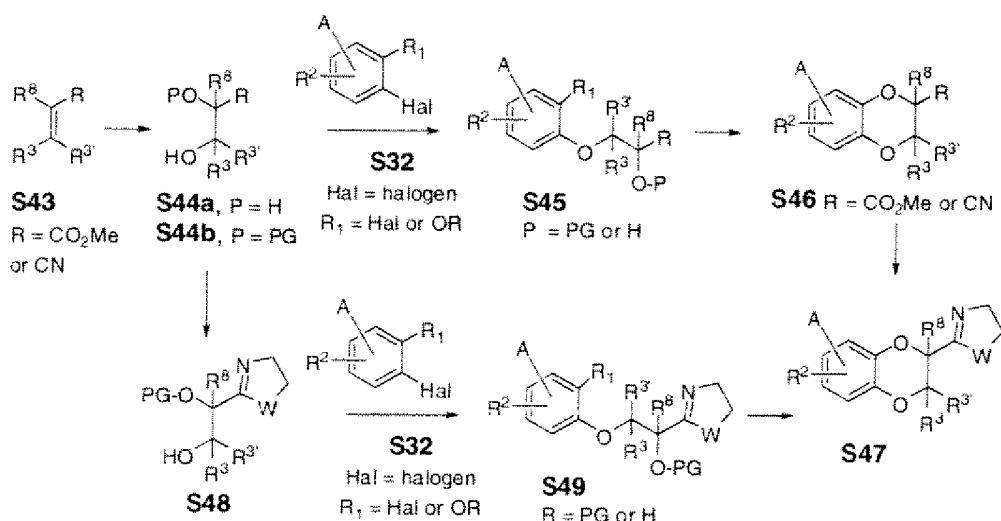
In another embodiment (Scheme 13), a substituted alkene **S43** undergoes a 20 dihydroxylation reaction (with OsO<sub>4</sub>) or asymmetric dihydroxylation (AD) to provide **S44a**, which is then mono-protected with an appropriate protecting group (PG). In a manner analogous to that described in Scheme 10, compound **S44b** is reacted with **S32** and then cyclized to **S46** (R = CO<sub>2</sub>Me or CN). Installation of the oxazoline (W =

O), thiazoline (W = S) or imidazoline (W = NH) occurs as previously described to provide **S47**.

Alternatively, the installation of the oxazoline (W = O), thiazoline (W = S) or imidazoline (W = NH) occurs by reaction of the appropriate reagent with **S44b** (as

5 described earlier) to provide **S48**. Conversion to **S47** occurs as described in Scheme 10.

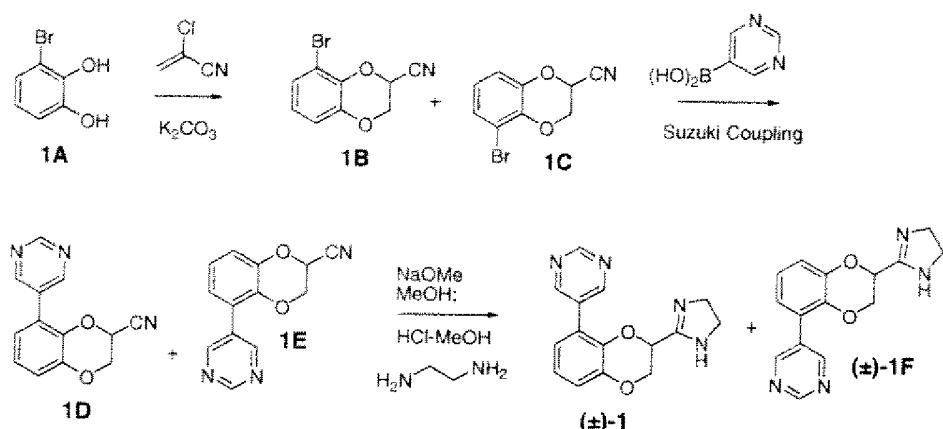
### SCHEME 13



10

The starting materials and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared by literature methods known to those skilled in the art.

15      Compounds of formulae **S3**, **S13**, **S14**, **S18**, **S21**, **S23**, **S24**, **S31**, **S35**, **S39**, **S42** and **S47** can be prepared by the general methods outlined above. Exemplary compounds were prepared as described in the examples below or from starting materials known in the art. These examples are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is 20 not to be considered limited in any way thereby.

PREPARATIVE EXAMPLE 15 **Step 1**

A mixture of 3-bromocatechol (1.00 g, 5.29 mmol), 2-chloroacrylonitrile (0.600 mL, 5.29 mmol), and  $K_2CO_3$  (0.731 g, 5.29 mmol) in anhydrous acetone (10 mL) was refluxed overnight and then concentrated. The residue was diluted with water and extracted with DCM (3x). The combined organic layer was washed with brine and concentrated. Chromatography (25% EtOAc-hexanes) provided the two nitriles **1B** and **1C** as a mixture in a 4:1 ratio (1.06g, 67%).

