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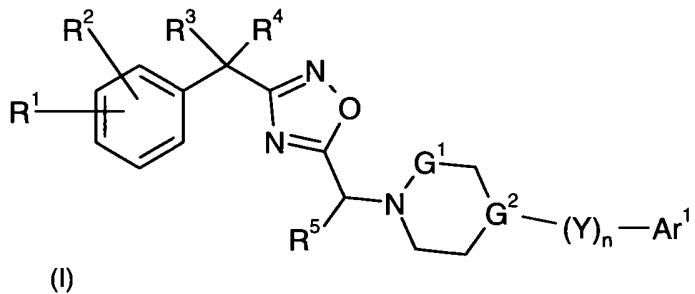
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## (54) Title: OXADIAZOLE COMPOUNDS AS CALCIUM CHANNEL ANTAGONISTS



**(57) Abstract:** This invention relates to novel compounds of formula (I) wherein  $R_1^1$ ,  $R_2^1$ ,  $R_3^1$ ,  $R_4^1$ ,  $R_5^1$ ,  $G_1^1$ ,  $G_2^1$ ,  $Y$ ,  $n$ , and  $Ar$  are as defined in the specification, pharmaceutical compositions containing said compounds useful as calcium channel antagonists, and to methods of causing vasodilation of treating a disease selected from hypertension, congestive heart failure, stroke, ischaemic heart disease, and angina pectoris and of reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) during surgery (e.g., coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA) or any percutaneous transluminal coronary intervention (PTCI), organ transplantation, or other non-cardiac surgeries), chronic pain, inflammatory pain, neuropathic pain, visceral pain, nociceptive pain, multiple sclerosis, neurodegenerative disorder, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, sciatica, fibromyalgia and causalgia.



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## OXADIAZOLE COMPOUNDS AS CALCIUM CHANNEL ANTAGONISTS

## BACKGROUND OF THE INVENTION

5 This invention relates to oxadiazole derivatives. More particularly, this invention relates to oxadiazole derivatives that are calcium channel antagonists. The oxadiazole derivatives of the invention modulate one or more of the L-type, N-type, and T-type calcium channels and are useful as pharmaceutical agents in the treatment of a variety of disorders ranging from pain, hypertension, angina, and/or obesity.

10 Voltage-gated calcium channels are membrane-spanning, multi-subunit proteins that open in response to membrane depolarization, allowing calcium ion entry from the extracellular milieu. Calcium channels were initially classified based on the time and voltage-dependence of channel opening and on the sensitivity to pharmacological block. The categories were low-voltage activated (primarily T-type) and high-voltage activated (L, N, P, Q or R-type). Recently, an alternative classification scheme was devised  
 15 based upon the molecular subunit composition, as summarized in Table 1 (Hockerman G H, Peterson B Z, Johnson B D, Catterall W A. 1997. *Annu Rev Pharmacol Toxicol* 37: 361-96).

There are four primary subunit types that make up calcium channels-- $\alpha_1$ ,  $\alpha_2\delta$ ,  $\beta$  and  $\gamma$ . The  $\alpha_1$  subunit is the primary determinant of the pharmacological properties and contains the channel pore and voltage sensor (Hockermann G H, Peterson B Z, Johnson B D, Catterall W A. 1997. *Annu Rev Pharmacol Toxicol* 37: 361-96; Striessnig J. 1999. *Cell Physiol Biochem* 9: 242-69). Ten isoforms of the  $\alpha_1$  subunit are known, as indicated in Table 1. The  $\alpha_2\delta$  subunit consists of two disulfide linked subunits,  $\alpha_2$ , which is primarily extracellular and a transmembrane  $\delta$  subunit. Four isoforms of  $\alpha_2\delta$  are known,  $\alpha_2\delta$ -1,  $\alpha_2\delta$ -2,  $\alpha_2\delta$ -3 and  $\delta_2\delta$ -4. The  $\beta$  subunit is a non-glycosylated cytoplasmic protein that binds to the  $\alpha_1$  subunit. Four isoforms are known, termed  $\beta_1$  to  $\beta_4$ . The  $\gamma$  subunit is a transmembrane protein that has been biochemically isolated as a component of  $Ca_v1$  and  $Ca_v2$  channels. The nomenclature for voltage-gated calcium channels is based upon the content of the  $\alpha_1$  subunit, as indicated in Table 1. Each type of  $\alpha_1$  subunit can associate with a variety of  $\beta$ ,  $\alpha_2\delta$  or  $\gamma$  subunits, so that each  $Ca_v$  type corresponds to many  
 25 different combinations of subunits.

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TABLE 1  
 Classification of Neuronal Calcium Channels

Cav Nomenclature	$\alpha_1$ subunit	Pharmacological name
$Ca_v1.1$	$\alpha_{1S}$	L- type
$Ca_v1.2$	$\alpha_{1C}$	L-type
$Ca_v1.3$	$\alpha_{1D}$	L- type
$Ca_v1.4$	$\alpha_{1F}$	
$Ca_v2.1$	$\alpha_{1A}$	P- or Q-type
$Ca_v2.2$	$\alpha_{1B}$	N-type

$\text{Ca}_v2.3$	$\alpha_{1E}$	R-type
$\text{Ca}_v3.1$	$\alpha_{1G}$	T-type
$\text{Ca}_v3.2$	$\alpha_{1H}$	T-type
$\text{Ca}_v3.3$	$\alpha_{1I}$	T-type

$\text{Ca}_v2$  currents are found almost exclusively in the central and peripheral nervous system and in neuroendocrine cells and constitute the predominant forms of presynaptic voltage-gated calcium current. Presynaptic action potentials cause channel opening and neurotransmitter release is steeply dependent upon the subsequent calcium entry. Thus,  $\text{Ca}_v2$  channels play a central role in mediating neurotransmitter release.

N-type calcium channels ( $\text{Ca}_v2.2$ ) contain high-affinity binding sites for the peptide toxins  $\omega$ -conotoxin-MVIIC and  $\omega$ -conotoxin-GVIA, respectively, and these peptides have been used to determine the distribution and function of each channel type.  $\text{Ca}_v2.2$  is highly expressed at the presynaptic nerve terminals of neurons from the dorsal root ganglion and neurons of lamina I and II of the dorsal horn (Westenbroek R E, Hoskins L, Catterall W A. 1998. *J Neurosci* 18: 6319-30; Cizkova D, Marsala J, Lukacova N, Marsala M, Jergova S, et al. 2002. *Exp Brain Res* 147: 456-63).  $\text{Ca}_v2.2$  channels are also found in presynaptic terminals between second and third order interneurons in the spinal cord. Both sites of neurotransmission are very important in relaying pain information to the brain.

Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase 2 (COX-2) inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opioids until high doses are reached. Gabapentin is currently the most widely used therapeutic for the treatment of neuropathic pain, although additional therapeutic agents are desirable, particularly those with broader ranges of activities.

The T-type calcium channel ( $\text{Ca}_v3.1$ ,  $\text{Ca}_v3.2$ , and  $\text{Ca}_v3.3$ ) may become over-expressed due to genetic or environmental causes, such as epilepsy (Tsakiridou, E. et al., *J. Neurosci*. 1995, 15, 3110-3117), high blood pressure (Self, D. A. et al., *J. Vacs. Res.* 1994, 31, 359-366), ventricular hypertrophy (Nuss, H. B. et al., *Circ. Res.* 1995, 73, 777-7825), pain (Shin, H. S. et al., *Science* 2003, 302, 117-119), and angina pectoris (Van der Vring, J. A. et al., *Am. J. Ther.* 1999, 6, 229- 233). A representative drug for blocking the T-type calcium channel is mibepradil of Hoffman La Roche Ltd. The drug was found to be effective in treating high blood pressure, angina pectoris and cerebral apoplexy. It was approved for treating high blood pressure in May, 1997. However, a side effect caused by a drug-drug interaction due to inhibition of CYP 3A4 hepatic enzyme was discovered. As such, the drug was withdrawn from the market in June, 1999.

Dihydropyridine (DHP) antagonists of L-type calcium channels ( $\text{Ca}_v1.1$ ,  $\text{Ca}_v1.2$ , and  $\text{Ca}_v1.3$ ) are widely used therapeutics in the treatment of hypertension, angina, arrhythmias, congestive heart failure, cardiomyopathy, atherosclerosis, and cerebral and peripheral vascular disorders (Janis and Triggle, 1990 CRC Press, Cleveland). In addition to L-type channel activity, some of the DHPs are sensitive to T-type channel activity. (N. Akaike, H. Kanaide, T, Kuga, M, Nakamura, J. Sadoshima and Tomoike "Low Voltage

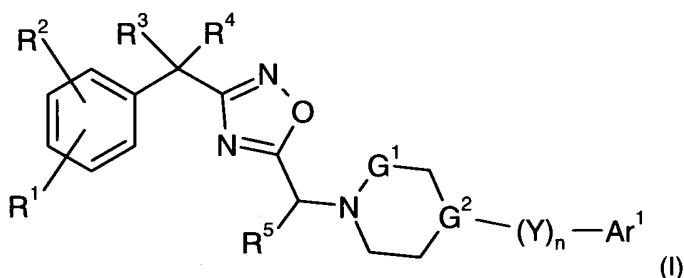
Activated Calcium Current in rat Aorta Smooth Muscle Cells In Primary Cultur" J Physiol. 416, 141-160, (1989).