**Step 2**

A 4:1 mixture of **1B** and **1C** (500 mg, 2.08 mmol) in DME-H<sub>2</sub>O (3:1, 15 mL) was treated with pyrimidine-5-boronic acid (516 mg, 4.16 mmol), Pd(dppf)Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> (425 mg, 0.52 mmol), K<sub>3</sub>PO<sub>4</sub> (884 mg, 4.2 mmol) and then microwaved at 125 °C for 15 min. The reaction was diluted with water and extracted with DCM (3x). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and chromatographed (0-4% of (7N NH<sub>3</sub>-MeOH) in DCM) to provide the desired products (402 mg, 80%, 3:1 mixture of **1D** and **1E**). LCMS m/z 240 (MH<sup>+</sup>).

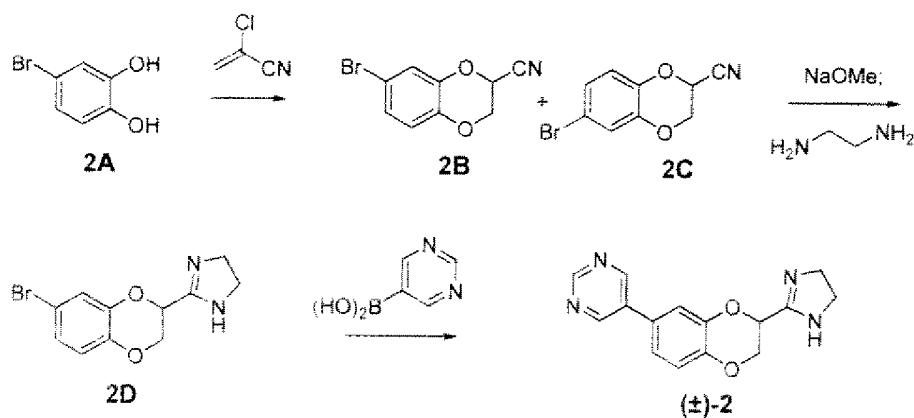
**Step 3**

A mixture of **1D** and **1E** (3:1, 0.390 g, 1.7 mmol) and NaOMe (0.5 M/MeOH, 0.7 mL, 0.33 mmol) in MeOH (2.5 mL) was stirred 1h at RT. The reaction was then cooled in an ice bath and slowly treated with ethylenediamine (0.125 mL, 1.86 mmol).

After 5 min, HCl-MeOH (1.25 M, 1.48 mL, 1.86 mmol) was added. The reaction was allowed to slowly warm to RT and stirred overnight. The mixture was concentrated, treated with 2N NH<sub>3</sub>-MeOH, concentrated and then subjected to chromatography (0-4% of (7N NH<sub>3</sub>-MeOH) in DCM) to provide the title compound ( $\pm$ )-1 (0.39 g, 66%, LCMS m/z 283, MH<sup>+</sup>) and a mixture of ( $\pm$ )-1 and ( $\pm$ )-1F (0.9 g, 20%, 1:2 ratio of ( $\pm$ )-1 and ( $\pm$ )-1F (LCMS m/z 283, MH<sup>+</sup>)). The mixture is further purified to provide pure ( $\pm$ )-1F.

The racemic compounds ( $\pm$ )-1 and ( $\pm$ )-1F, or their precursors, are resolved to pure enantiomers by HPLC separation on an appropriate chiral column, such as a Chiracel OD, Chiralpak AD, Lux Cellulose-2 or other related cellulose or amylose derivatized column, using the appropriate solvent system (such as IPA-hexane, EtOH-hexane, or MeOH-supercritical CO<sub>2</sub>) and optional additive (such as 0.1% Et<sub>2</sub>NH or TEA).

## 15 PREPARATIVE EXAMPLE 2



### Step 1

A mixture of 4-bromocatechol 2A (5.00 g, 26.4 mmol), 2-chloroacrylonitrile (3.0 mL, 26.4 mmol), and K<sub>2</sub>CO<sub>3</sub> (3.66 g, 26.4 mmol) in acetone (50 mL) was refluxed overnight. The reaction was concentrated, diluted with water, and extracted with DCM (3x). The organic layer was washed with brine and concentrated. Chromatography (10-20% EtOAc/hex) provided 2B with a trace amount of 2C.

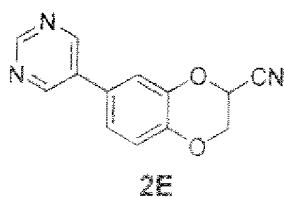
**Step 2**

A stirred mixture of **2B** (1.00 g, 4.16 mmol) and NaOMe (0.5 M/MeOH, 0.716 mL) in MeOH (5.0 mL, 120 mmol) was stirred overnight at RT. The reaction was cooled in an ice bath and slowly treated with a solution of ethylenediamine (0.310 mL, 5 4.64 mmol) in MeOH (0.6 mL, 10 mmol). After a few minutes, HCl (1.25 M/MeOH, 3.50 mL) was added dropwise. The mixture was allowed to warm to at RT and was stirred 2d. The reaction was made slightly acidic with methanolic HCl and filtered. The filtrate was concentrated and taken up in water. The solution was basified with 2N NaOH and extracted with DCM. The organic layer 10 was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The reaction was chromatographed (0-10% of NH<sub>3</sub>-MeOH in DCM,) to obtain **2D**. LCMS m/z 283/285 (MH<sup>+</sup>).

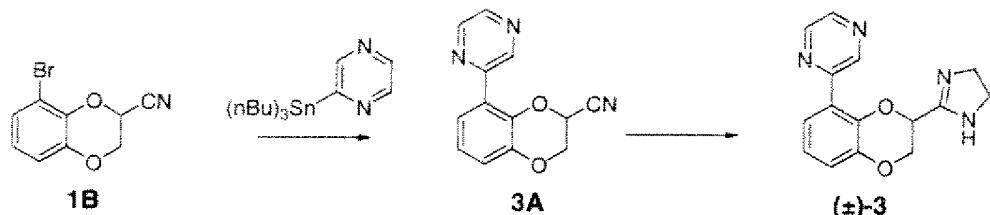
**Step 3**

A mixture of **2D** (20 mg, 0.071 mmol) and pyrimidine-5-boronic acid (17.5 mg, 15 0.14 mmol), Pd(dppf)Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> (14.4 mg, 0.018 mmol), and K<sub>3</sub>PO<sub>4</sub> (30 mg, 0.14 mmol) in a solution of DME (1 mL, 10 mmol) were microwaved for 15 minutes at 100 °C. The mixture was diluted with DCM and water. The layers were separated and the aqueous layer was extracted with DCM (2x). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The 20 reaction was chromatographed (0-10% of NH<sub>3</sub>-MeOH in DCM) to obtain the title compound ( $\pm$ )-**2**. LCMS m/z 283 (MH<sup>+</sup>).

In an alternative approach, compound **2B** was coupled pyrimidine-5-boronic acid as described in Step 3 to provide **2E** (LCMS m/z 240, MH<sup>+</sup>). Compound **2E** is 25 then converted to ( $\pm$ )-**2** with NaOMe and ethylenediamine (as described in Step 2) or with HCl gas/MeOH and ethylenediamine (as described in *J. Med. Chem.* **1983**, *26*, 823 or *J. Med. Chem.* **2008**, *51*, 4289).