Specific calcium channel antagonists approved for cardiovascular use in the United States fall into several chemical classes: the dihydropyridines (e.g., amlodipine, felodipine, nifedipine, nicardipine, 5 isradipine, nimodipine); the benzothiazepines (e.g., diltiazem), phenylalkylamines (e.g., verapamil); and diarylaminopropylamine ether (e.g., bepridil). While there are several alternatives from which a physician may choose, there remains a need for novel calcium channel blockers, particularly in a distinct chemical class. It is an object of this invention to provide a novel class of calcium channel antagonists which inhibit one or more of the N-type, T-type, and L-type calcium channels.

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### SUMMARY OF THE INVENTION

The present invention relates to a compound of formula (I)



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or a pharmaceutically acceptable salt thereof, wherein

R¹ and R² are each independently -H, -OH, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, substituted C₁-C₆ alkyl, or substituted C₁-C₆ alkoxy;

R³ and R⁴ are each independently -H or C₁-C₆ alkyl or R³ and R⁴ taken together with the carbon atom to which they are attached form C₃-C₆ cycloalkyl, or cycloheteroalkyl, provided that if one of R³ and R⁴ is -H, then the other is C₁-C₆ alkyl;

R⁵ is -H, C₁-C₆ alkyl, C₁-C₆ alkoxy, -(CH₂)q-C(O)O-W, wherein W is -H or C₁-C₆ alkyl and q is 1-6;

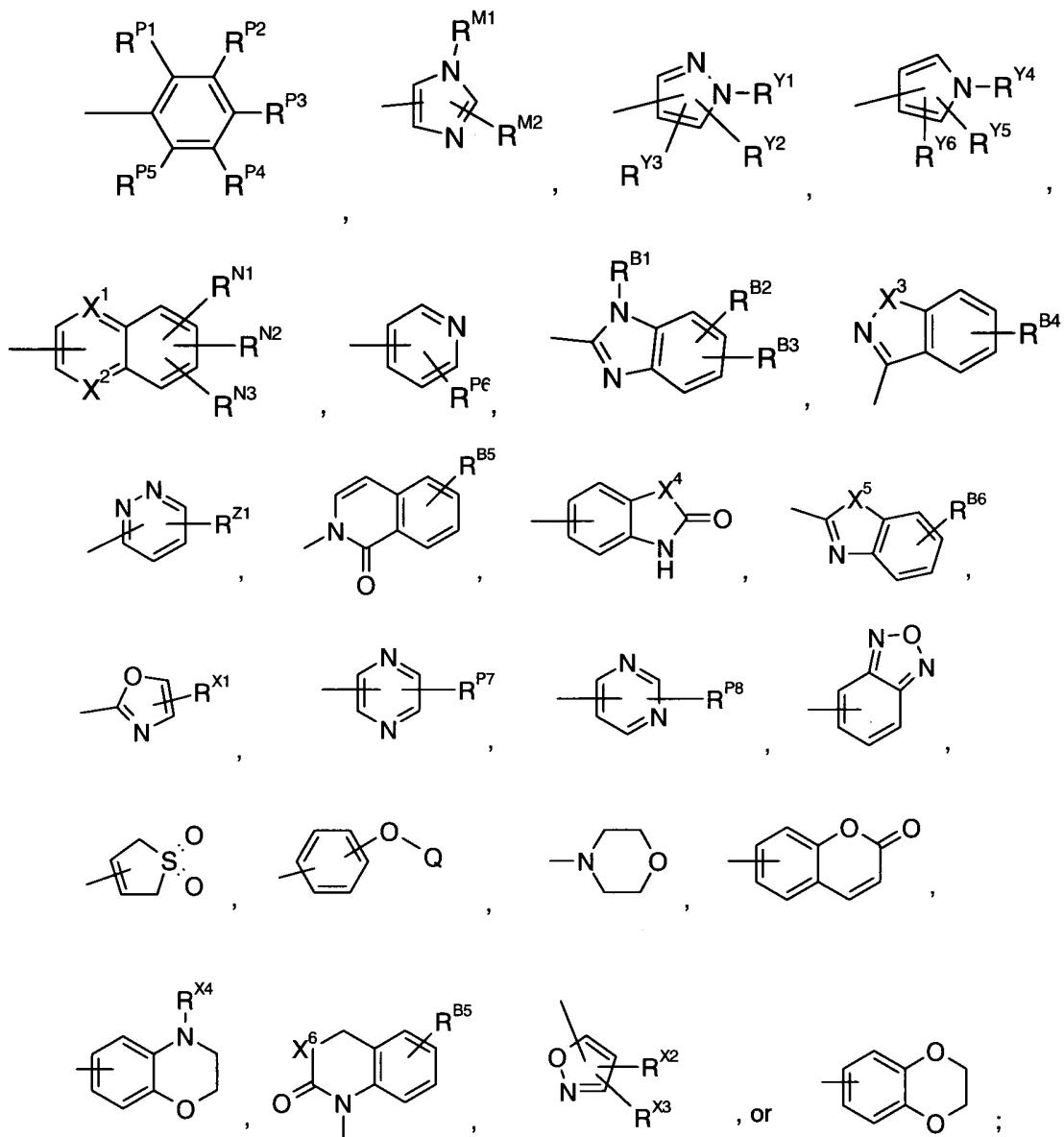
G¹ is methylene or ethylene;

G² is C(R⁶) or N, wherein R⁶ is -H, -OH or C₁-C₆ alkyl;

Y is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -O-, -C(O)-, -C(O)CH₂-, -S-, -S(O)-, -S(O)₂-, -NHC(O)-, -NHC(O)CH(R⁷)-, or -NHS(O)₂-, wherein R⁷ is -H or C₁-C₄ alkyl;

Ar¹ is a radical of the formulae

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5       wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>P7</sup>, R<sup>P8</sup>, R<sup>N1</sup>, R<sup>N2</sup>, R<sup>N3</sup>, and R<sup>Z1</sup> are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or -NR<sup>8</sup>R<sup>9</sup>, wherein R<sup>8</sup> and R<sup>9</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>M1</sup>, R<sup>M2</sup>, R<sup>B1</sup>, R<sup>B2</sup>, R<sup>B3</sup>, R<sup>B4</sup>, R<sup>B5</sup>, R<sup>B6</sup>, R<sup>X1</sup>, R<sup>X2</sup>, R<sup>X3</sup>, R<sup>X4</sup>, R<sup>Y1</sup>, R<sup>Y2</sup>, R<sup>Y3</sup>, R<sup>Y4</sup>, R<sup>Y5</sup>, and R<sup>Y6</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; X<sup>1</sup> and X<sup>2</sup> are independently CH or N; X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> are each independently NH, O, or S; X<sup>6</sup> is CH<sub>2</sub> or O; Q is substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, napthyl, 2-pyridyl, or 3-pyridyl; and

10      n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

The present invention also relates to a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention further relates to a method of blocking calcium channels, the method comprising administering to a patient in need of calcium channel blocking a therapeutically effective amount of a compound of formula (I) to block calcium channels.

5 Another embodiment of the invention relates to a method of treating pain in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention relates to a method of causing vasodilation in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

10 A further embodiment of the invention relates to a method of treating a disease selected from hypertension, congestive heart failure, stroke, ischaemic heart disease, and angina pectoris comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 Another aspect of this invention is directed to methods of reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) during surgery (e.g., coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA) or any percutaneous transluminal coronary intervention (PTCI), organ transplantation, or other non-cardiac surgeries) comprising administering to a mammal (e.g., a female or male human) a therapeutically effective amount of a compound of formula (I) or (II), or a pharmaceutically acceptable salt 20 of said compound.

#### DETAILED DESCRIPTION OF THE INVENTION

##### Definitions:

The term "halogen" or "halo" refers to a fluorine atom, chlorine atom, bromine atom, or iodine 25 atom.

The term "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a branched or straight chained alkyl radical containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec butyl, t-butyl, pentyl, hexyl, and the like.

30 The term "C<sub>1</sub>-C<sub>4</sub> alkyl" refers to a branched or straight chained alkyl radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, and the like.

The term "substituted C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a C<sub>1</sub>-C<sub>6</sub> alkyl substituted with from 1 to 3 substituents selected from halogen and C<sub>1</sub>-C<sub>4</sub> alkoxy. Included within this definition is -CH<sub>2</sub>F, -CHF<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>CHF<sub>2</sub>, -CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -CHCl<sub>2</sub>, -CCl<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>Cl, -CH<sub>2</sub>CHCl<sub>2</sub>, -CH<sub>2</sub>CCl<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Cl, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, and the like.

35 The term "C<sub>1</sub>-C<sub>6</sub> alkoxy" refers to a straight or branched alkoxy group containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, pentoxy, hexoxy, and the like.

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The term "C<sub>1</sub>-C<sub>4</sub> alkoxy" refers to a straight or branched alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, and the like.

5 The term "substituted C<sub>1</sub>-C<sub>6</sub> alkoxy" refers to a C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with from 1 to 3 substituents selected from halogen and C<sub>1</sub>-C<sub>4</sub> alkyl.

The term "C<sub>3</sub>-C<sub>6</sub> cycloalkyl" refers to a cyclic alkyl radical containing from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl,

10 The term "C<sub>1</sub>-C<sub>4</sub> haloalkyl" refers to a C<sub>1</sub>-C<sub>4</sub> alkyl is substituted with from 1 to 3 halo atoms per monovalent carbon and 1 to 2 halo atoms per divalent carbons, such as -CF<sub>3</sub>, -CH<sub>2</sub>F, -CHF<sub>2</sub>, -CF<sub>3</sub>, -CHFCH<sub>3</sub>, -CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>Br, -CHBr<sub>2</sub>, -CH<sub>2</sub>CHBr<sub>2</sub>, -CCl<sub>3</sub>, -CHCl<sub>2</sub>, -CH<sub>2</sub>Cl, -CCl<sub>3</sub>, and the like.