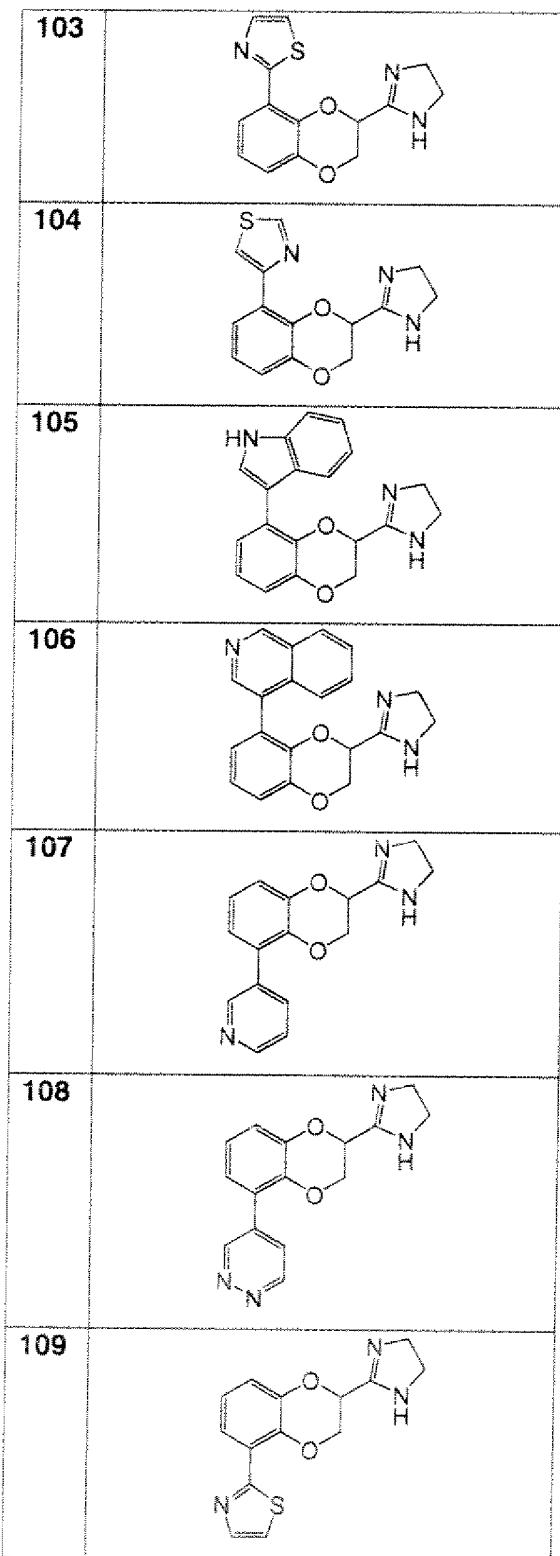
### PREPARATIVE EXAMPLE 3

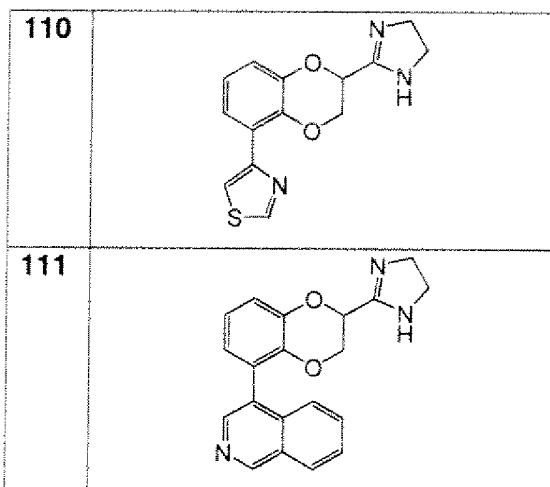


5 A solution of compound **1B** in dioxane (0.3M) in a microwave vial is treated with  
 2-tributylstannylpyrazine (2 eq),  $(PPh_3)_4Pd$  (0.2 eq) and KF (3 eq). The reaction  
 mixture is heated in an oil bath at 100 °C overnight. The mixture is basified with 10%  
 NaOH and diluted with DCM. The aqueous layer is extracted with DCM in three  
 portions. The combined organic phase is dried over anhydrous sodium sulfate and  
 10 concentrated to dryness to provide **3A**, which is further elaborated to ( $\pm$ )-**3** as  
 previously described.

The following compounds are prepared in a similar manner to the procedures and schemes described in the examples above.

Cpd	Structure
100	
101	
102	



**ASSAY:**

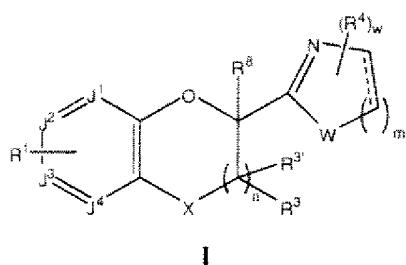
Efficacy agonist activity values (Emax, GTP $\gamma$ S assay) for  $\alpha$ 2A and  $\alpha$ 2C were determined by following the general procedure detailed by Umland *et. al* ("Receptor reserve analysis of the human  $\alpha_{2c}$ -adrenoceptor using [ $^{35}$ S]GTP $\gamma$ S and cAMP functional assays" European Journal of Pharmacology **2001**, 411, 211-221). For the purposes of the present invention, a compound is defined to be a specific or at least functionally selective agonist of the  $\alpha$ 2C receptor subtype if the compound's efficacy at the  $\alpha$ 2C receptor is  $\geq$  30% Emax (GTP $\gamma$ S assay) and its efficacy at the  $\alpha$ 2A receptor is  $\leq$  35% Emax (GTP $\gamma$ S assay). Additionally, for the purposes of this invention, a compound is defined to be an antagonist of the  $\alpha$ 2C receptor subtype if the compound's efficacy at the  $\alpha$ 2C receptor is  $<$  30% Emax (GTP $\gamma$ S assay) and the  $K_i$  at the  $\alpha$ 2C receptor subtype is  $<$  500 nM, preferentially  $<$  200 nM, and most preferentially  $<$  20 nM.

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

## CLAIMS

What is claimed is:

1. A compound represented by Formula I



or a pharmaceutically acceptable salt thereof

wherein:

- J<sup>1</sup>, J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are independently -N-, -N(O)-, or -C(R<sup>2</sup>)-;
- X is -C(R<sup>6</sup>)(R<sup>6</sup>)-, -N(R<sup>6</sup>)-, -O- or -S-;
- W is -N(R<sup>14</sup>)-, -O- or -S-;
- is a single or double bond, provided that there cannot be two continuous double bonds;
- R<sup>1</sup> is a ring selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heterocyclenyl, and heteroaryl, each of which is optionally substituted with at least one R<sup>12</sup>;
- R<sup>2</sup> is absent or independently selected from the group consisting of H, halo, -CN, -NO<sub>2</sub>, -OH, -SF<sub>6</sub>, -OSF<sub>6</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>YR<sup>7</sup>, -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)YR<sup>7</sup>, -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>N(R<sup>7</sup>)CN, -[C(R<sup>a</sup>)(R<sup>b</sup>)]<sub>q</sub>OYR<sup>7</sup>, and -(CH<sub>2</sub>)<sub>q</sub>ON=CR<sup>7</sup>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R<sup>5</sup>;
- Y is selected from the group consisting of a bond, -C(=O)-, -C(=O)NR<sup>7</sup>-, -C(=O)O-, -C(=O)N(R<sup>c</sup>)-O-, -C(=NR<sup>7</sup>)-, -C(=NOR<sup>7</sup>)-, -C(=NR<sup>7</sup>)NR<sup>7</sup>-, -C(=NR<sup>7</sup>)NR<sup>7</sup>O-, -C(=N-CN)-, -S(O)<sub>p</sub>-, -SO<sub>2</sub>NR<sup>7</sup>-, and -C(=S)NR<sup>7</sup>-;
- wherein R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of H, alkyl, alkoxy, and halo, and
- R<sup>c</sup> is H or alkyl;

- R<sup>3</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup> and -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycll, and heterocyclalkyl groups optionally substituted with at least one R<sup>5</sup>;
- R<sup>3</sup> is independently selected from the group consisting of H, -OH, halo, and alkyl, and alkoxy; or
- R<sup>3</sup> and R<sup>3</sup> may be taken together to form (=O), provided that when n > 1, there are no more than 1 (=O) groups;
- R<sup>4</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>7</sup>, -C(O)-OR<sup>7</sup>, -C(O)-NR<sup>7</sup>, and (=O), and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycll, and heterocyclalkyl groups optionally substituted with at least one R<sup>5</sup>;
- R<sup>5</sup> is independently selected from the group consisting of H, halo, -OH, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycll, and heterocyclalkyl groups, each of which is optionally substituted with at least one (preferably 1 to 5, more preferably 1 to 3) of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O) groups,
- R<sup>6</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup> and -C(O)-N(R<sup>7</sup>)R<sup>10</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycll, and heterocyclalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O) groups, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;
- R<sup>6</sup> is independently selected from the group consisting of H, -S(O)<sub>p</sub>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, -C(O)-N(R<sup>7</sup>)R<sup>10</sup> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycll, and heterocyclalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> and/or 1

or 2 (=O) groups substituents, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>; or

when X is -C(R<sup>6</sup>)(R<sup>6'</sup>), R<sup>6</sup> and R<sup>6'</sup> taken together can form (=O);

R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl,  
5 alkynyl, cycloalkyl, cycloalkylalkyl, cycloenyl, cyclocyclylalkyl, aryl, arylalkyl,  
heterocycl, heterocyclalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and  
heteroarylalkyl groups, each of which is optionally substituted one or more times by  
R<sup>12</sup>;

R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl,  
10 alkynyl, cycloalkyl, cycloalkylalkyl, cycloenyl, cyclocyclylalkyl, aryl, arylalkyl,  
heterocycl, heterocyclalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and  
heteroarylalkyl groups, each of which is optionally substituted one or more times by  
R<sup>12</sup>; or

a) when a variable is -NR<sup>7</sup>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup> or -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>, R<sup>7</sup> and R<sup>7</sup>  
15 together with the nitrogen atom to which they are attached independently form  
a 3- to 8-membered heterocycl, heterocyclyl or heteroaryl ring having, in  
addition to the N atom, 1 or 2 additional hetero atoms independently selected  
from the group consisting of O, N, -N(R<sup>9</sup>)- and S, wherein said rings are  
optionally substituted by 1 to 5 independently selected R<sup>12</sup> moieties and/or 1 or  
20 2 (=O) groups, or

b) when a variable is -(CH<sub>2</sub>)<sub>q</sub>ON=CR<sup>7</sup>R<sup>7</sup>, R<sup>7</sup> and R<sup>7</sup> together with the  
carbon atom to which they are attached independently form a 3- to 8-  
membered cycloalkyl, cycloalkenyl, aryl, heterocycl, heterocyclyl or  
heteroaryl ring, wherein said heterocycl, heterocyclyl or heteroaryl rings  
25 have 1-3 heteroatoms which are independently selected from the group  
consisting of O, N, -N(R<sup>9</sup>)- and S, wherein said rings are optionally substituted  
by 1 to 5 independently selected R<sup>12</sup> moieties and/or 1 or 2 (=O) groups,