15 The term "cycloheteroalkyl" refers to a cyclic alkyl moiety containing five carbons and one ring atom of -O- or -N(R<sup>H1</sup>), wherein R<sup>H1</sup> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl as is further depicted in the formula (III) compounds disclosed herein. Examples of a "cycloheteroalkyl" include tetrahydro-2H-pyran-4-yl, tetrahydropyridin-4-yl, N-methylpiperidin-4-yl

The designation "~~~" or "—" refers to a bond for which the stereochemistry is not designated.

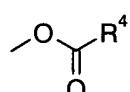
The designation "—" refers to a bond that protrudes forward out of the plane of the page.

The designation "....." refers to a bond that protrudes backward out of the plane of the page.

20 The designation "-C(O)-" or "C(O)" refers to a carbonyl group of the formula:

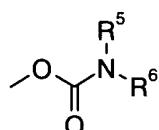


The designation "-OC(O)R<sup>4</sup>" refers to a carboxylic acid (R<sup>4</sup> is H) or an ester (R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl) of the formula:



25 wherein R<sup>4</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl.

The designation "-OC(O)NR<sup>5</sup>R<sup>6</sup>" refers to a carbamate of the formula:



wherein R<sup>5</sup> and R<sup>6</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl.

The designation "-N(R<sup>7</sup>)-" refers to a divalent amine of the formula:



30 wherein R<sup>7</sup> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl.

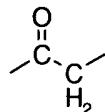
The designation "C(R<sup>8</sup>)" refers to a moiety of the formula:

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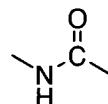


wherein R<sup>8</sup> is -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl.

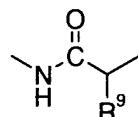
The designation “-C(O)CH<sub>2</sub>” refers to a moiety of the formula:



5 The designation “-NHC(O)-“ refers to an amide of the formula:

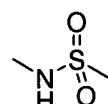


The designation “-NHC(O)CH(R<sup>9</sup>)-“ refers to an amide of the formula:

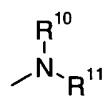


wherein R<sup>9</sup> is -H or C<sub>1</sub>-C<sub>4</sub> alkyl.

10 The designation “-NHS(O)<sub>2</sub>“ refers to a sulfonamide of the formula:

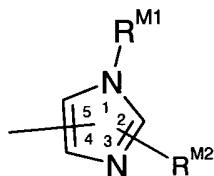


The designation “-NR<sup>10</sup>R<sup>11</sup>“ refers to an amine of the formula:



wherein R<sup>10</sup> and R<sup>11</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl.

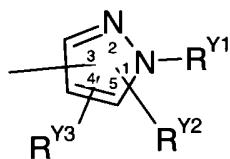
15 The designation



refers to a 1H-imidazole and it is understood that the radical is attached at any of the 1-, 2-, 4-, or 5-positions; it is further understood that when the radical is attached at the 1-position, the substituent represented by R<sup>M1</sup> is absent and the substituent represented by R<sup>M2</sup> is attached at any of the 2-, 4-, or 5-positions; when the radical is attached at the 2-position, the substituent represented by R<sup>M2</sup> is attached at either of the 4- or 5-positions; when the radical is attached at the 4-position, the substituent represented by R<sup>M2</sup> can be attached to either of the 2- or 5-positions; when the radical is attached at the 5-position, the substituent represented by R<sup>M2</sup> can be attached to either of the 2- or 4-positions.

25 The designation

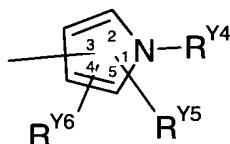
-8-



refers to a pyrazole and it is understood that the radical is attached at any of the 1-, 3-, 4-, or 5-positions; it is further understood that when the radical is attached at the 1-position, the substituent represented by R<sup>Y1</sup> is absent and the substituents represented by R<sup>Y2</sup> or R<sup>Y3</sup> can be attached at any of the 3-, 4-, or 5-positions; when the radical is attached at the 3-position, the substituents represented by R<sup>Y2</sup> or R<sup>Y3</sup> can be attached at either of the 4- or 5-positions; when the radical is attached at the 4-position, the substituents represented by R<sup>Y2</sup> or R<sup>Y3</sup> can be attached at either of the 3- or 5-positions; when the radical is attached at the 5-position, the substituents represented by R<sup>Y2</sup> or R<sup>Y3</sup> can be attached at either of the 3- or 4-positions.

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The designation

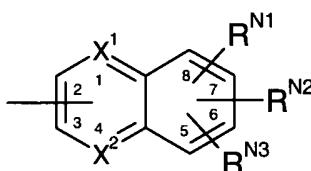


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refers to a pyrole and it is understood that the radical is attached at any of the 1-, 2-, 3-, 4-, or 5-positions; it is further understood that when the radical is attached at the 1-position, the substituent represented by R<sup>Y4</sup> is absent and the substituents represented by R<sup>Y5</sup> or R<sup>Y6</sup> can be attached at any of the 2-, 3-, 4-, or 5-positions; when the radical is attached at the 2-position, the substituents represented by R<sup>Y5</sup> or R<sup>Y6</sup> can be attached at any of the 3-, 4-, or 5-positions; when the radical is attached at the 3-position, the substituents represented by R<sup>Y5</sup> or R<sup>Y6</sup> can be attached at any of the 2-, 4-, or 5-positions; when the radical is attached at the 4-position, the substituents represented by R<sup>Y5</sup> or R<sup>Y6</sup> can be attached at any of the 2-, 3-, or 5-positions; when the radical is attached at the 5-position, the substituents represented by R<sup>Y5</sup> or R<sup>Y6</sup> can be attached at any of the 2-, 3-, or 4-positions.

The designation



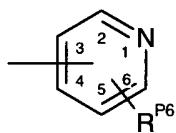
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refers to a naphthalene (when X<sup>1</sup> and X<sup>2</sup> are both CH), a quinoline (when one of X<sup>1</sup> and X<sup>2</sup> is N and the other is CH), or a quinoxaline (when X<sup>1</sup> and X<sup>2</sup> are both N) and it is understood that the radical is attached at any of the 1 through 8 positions when both X<sup>1</sup> and X<sup>2</sup> are CH, any of positions 2 through 8 when X<sup>1</sup> is N, and any of positions 2, 3 and 5-8 when both X<sup>1</sup> and X<sup>2</sup> are N; it is further understood that when the radical is attached at any given position, the substituents represented by R<sup>N1</sup>, R<sup>N2</sup>, and R<sup>N3</sup> can be attached at any of the other non-nitrogen positions, for example, if the radical is attached at the 1-position and X<sup>1</sup> and X<sup>2</sup> are both CH, the substituents represented by R<sup>N1</sup>, R<sup>N2</sup>, or R<sup>N3</sup> can be attached at any of the 2-, 3-, 4-, 5-, 6-, 7-, or 8-positions.

The designation

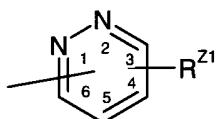
-9-



refers to a pyridine and it is understood that the radical is attached at any of the 2-, 3-, 4-, 5-, or 6-positions; it is further understood that when the radical is attached at any given position, the substituent represented by  $R^{P6}$  can be attached at any of the other non-nitrogen positions, for example, if the radical is attached at the 2-position, the substituent represented by  $R^{P6}$  can be attached at any of the 3-, 4-, 5-, or 6-positions.

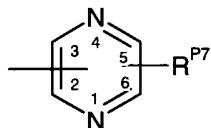
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The designation



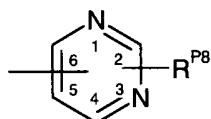
10 refers to a pyridazine and it is understood that the radical is attached to any of the 3-, 4-, 5-, or 6-positions; it is further understood that when the radical is attached at any given position, the substituent represented by  $R^{Z1}$  can be attached at any of the other non-nitrogen positions, for example, if the radical is attached at the 3-position, the substituent represented by  $R^{Z1}$  can be attached at any of the 4-, 5-, or 6-positions.

The designation



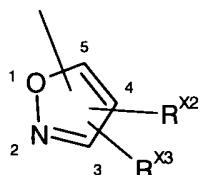
15 refers to a pyrazine and it is understood that the radical is attached to any of the 2-, 3-, 5-, or 6-positions; it is further understood that when the radical is attached at any given position, the substituent represented by  $R^{P7}$  can be attached at any of the other non-nitrogen positions, for example, if the radical is attached at the 2-position, the substituent represented by  $R^{P7}$  can be attached at any of the 3-, 5-, or 6-positions.

20 The designation



25 refers to a pyrimidine and it is understood that the radical is attached to any of the 2-, 4-, 5-, or 6-positions; it is further understood that when the radical is attached at any given position, the substituent represented by  $R^{P8}$  can be attached at any of the other non-nitrogen positions, for example, if the radical is attached at the 2-position, the substituent represented by  $R^{P8}$  can be attached at any of the 4-, 5-, or 6-positions.

The designation



refers to an isoxazole and it is understood that the radical is attached to any of the 3-, 4-, or 5-positions; it is further understood that when the radical is attached at any given position, the substituents represented by R<sup>x2</sup> and R<sup>x3</sup> can be attached at any of the non-nitrogen or non-oxygen positions, for example, if the radical is attached at the 3-position, then the substituents represented by R<sup>x2</sup> and R<sup>x3</sup> can be attached at either of the 4- or 5- positions.

As is appreciated by one of ordinary skill in the art some of the compounds of the formula (I) exist as stereoisomers. Any reference in this application to one of the compounds of the formula (I) is meant to encompass either specific stereoisomers or a mixture of stereoisomers. Where indicated, the compounds follow the (+)- and (-)- designation or the Cahn-Ingold-Prelog designation of (R)- and (S)- for the stereochemistry of compounds represented by formula (I) and intermediates thereof.

The specific stereoisomers can be prepared by stereospecific synthesis using enantiomerically pure or enantiomerically enriched starting materials. The specific stereoisomers of either starting materials or products can be resolved and recovered by techniques known in the art, such as chromatography on chiral stationary phases, enzymatic resolution, or fractional recrystallization of addition salts formed by reagents used for that purpose. Useful methods of resolving and recovering specific stereoisomers are known in the art and described in Stereochemistry of Organic Compounds, E. L. Eliel and S. H. Wilen, Wiley (1994) and Enantiomers, Racemates, and Resolutions, J. Jacques, A. Collet, and S. H. Wilen, Wiley (1981).

In order to prepare one optical isomer over its enantiomer, a number of routes are available. As an example, a mixture of enantiomers may be prepared, and then the two enantiomers may be separated. A commonly employed method for the separation of a racemic mixture is the use of chiral high pressure liquid chromatography. Further details regarding resolution of enantiomeric mixtures may be found in J. Jacques, et al, Enantiomers, Racemates, and Resolutions, (1991).

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactions to afford a medium within which to effect the desired reaction.

Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

5 For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

10 Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

15 Included within the scope of the claimed compounds of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

20 *Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

25 Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

30 Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine.

35 Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art. [see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).]

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as <sup>2</sup>H and <sup>3</sup>H, carbon, such as <sup>11</sup>C, <sup>13</sup>C and <sup>14</sup>C, chlorine, such as <sup>36</sup>Cl, fluorine, such as <sup>18</sup>F, iodine, such as <sup>123</sup>I and <sup>125</sup>I, nitrogen, such as <sup>13</sup>N and <sup>15</sup>N, oxygen, such as <sup>15</sup>O, <sup>17</sup>O and <sup>18</sup>O, phosphorus, such as <sup>32</sup>P, and sulphur, such as <sup>35</sup>S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* <sup>3</sup>H, and carbon-14, *i.e.* <sup>14</sup>C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* <sup>2</sup>H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as <sup>11</sup>C, <sup>18</sup>F, <sup>15</sup>O and <sup>13</sup>N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

The compounds of the present invention may be administered as prodrugs. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of such prodrugs include:

- (i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C<sub>1</sub>-C<sub>8</sub>)alkyl;
- (ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxymethyl; and
- (iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH<sub>2</sub> or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C<sub>1</sub>-C<sub>10</sub>)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

As with any group of structurally related compounds which possesses a particular utility, certain groups and configurations are preferred for the compounds of formula (I) and their end-use application.

5 Preferred embodiments of compounds of formula (I) or stereoisomers or pharmaceutically acceptable salts thereof are given below:

(1) Compounds wherein R<sup>1</sup> and R<sup>2</sup> are:

- (a) each independently -H, -CF<sub>3</sub>, halo, or C<sub>1</sub>-C<sub>4</sub> alkyl;
- (b) each independently -H, fluoro, chloro, -CF<sub>3</sub>, or C<sub>1</sub>-C<sub>4</sub> alkyl; or
- (c) one of R<sup>1</sup> and R<sup>2</sup> is -H and the other is fluoro;

10 (2) Compounds wherein R<sup>3</sup> and R<sup>4</sup> are:

- (a) taken together with the carbon atom to which they are attached form C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- (b) taken together with the carbon atom to which they are attached form cycloheteroalkyl;
- (c) taken together with the carbon atom to which they are attached form tetrahydro-2H-15 pyran-4-yl;

(3) Compounds wherein R<sup>5</sup> is -H;

15 (4) Compounds wherein G<sup>1</sup> is:

- (a) methylene; or
- (b) ethylene;

20 (5) Compounds wherein G<sup>2</sup> is:

- (a) C(R<sup>6</sup>), wherein R<sup>6</sup> is -H, -OH, or C<sub>1</sub>-C<sub>6</sub> alkyl;
- (b) C(R<sup>6</sup>), wherein R<sup>6</sup> is -H; or
- (c) N;

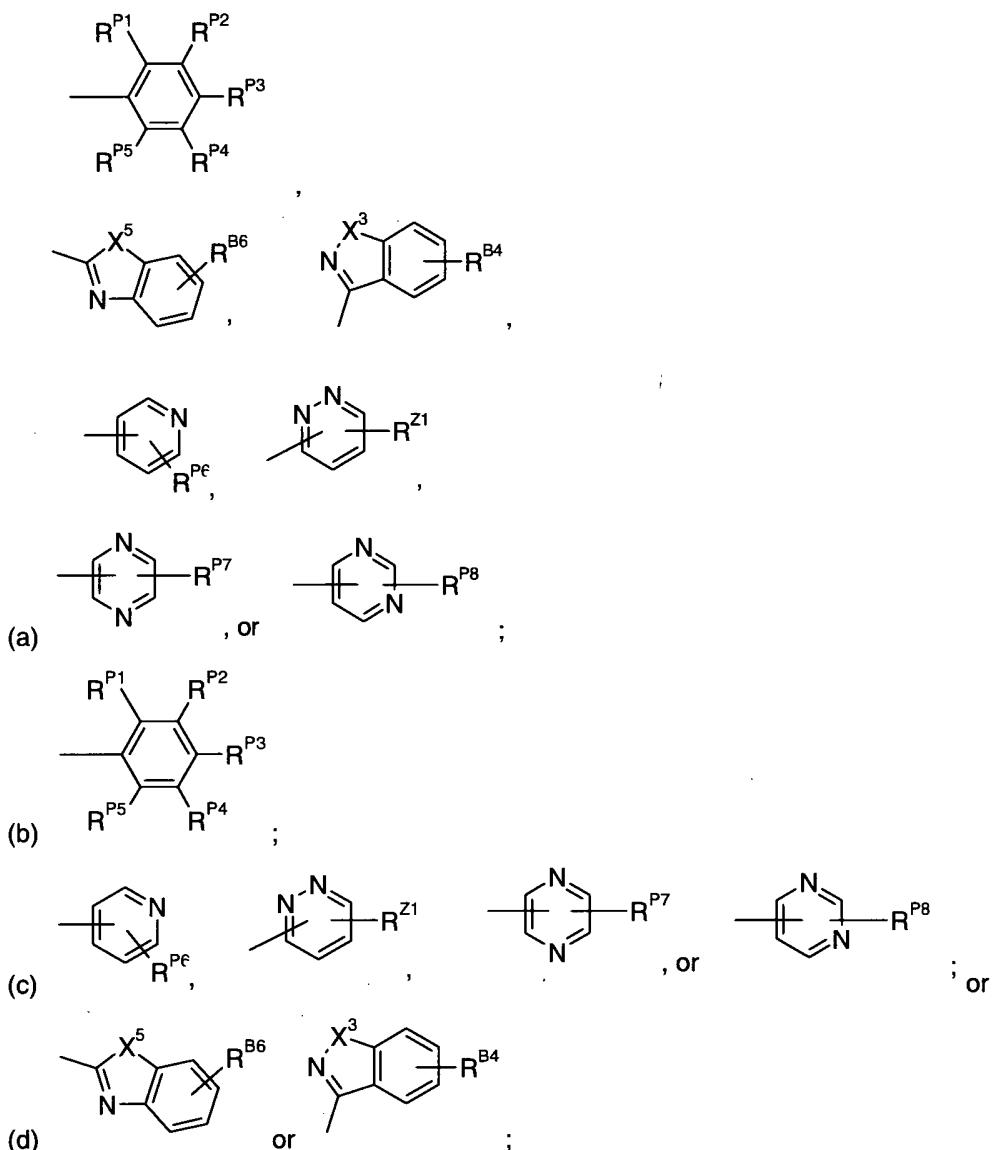
25 (6) Compounds wherein Y is

- (a) -C(O)-, -S(O)<sub>2</sub>-, -NHC(O)- or -NHS(O)<sub>2</sub>-,
- (b) -C(O)-, or -S(O)<sub>2</sub>-,

(7) Compounds wherein n is

- (a) 0; or
- (b) 1;

30 (8) Compounds wherein Ar<sup>1</sup> is



- 5        (9) Compounds wherein  $R^{P1}$ ,  $R^{P2}$ ,  $R^{P3}$ ,  $R^{P4}$ ,  $R^{P5}$ ,  $R^{P6}$ ,  $R^{Z1}$ ,  $R^{P7}$  and  $R^{P8}$  are each independently  
–H, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or –CF<sub>3</sub>;  
          (10) Compounds wherein  $R^{B4}$  and  $R^{B6}$  are each independently –H or methyl;  
          (11) Compounds wherein  $X^5$  is  
                (a) S; or  
                (b) NH;

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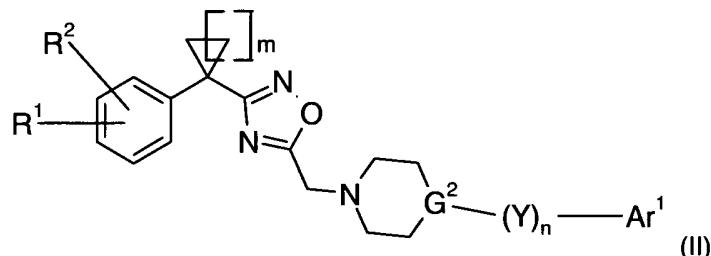
(12) Compounds wherein  $X^3$  is NH or S.