R<sup>8</sup> is independently selected from the group consisting of H, -OH,  
halo, -CN, -NO<sub>2</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -S(O)<sub>p</sub>NR<sup>7</sup>R<sup>7</sup> and alkyl, alkoxy, alkenyl, alkenyloxy,  
30 alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl,  
heterocycl, and heterocyclalkyl groups optionally substituted with at least one R<sup>5</sup>;

R<sup>9</sup> is independently selected from the group consisting of H, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, and -S(O)<sub>p</sub>-R<sup>10</sup> and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> substituents and/or 1 or 2 (=O) groups;

5 and

R<sup>10</sup> is independently selected from the group constituting of H, and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> substituents and/or 1 or 2 (=O);

10 R<sup>11</sup> is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O)

15 groups;

R<sup>11</sup> is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

16 R<sup>12</sup> is independently selected from the group consisting of H, halo, -  
20 OH, -CN, -NO<sub>2</sub>, -SF<sub>5</sub>, -OSF<sub>5</sub>, -N(R<sup>11</sup>)<sub>2</sub>, -C(O)-OR<sup>13</sup>, -C(O)-R<sup>13</sup>, -N(R<sup>13</sup>)-C(O)-R<sup>13</sup>, -  
N(R<sup>13</sup>)-C(O)<sub>2</sub>-R<sup>13</sup>, -C(O)-N(R<sup>11</sup>)<sub>2</sub>, N(R<sup>11</sup>)-S(O)<sub>2</sub>-R<sup>11</sup>, -S(O)<sub>2</sub>-N(R<sup>11</sup>)<sub>2</sub> and -S(O)<sub>p</sub>R<sup>11</sup>  
and/or 1 or 2 (=O) groups, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl,  
cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy,  
heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyoxy, heterocyclylalkyl,  
25 heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclalkoxy, and  
heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least  
once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -  
OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted  
cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted  
30 heterocyclenyoxy, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O) groups,  
wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy,

optionally substituted heteroaryloxy, and heterocyclyenoxy when substituted are substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R<sup>11</sup>;

R<sup>13</sup> is independently H, alkyl, or aryl;

- R<sup>14</sup> is selected from the group consisting of H, -C(O)-R<sup>10</sup>, -C(O)-OR<sup>10</sup>, -C(O)-N(R<sup>7</sup>)(R<sup>7</sup>), and -S(O)<sub>p</sub>-R<sup>10</sup>, SO<sub>2</sub>-NR<sup>7</sup>R<sup>7</sup> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocycl, and heterocyclalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> and/or 1 or 2 (=O) groups substituents, and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;

10 q is independently an interger from 0-10;

n is 1 or 2;

m is an integer from 1-3;

p is independently an integer from 0-2; and

w is independently an integer from 0-6,

15 provided that when X is O and W is NH, m is 1 and n is 1, then R<sup>1</sup> cannot be phenyl.

2. The compound according to claim 1 wherein

W is -N(R<sup>14</sup>)- or -O- ;

- R<sup>1</sup> is selected from the group consisting of R<sup>1</sup> is optionally substituted aryl, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted 20 pyridyl, optionally substituted pyrimidyl, optionally substituted furanyl, optionally substituted thiophenyl, optionally substituted quinolinyl, optionally substituted indolyl, optionally substituted pyrrolyl, and optionally substituted pyrrolidinyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, optionally substituted isoxazolyl, optionally substituted imidazole, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted tetrazolyl, optionally substituted imidazopyrimidinyl, optionally substituted thiazolyl, optionally substituted isothiazolyl, 25 optionally substituted indazolyl, optionally substituted benzofuranyl, optionally substituted benzothiphenyl, optionally substituted isoquinolyl, optionally substituted benzimidazolyl, optionally substituted benzthiazolyl, optionally substituted quinoxaliny, wherein said groups may be optionally substituted 1 to 3 times with substitutents selected from the group consisting of alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, -C(O)-amino; -C(O)-alkylamino, -C(O)-dialkylamino, -

C(O)-OH, -C(O)-Oalkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said aryl and heteroaryl are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxyl;

5 R<sup>2</sup> is independently selected from the group consisting of H, -OH, halo, -CN, -NO<sub>2</sub>, -S(O)<sub>p</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, and alkyl and alkoxy groups optionally substituted with at least one R<sup>5</sup>;

R<sup>3</sup> is independently selected from the group consisting of H and halo and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl,

10 heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R<sup>5</sup>;

R<sup>4</sup> is independently selected from the group consisting of H, halo, -OH, -CN, and NO<sub>2</sub> and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl

15 groups optionally substituted with at least one R<sup>5</sup>;

R<sup>5</sup> is independently selected from the group consisting of H, halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup>, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O);

20 R<sup>6</sup> is selected from the group consisting of H and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O), and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;