It is understood that further preferred embodiments of formula (I) can be selected by requiring one or more of the preferred embodiments (1) through (12) above of compounds of formula (I) or stereoisomers or pharmaceutically acceptable salts thereof or by reference to the examples given herein.

15 For example, further preferred embodiments of the invention can be obtained by combining (1)(a) and (2)(a); (1)(b) and (2)(a); (1)(c) and (2)(a); (1)(a) and (2)(b); (1)(b) and (2)(b); (1)(c) and (2)(b); (1)(b), (2)(a), and (3); (1)(c), (2)(a), and (3); (2)(b) and (3); (2)(a), (3), (4)(a), and (5)(b); (1)(b), (2)(a), (3), (4)(a), (5)(c); (2)(b), (3), (4)(a), (5)(b), and (6)(a); (2)(a), (3), (4)(a), (5)(b), and (6)(b); (1)(c), (2)(a), (3), (4)(a),

(5)(c), and (6)(a); (1)(c), (2)(a), (3), (4)(a), (5)(a), and (6)(b); (1)(b), (2)(a), (3), (6)(a), and (7)(b); (1)(c), (2)(c), (3), (6)(a), and (7)(b); (2)(a), (3), (6)(b), (7)(b), and (8)(a); (2)(a), (3), (6)(b), (7)(b), and (8)(b); (2)(a), (3), (6)(b), (7)(b), and (8)(c); (2)(a), (3), (6)(b), (7)(b), and (8)(d); (2)[(a) or (b)], (6)(a), (7)(b), and (8)(a); (3), (6)(b), (7)(b), and (8)(c); (3), (6)(a), (7)(a), and (8)(b); (2)(a), (3), (7)(a), (8)(a), and (9); (2)(b), (3), (6)(b), (7)(b), (8)(a), and (9); (2)(b), (3), (6)(b), (7)(b), (8)(a), and (9); (2)(a), (6)(b), (7)(b), (8)(a), and (9); (7)(a), (8)(a), and (9); (6)(a), (7)(b), (8)(d), and (9); (2)(a), (7)(b), (8)(a), and (9); (2)(b), (7)(b), (8)(a), and (9); (7)(b) and (9); (4)(a), (6)(a), (7)(b), (8)(a), and (9); (4)(b), (6)(b), (7)(b), (8)(a), and (9); (2)(a), (4)(a), (6)(a), (7)(b), (8)(a), and (9); (2)(a), (4)(b), (6)(b), (7)(b), (8)(d), and (9); (2)(a), (5)(b), and (7)(b); (2)(a), (5)(c), and (7)(b); (1)(c), (4)(a), and (7)(a); (1)(b), (4)(a), (7)(b), (9), and (10); (1)(b), (2)(a), (4)(a), (7)(a), (9), and (10); (1)(c), (2)(b), (4)(a), (6)(a), (9), (10), and (11)(a); (1)(b), (2)(a), (4)(a), (6)(a), (7)(b), (9), (10), and (11)(b); (1)(b), (2)(a), (4)(a), (6)(b), (7)(b), (9), (10), (11)(a), and (12); (1)(b), (2)(b), (4)(a), (6)(a), (9), (10), (11)(b), and (12); (8)(a), (11)(a), and (12); (8)(a), (11)(b), and (12); (2)(a), (8)(a), (11)(a), and (12); (2)(b), (8)(a), (11)(b), and (12); and the like, or by solely requiring (1)(b); (2)(a); (3); (4)(a); (4)(b); (5)(a); (5)(c); (6)(a); (6)(b); (7)(a); (7)(b); (8)(a); (8)(b); (8)(c); (8)(d); (9); (10); (11)(a); (11)(b); (12) and the like. It is further understood that the stereoisomers and pharmaceutically acceptable salts are included in the term "compound" unless specifically disclaimed.

Additional embodiments of the invention are represented by compounds of formula (II)



or a pharmaceutically acceptable salt thereof, wherein

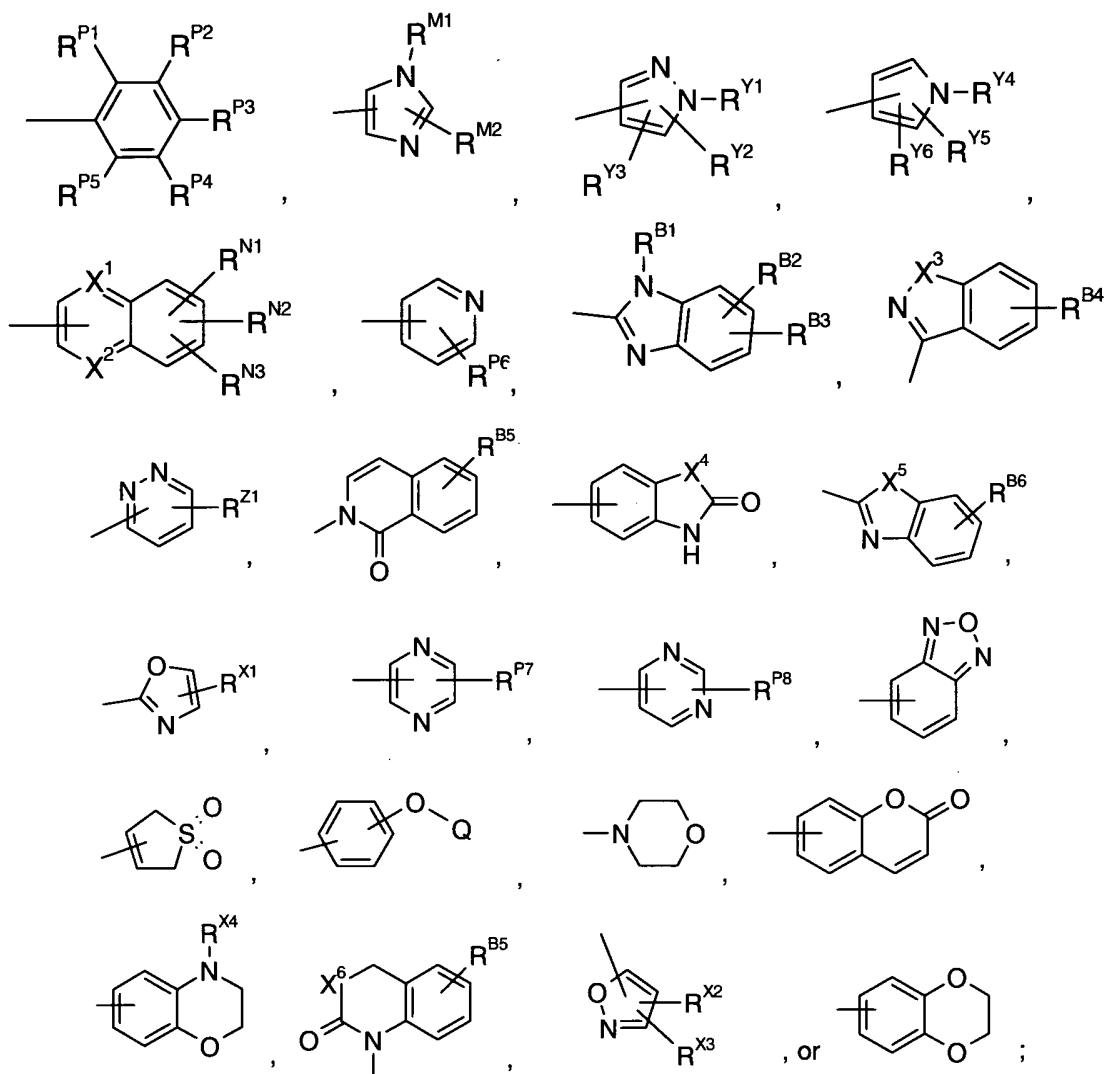
20       R<sup>1</sup> and R<sup>2</sup> are each independently -H, -OH, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

          G<sup>2</sup> is C(R<sup>6</sup>) or N, wherein R<sup>6</sup> is -H, -OH or C<sub>1</sub>-C<sub>6</sub> alkyl;

          Y is -CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- , -O- , -C(O)- , -C(O)CH<sub>2</sub>- , -S- , -S(O)- , -S(O)<sub>2</sub>- , -NHC(O)- , -NHC(O)CH(R<sup>7</sup>)- , or -NHS(O)<sub>2</sub>- , wherein R<sup>7</sup> is -H or C<sub>1</sub>-C<sub>4</sub> alkyl;

25       Ar<sup>1</sup> is a radical of the formulae

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wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>P7</sup>, R<sup>P8</sup>, R<sup>N1</sup>, R<sup>N2</sup>, R<sup>N3</sup>, and R<sup>Z1</sup> are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or -NR<sup>8</sup>R<sup>9</sup>, wherein R<sup>8</sup> and R<sup>9</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>M1</sup>, R<sup>M2</sup>, R<sup>B1</sup>, R<sup>B2</sup>, R<sup>B3</sup>, R<sup>B4</sup>, R<sup>B5</sup>, R<sup>B6</sup>, R<sup>X1</sup>, R<sup>X2</sup>, R<sup>X3</sup>, R<sup>X4</sup>, R<sup>Y1</sup>, R<sup>Y2</sup>, R<sup>Y3</sup>, R<sup>Y4</sup>, R<sup>Y5</sup>, and R<sup>Y6</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; X<sup>1</sup> and X<sup>2</sup> are independently CH or N; X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> are each independently NH, O, or S; X<sup>6</sup> is CH<sub>2</sub> or O; Q is -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, naphthyl, 2-pyridyl, or 3-pyridyl;

10 m is 1, 2, 3, or 4; and

n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

Preferred embodiments of compounds of formula (II) or stereoisomers or pharmaceutically acceptable salts thereof are given below:

15 (1) Compounds wherein R<sup>1</sup> and R<sup>2</sup> are:

- (a) each independently -H, -CF<sub>3</sub>, halo, or C<sub>1</sub>-C<sub>4</sub> alkyl;
- (b) each independently -H, fluoro, chloro, or C<sub>1</sub>-C<sub>4</sub> alkyl; or
- (c) one of R<sup>1</sup> and R<sup>2</sup> is -H and the other is fluoro;

(2) Compounds wherein G<sup>2</sup> is:

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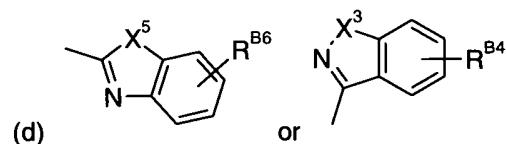
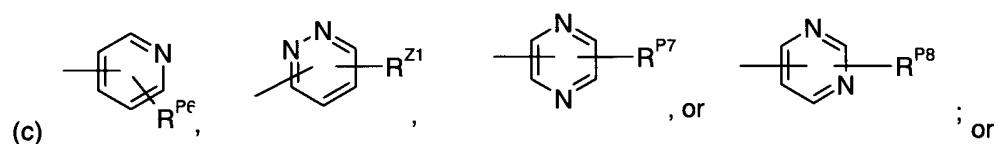
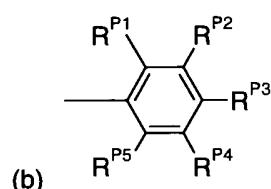
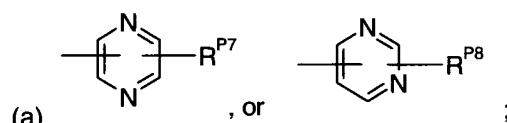
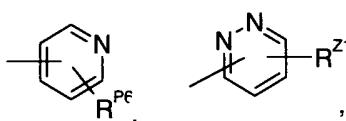
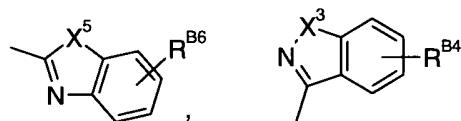
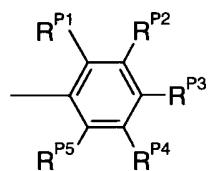
- (a)  $C(R^6)$ , wherein  $R^6$  is  $-H$ ,  $-OH$ , or  $C_1-C_6$  alkyl;  
 (b)  $C(R^6)$ , wherein  $R^6$  is  $-H$ ; or  
 (c) N;

(3) Compounds wherein Y is:

- 5 (a)  $-C(O)-$ ,  $-S(O)_2-$ ,  $-NHC(O)-$  or  $-NHS(O)_2-$ ;  
 (b)  $-C(O)-$ , or  $-S(O)_2-$ ;

(4) Compounds wherein n is

- (a) 0; or  
 (b) 1;

10 (5) Compounds wherein Ar<sup>1</sup> is:

- 15 (6) Compounds wherein  $R^{P1}$ ,  $R^{P2}$ ,  $R^{P3}$ ,  $R^{P4}$ ,  $R^{P5}$ ,  $R^{P6}$ ,  $R^{Z1}$ ,  $R^{P7}$  and  $R^{P8}$  are each independently  $-H$ , halo,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, or  $-CF_3$ ;  
 (7) Compounds wherein  $R^{B4}$  and  $R^{B6}$  are each independently  $-H$  or methyl;  
 (8) Compounds wherein  $X^5$  is

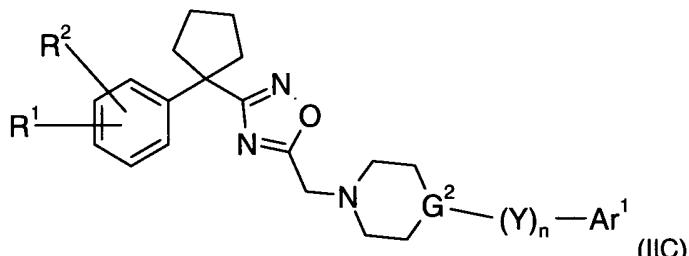
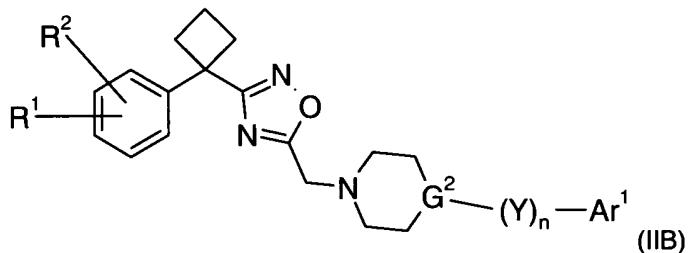
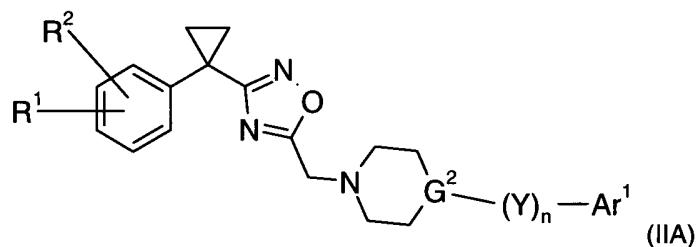
(a) S; or

(b) NH;

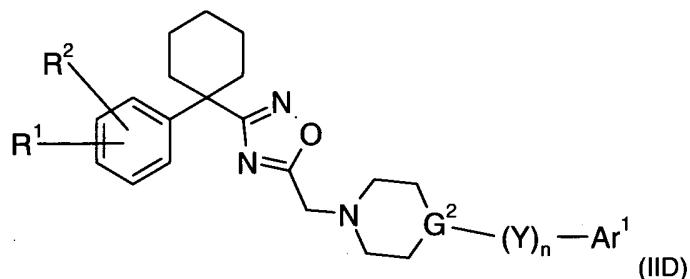
(9) Compounds wherein  $X^3$  is NH or S.

It is understood that further preferred embodiments of formula (II) can be selected by requiring one or more of the preferred embodiments (1) through (9) above of compounds of formula (II) or stereoisomers or pharmaceutically acceptable salts thereof or by reference to the examples given herein. For example, further preferred embodiments of the invention can be obtained by combining (1)(a) and (2)(a); (1)(a) and (2)(b); (1)(b) and (2)(a); (1)(b) and (2)(b); (1)(c) and (2)(a); (1)(c) and (2)(b); (1)(a) and (2)(c); (1)(c) and (2)(c); (2)(a) and (3)(a); (2)(b) and (3)(a); (2)(a) and (3)(b); (1)(b) and (3)(a); (1)(b) and (4)(a); (1)(b) and (5)(a); (1)(b), (4)(b) and (5)(b); (1)(b), (3)(a), (4)(b) and (5)(a); (3)(b), (4)(b), and (5)(a); (2)(a), (3)(a), (4)(b), and (5)(a); (2)(b), (3)(a), (4)(b), and (5)(a); (2)(a), (3)(a), (4)(b), and (5)(c); (2)(a), (3)(a), (4)(b), and (5)(d); (1)(b), (3)(a), (4)(b), and (5)(c); (1)(b), (2)(c), (3)(b), (4)(b), and (5)(b); (1)(b), (3)(b), (5)(a), and (6); (1)(b), (3)(b), (5)(b), and (6); (1)(b), (3)(b), (5)(c), and (6); (1)(b), (3)(b), (5)(d), and (6); (1)(b), (3)(a), (5)(a), and (6); (1)(b), (3)(a), (5)(a), (6), and (7); (1)(b), (3)(a), (5)(a), (6), (7), and (8)(a); (1)(b), (3)(b), (5)(a), (6), (7), and (8)(b); (1)(b), (3)(b), (5)(a), (6), (7), (8)(a) and (9); (1)(b), (3)(a), (5)(a), (6), (7), (8)(b), and (9); (3)(a), (5)(c), (6), (7), (8)(b), and (9); (5)(a), (6), (7), (8)(a) and (9); (5)(a), (6), (7), (8)(b) and (9); (5)(b), (6), (7), (8)(a) and (9); (5)(c), (6), (7), (8)(a) and (9); (5)(d), (6), (7), (8)(a) and (9); (5)(a), (6), (7), and (9); and the like; or by solely requiring (1)(b); (2)(a); (2)(b); (3)(a); (4)(a); (4)(b); (5)(a), (7); and the like. It is further understood that the stereoisomers and pharmaceutically acceptable salts are included in the term "compound" unless specifically disclaimed.

Further embodiments of the invention are represented by compounds or pharmaceutically acceptable salts of formulae (IIA), (IIB), (IIC), and (IID):



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wherein R<sup>1</sup>, R<sup>2</sup>, G<sup>2</sup>, Y, Ar<sup>1</sup>, and n in each of (IIA), (IIB), (IIC), and (IID) are as defined in formula (II).