25 R<sup>6</sup> is selected from the group consisting of H and alkyl, alkoxy and aryl, each of which is with at least one of halo, -OH, -CN, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, and -S(O)<sub>p</sub>R<sup>7</sup> substituents and/or 1 or 2 (=O), and -C(=O)R<sup>7</sup>, -C(=O)OR<sup>7</sup>, -C(=O)NR<sup>7</sup>R<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup> and -SO<sub>2</sub>NR<sup>7</sup>R<sup>7</sup>;

30 R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloenyl, cyclocyclenylalkyl, aryl, arylalkyl,

heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times by R<sup>12</sup>;

R<sup>7</sup> is independently selected from the group consisting of H and alkyl, alkenyl, 5 alkynyl, cycloalkyl, cycloalkylalkyl, cycloclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times by R<sup>12</sup>;

R<sup>8</sup> is selected from the group consisting of H, -OH, halo, -CN and -NR<sup>7</sup>R<sup>7</sup>, and 10 alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R<sup>5</sup>;

R<sup>11</sup> is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, 15 heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> substituents and/or 1 or 2 (=O);

R<sup>11'</sup> is independently selected from the group consisting of H, alkyl, alkoxy, 20 alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R<sup>12</sup> is independently selected from the group consisting of H, halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup>, and/or 1 or 2 (=O), and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, 25 heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyoxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclialkoxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least one by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally 30 substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyoxy, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O), wherein said optionally substituted alkoxy, aryloxy,

optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyoxy when substituted are substituted one or more times by R<sup>11</sup>;

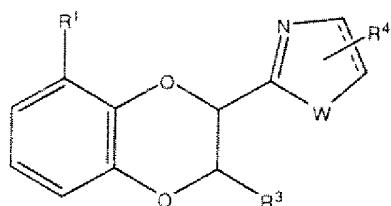
R<sup>13</sup> is independently selected from the group consisting of H or alkyl; and

- R<sup>14</sup> is selected from the group consisting of H and alkyl, cycloalkyl, aryl,  
 5 arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one halo, -OH, -CN, -NO<sub>2</sub>, -N(R<sup>11</sup>)<sub>2</sub>, and -S(O)<sub>p</sub>R<sup>11</sup> and/or 1 or 2 (=O); and

q is 0 or 1,

or a pharmaceutically acceptable salt thereof.

- 10 3. The compound according to claim 2, which has the formula



or a pharmaceutically acceptable salt thereof.

- 15 4. The compound according to claim 3, wherein

R<sup>1</sup> is a ring selected from the group consisting of pyrazole, pyrimidine, oxazole and isoxazole wherein wherein said rings may be optionally substituted 1 to 3 times with substitutents selected from the group consisting of alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, -C(O)-amino; -C(O)-alkylamino, -

- 20 C(O)-dialkylamino, -C(O)-OH, -C(O)-Oalkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said rings are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxy;

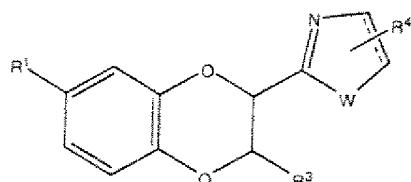
----- is a single bond;

- 25 W is -N(R<sup>14</sup>); and

R<sup>14</sup> is H or alkyl

or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 2, which has the formula



or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5 wherein

- 5        R<sup>1</sup> is a ring selected from the group consisting of pyrazole, pyrimidine, oxazole and isoxazole wherein wherein said rings may be optionally substituted 1 to 3 times with substitutents selected from the group consisting of alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, -C(O)-amino; -C(O)-alkylamino, -C(O)-dialkylamino, -C(O)-OH, -C(O)-Oalkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, 10      amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said rings are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxy;

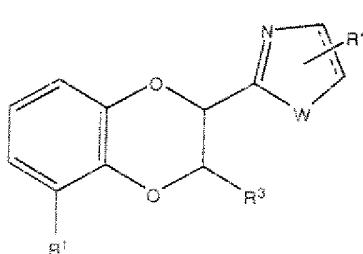
— is a single bond;

W is -N(R<sup>14</sup>); and

- 15      R<sup>14</sup> is H or alkyl,

or a pharmaceutically acceptable salt, thereof.

7. The compound according to claim 1, which is selected from the group consisting of



- 20      or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 5 wherein

- R<sup>1</sup> is a ring selected from the group consisting of pyrazole, pyrimidine, oxazole and isoxazole wherein wherein said rings may be optionally substituted 1 to 3 times with substitutents selected from the group consisting of alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, -C(O)-amino; -C(O)-alkylamino, -C(O)-dialkylamino, -C(O)-OH, -C(O)-Oalkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, 25      amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said rings are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxy;