Compounds of formula (IIA) are those compounds of formula (II) where m is 1. Compounds of formula (IIB) are those compounds of formula (II) where m is 2. Compounds of formula (IIC) are those compounds of formula (II) where m is 3. Compounds of formula (IID) are those compounds of formula (II) where m is 4.

Preferred embodiments of compounds of formulae (IIA), (IIB), (IIC), or (IID), or stereoisomers or pharmaceutically acceptable salts thereof are given below:

10 (1) Compounds wherein R<sup>1</sup> and R<sup>2</sup> are:

- a. each independently -H, -CF<sub>3</sub>, halo, or C<sub>1</sub>-C<sub>4</sub> alkyl;
- b. each independently -H, fluoro, chloro, or C<sub>1</sub>-C<sub>4</sub> alkyl; or
- c. one of R<sup>1</sup> and R<sup>2</sup> is -H and the other is fluoro;

(2) Compounds wherein G<sup>2</sup> is:

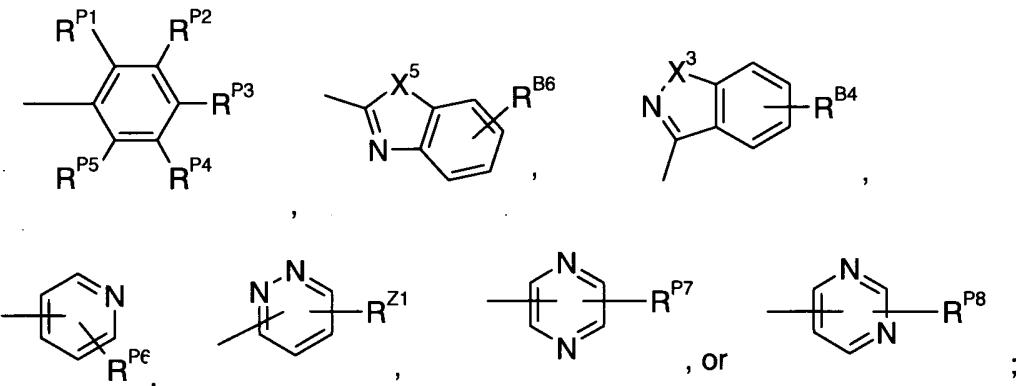
- a. C(R<sup>6</sup>), wherein R<sup>6</sup> is -H, -OH, or C<sub>1</sub>-C<sub>6</sub> alkyl; or
- b. N;

(3) Compounds wherein Y is -C(O)-, -S(O)<sub>2</sub>-, -NHC(O)- or -NHS(O)<sub>2</sub>-;

(4) Compounds wherein n is

- a. 0; or
- b. 1;

(5) Compounds wherein Ar<sup>1</sup> is



(6) Compounds wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>Z1</sup>, R<sup>P7</sup> and R<sup>P8</sup> are each independently -H, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or -CF<sub>3</sub>;

(7) Compounds wherein R<sup>B4</sup> and R<sup>B6</sup> are each independently -H or methyl;

(8) Compounds wherein X<sup>5</sup> is

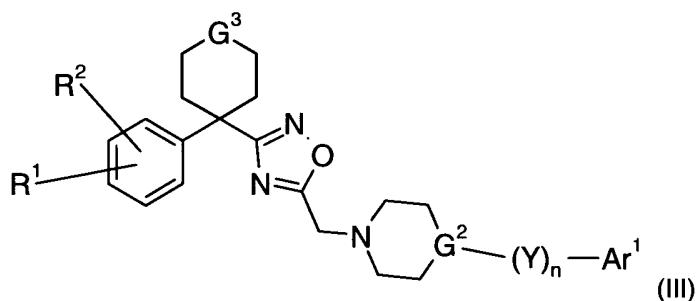
-20-

- a. S; or
- b. NH;

(9) Compounds wherein X<sup>3</sup> is NH or S.

It is understood that further preferred embodiments of formulae (IIA), (IIB), (IIC), and (IID) can be selected by requiring one or more of the preferred embodiments (1) through (9) above of compounds of any of formulae (IIA), (IIB), (IIC), or (IID), or stereoisomers or pharmaceutically acceptable salts thereof or by reference to the examples given herein. For example, further preferred embodiments of the invention can be obtained by combining (1)(a) and (2)(a); (1)(a) and (2)(b); (1)(b) and (2)(a); (1)(b) and (2)(b); (1)(c) and (2)(a); (1)(c) and (2)(b); (2)(a) and (3); (2)(b) and (3); (1)(b) and (3); (1)(b) and (4)(a); (1)(b), (4)(a) and (5); (1)(b), (4)(b) and (5); (1)(b), (3), (4)(b) and (5); (3), (4)(b), and (5); (2)(a), (3), (4)(b), and (5); (2)(b), (3), (4)(b), and (5); (1)(b), (2)(a), (3), (4)(b), and (5); (1)(b), (2)(b), (3), (4)(b), and (5); (1)(b), (3), (4)(b), (5), and (6); (1)(b), (3), (5), and (6); (1)(b), (3), (5), (6), and (7); (1)(b), (3), (5), (6), (7), and (8)(a); (1)(b), (3), (5), (6), (7), and (8)(b); (1)(b), (3), (5), (6), (7), (8)(a) and (9); (1)(b), (3), (5), (6), (7), (8)(b), and (9); (5), (6), (7), (8)(a) and (9); (5), (6), (7), (8)(b) and (9); (5), (6), (7), and (9); and the like; or by solely requiring (1)(b); (2)(a); (2)(b); (3); (4)(a); (4)(b); (5), (7); and the like. It is further understood that the stereoisomers and pharmaceutically acceptable salts are included in the term "compound" unless specifically disclaimed.

Further embodiments of the invention are represented by compounds of formula (III)



or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are each independently -H, -OH, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

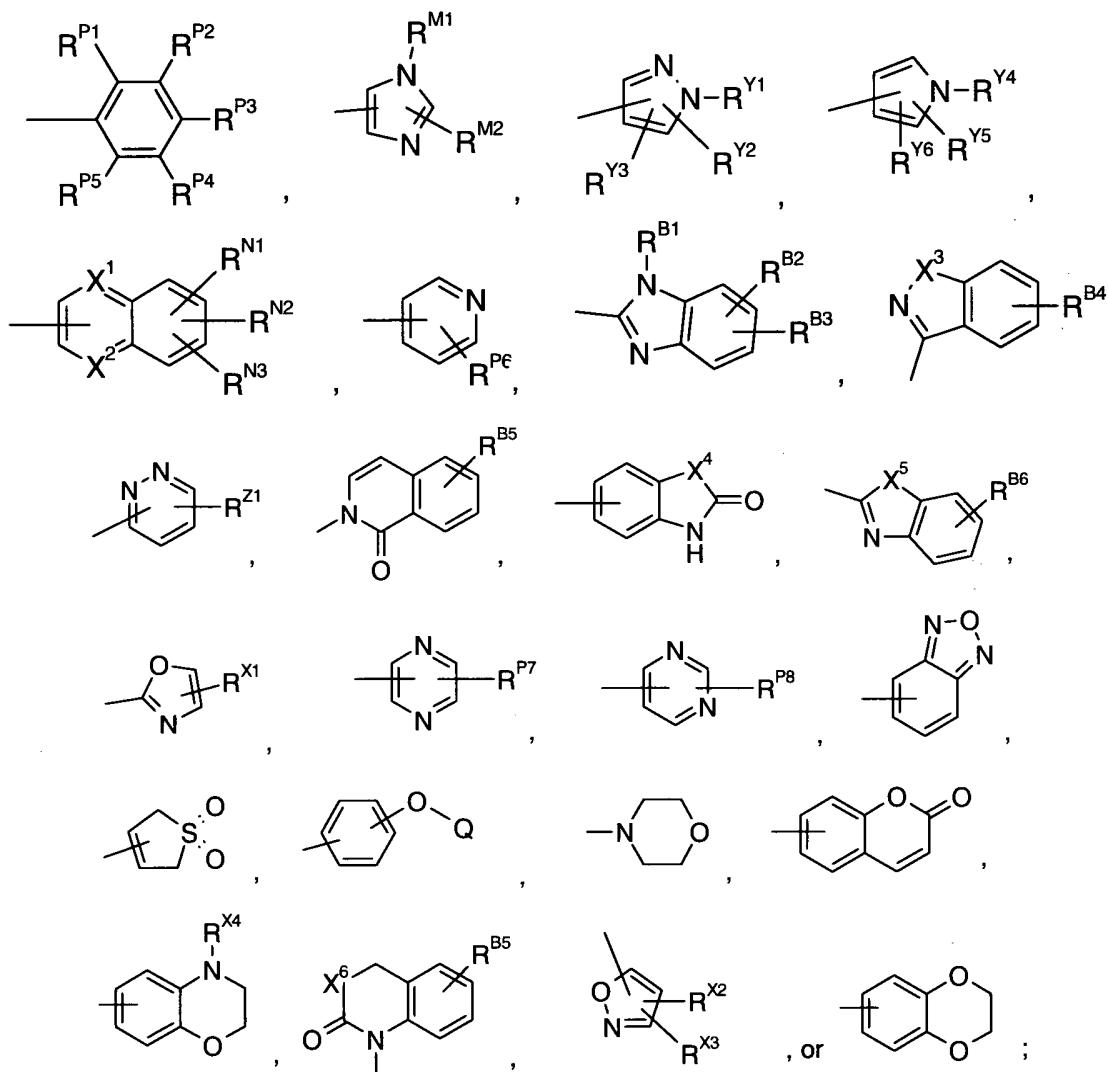
G<sup>2</sup> is C(R<sup>6</sup>) or N, wherein R<sup>6</sup> is -H, -OH or C<sub>1</sub>-C<sub>6</sub> alkyl;