C(O)-dialkylamino, -C(O)-OH, -C(O)-Oalkyl, amino-C(O)-alkyl, amino-C(O)-O-alkyl, amino-S(O)<sub>2</sub>-alkyl, alkoxy, haloalkoxy, aryl, and heteroaryl, wherein said rings are optionally substituted 1 to 3 times by alkyl, haloalkyl, nitro, cyano, halo, hydroxyl, amino, alkylamino, dialkylamino, alkoxy, and haloalkoxy;

- 5        ----- is a single bond;  
W is -N(R<sup>14</sup>); and  
R<sup>14</sup> is H or alkyl,  
or a pharmaceutically acceptable salt thereof.
9. A pharmaceutical composition comprising at least one compound of claim 1, or a  
10 pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable  
carrier, adjuvant or vehicle, provided that when the composition is a liquid, aqueous  
composition one or more solubility enhancing components are excluded with the  
exception of cyclodextrin.
10. The pharmaceutical composition of claim 9, further comprising one or more  
15 additional therapeutic agents.
11. The pharmaceutical composition of claim 10, further comprising one or more  
additional therapeutic agents, wherein said additional therapeutic agents are selected  
from the group consisting of steroids, glucocorticosteroids, PDE-4 inhibitors, anti-  
muscarinic agents, muscle relaxants, cromolyn sodium, H<sub>1</sub> receptor antagonists, 5-  
20 HT<sub>1</sub> agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II  
receptor agonists, β-blockers, long and short acting β-agonists, leukotriene  
antagonists, diuretics, aldosterone antagonists, ionotropic agents, natriuretic peptides,  
pain management/analgesic agents, anti-anxiety agents, anti-migraine agents,  
sedatives, NMDA receptor antagonists, alpha-adrenergics not including alpha-1  
25 receptor antagonists, anticonvulsants, tachykinin (NK) antagonists, COX-2 inhibitors,  
neuroleptics, vanilloid receptor agonists or antagonists, beta-adrenergics, local  
anaesthetic, corticosteroids, serotonin receptor agonists or antagonists, PDEV  
inhibitors, alpha-2-delta ligands, cannabinoids and therapeutic agents suitable for  
treating heart conditions, psychotic disorders, or glaucoma.
- 30 12. A method for treating one or more conditions associated with α2C adrenergic  
receptors, comprising administering to a mammal in need of such treatment a  
compound of claim 1 or a pharmaceutically acceptable salt thereof.

13. The method of claim 12 wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, chronic heart failure, cardiac ischemia, manic disorders, depression, anxiety, migraine, stress-induced urinary incontinence, neuronal damage from ischemia,  
5 schizophrenia, attention deficit hyperactivity disorder, and symptoms of diabetes.
14. The method of claim 13 wherein the condition is congestion.
15. The method of claim 14, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.
- 10 16. The method of claim 14, wherein the congestion is caused by polyps or is associated with the common cold.
17. The method of claim 12, wherein the condition is pain.
18. The method of claim 17, wherein the pain is associated with neuropathy, inflammation, arthritis, or diabetis.
- 15 19. The method of claim 12, wherein the condition is Alzheimer's disease, depression, anxiety or Parkinson's disease.

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/059641

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C07D407/14 C07D417/14 A61K31/4178 A61P11/02

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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GENTILI F ET AL: "Alpha2-Adrenoreceptors Profile Modulation. 4. From Antagonist to Agonist Behaviour" J. MED. CHEM., vol. 51, 25 June 2008 (2008-06-25), pages 4289-4299, XP002557308 cited in the application table 3 -----	1-19
A	WO 2008/100459 A (SCHERING CORP [US]; ZHENG JUNYING [US]; MCCORMICK KEVIN D [US]; CHAO J) 21 August 2008 (2008-08-21) page 5, line 20 - page 10, line 22 -----	1-19
A	WO 2007/024949 A (SCHERING CORP [US]; PHARMACOPEIA DRUG DISCOVERY [US]; MCCORMICK KEVIN) 1 March 2007 (2007-03-01) page 3, line 15 - page 6, line 3 -----	1-19

Further documents are listed in the continuation of Box C.

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

- \*T\* 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
- \*X\* 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
- \*Y\* 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

Date of mailing of the international search report

26 November 2009

08/12/2009

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Authorized officer

Usuelli, Ambrogio

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/059641

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 2008100459	A 21-08-2008	AR	065308 A1		27-05-2009
		CA	2678069 A1		21-08-2008
		CL	4292008 A1		18-08-2008
		PE	06502009 A1		29-05-2009
WO 2007024949	A 01-03-2007	AR	057771 A1		19-12-2007
		AU	2006283109 A1		01-03-2007
		CA	2620173 A1		01-03-2007
		CN	101374830 A		25-02-2009
		EC	SP088221 A		26-03-2008
		EP	1934203 A2		25-06-2008
		JP	2009185016 A		20-08-2009
		JP	2009506051 T		12-02-2009
		KR	20080037070 A		29-04-2008
		ZA	200802495 A		31-12-2008