G<sup>3</sup> is -O- or -N(R<sup>H1</sup>), wherein R<sup>H1</sup> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl;

Y is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -O-, -C(O)-, -C(O)CH<sub>2</sub>-, -S-, -S(O)-, -S(O)<sub>2</sub>-, -NHC(O)-, -NHC(O)CH(R<sup>7</sup>)-, or -NHS(O)<sub>2</sub>-, wherein R<sup>7</sup> is -H or C<sub>1</sub>-C<sub>4</sub> alkyl;

Ar<sup>1</sup> is a radical of the formulae

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wherein  $R^{P1}$ ,  $R^{P2}$ ,  $R^{P3}$ ,  $R^{P4}$ ,  $R^{P5}$ ,  $R^{P6}$ ,  $R^{P7}$ ,  $R^{P8}$ ,  $R^{N1}$ ,  $R^{N2}$ ,  $R^{N3}$ , and  $R^{Z1}$  are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or  $-NR^8R^9$ , wherein  $R^8$  and  $R^9$  are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl;  $R^{M1}$ ,  $R^{M2}$ ,  $R^{B1}$ ,  $R^{B2}$ ,  $R^{B3}$ ,  $R^{B4}$ ,  $R^{B5}$ ,  $R^{B6}$ ,  $R^{X1}$ ,  $R^{X2}$ ,  $R^{X3}$ ,  $R^{X4}$ ,  $R^{Y1}$ ,  $R^{Y2}$ ,  $R^{Y3}$ ,  $R^{Y4}$ ,  $R^{Y5}$ , and  $R^{Y6}$  are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl;  $X^1$  and  $X^2$  are independently CH or N;  $X^3$ ,  $X^4$ , and  $X^5$  are each independently NH, O, or S;  $X^6$  is CH<sub>2</sub> or O; Q is -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, napthyl, 2-pyridyl, or 3-pyridyl; and

10

n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

Preferred embodiments of compounds of formula (III), or stereoisomers or pharmaceutically acceptable salts thereof are given below:

(1) Compounds wherein R<sup>1</sup> and R<sup>2</sup> are:

15

- a. each independently -H, -CF<sub>3</sub>, halo, or C<sub>1</sub>-C<sub>4</sub> alkyl;
- b. each independently -H, fluoro, chloro, or C<sub>1</sub>-C<sub>4</sub> alkyl; or
- c. one of R<sup>1</sup> and R<sup>2</sup> is -H and the other is fluoro;

(2) Compounds wherein G<sup>2</sup> is:

- a. C(R<sup>6</sup>), wherein R<sup>6</sup> is -H, -OH, or C<sub>1</sub>-C<sub>6</sub> alkyl; or

b. N;

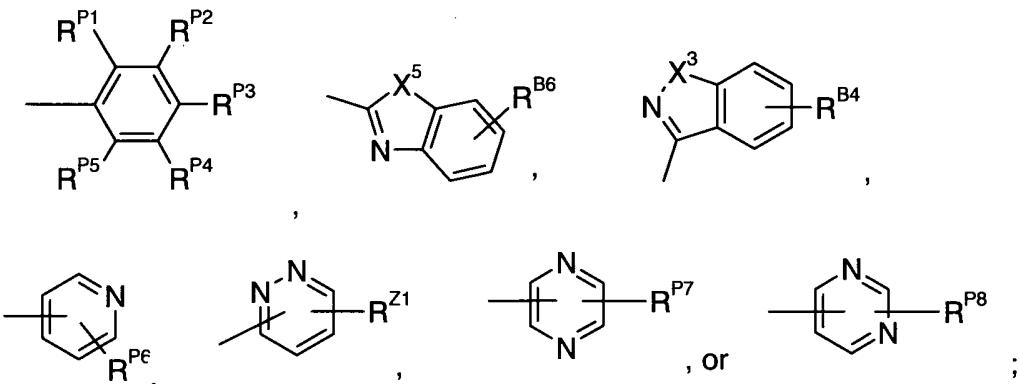
(3) Compounds wherein Y is -C(O)-, -S(O)<sub>2</sub>-, -NHC(O)- or -NHS(O)<sub>2</sub>-;

(4) Compounds wherein n is

a. 0; or

5 b. 1;

(5) Compounds wherein Ar<sup>1</sup> is



(6) Compounds wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>Z1</sup>, R<sup>P7</sup> and R<sup>P8</sup> are each independently -H, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or -CF<sub>3</sub>;

10 (7) Compounds wherein R<sup>B4</sup> and R<sup>B6</sup> are each independently -H or methyl;

(8) Compounds wherein X<sup>5</sup> is

a. S; or

b. NH;

(9) Compounds wherein X<sup>3</sup> is NH or S.

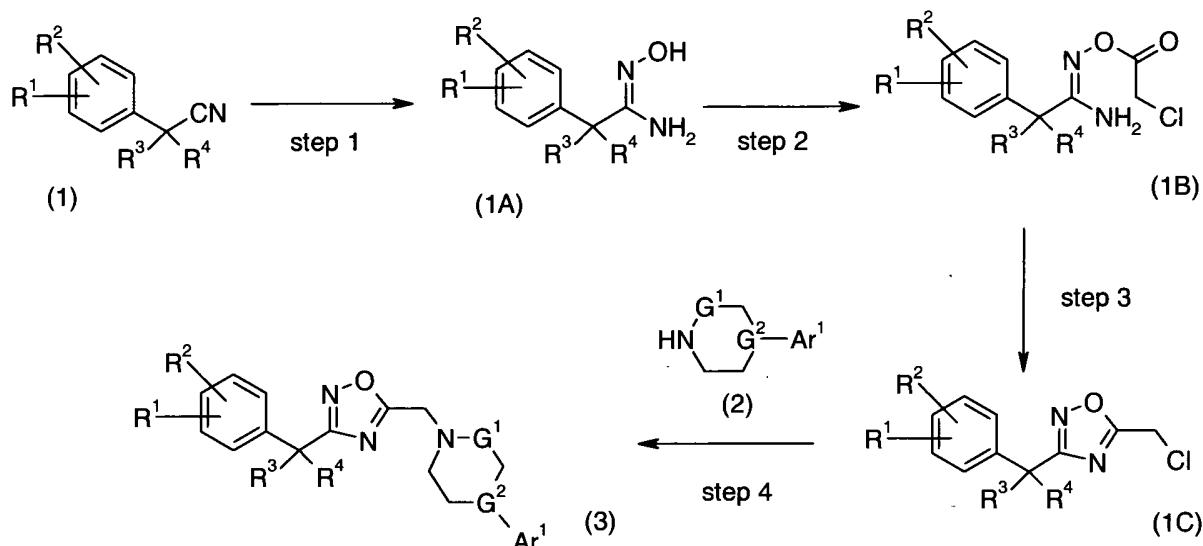
15 It is understood that further preferred embodiments of formula (III) can be selected by requiring one or more of the preferred embodiments (1) through (9) above of compounds of any of formula (III) or stereoisomers or pharmaceutically acceptable salts thereof or by reference to the examples given herein. For example, further preferred embodiments of the invention can be obtained by combining (1)(a) and (2)(a); (1)(a) and (2)(b); (1)(b) and (2)(a); (1)(b) and (2)(b); (1)(c) and (2)(a); (1)(c) and (2)(b); (2)(a) and (3); (2)(b) and (3); (1)(b) and (4)(a); (1)(b), (4)(a) and (5); (1)(b), (4)(b) and (5); (1)(b), (3), (4)(b) and (5); (3), (4)(b), and (5); (2)(a), (3), (4)(b), and (5); (2)(b), (3), (4)(b), and (5); (1)(b), (2)(a), (3), (4)(b), and (5); (1)(b), (2)(b), (3), (4)(b), and (5); (1)(b), (3), (4)(b), (5), and (6); (1)(b), (3), (5), and (6); (1)(b), (3), (5), (6), and (7); (1)(b), (3), (5), (6), (7), and (8)(a); (1)(b), (3), (5), (6), (7), and (8)(b); (1)(b), (3), (5), (6), (7), (8)(a) and (9); (1)(b), (3), (5), (6), (7), (8)(b), and (9); (5), (6), (7), (8)(a) and (9); (5), (6), (7), (8)(b) and (9); (5), (6), (7), and (9); and the like; or by solely requiring (1)(b); (2)(a); (2)(b); (3); (4)(a); (4)(b); (5), (7); and the like. It is further understood that the stereoisomers and pharmaceutically acceptable salts are included in the term "compound" unless specifically disclaimed.

#### REACTION SCHEMES

30 Compounds of formula (I) and intermediates thereof can be prepared as described in Reaction Schemes A through E. All the substituents, unless otherwise indicated, are as previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art. Scheme A provides

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a synthetic process for making benzyl oxadiazole compounds of formula (3) which represent compounds of formula (I) wherein n is 0 and all of the remaining substituents are as defined in formula (I).

Scheme A

5 In Scheme A, step 1, the phenyl carbonitrile of formula (1) is treated with hydroxylamine hydrochloride to provide the oxime of formula (1A). For example, the phenyl carbonitrile (1) is dissolved in a suitable alcoholic solvent, such as ethanol, and contacted with hydroxylamine hydrochloride and a suitable base such as sodium ethoxide, sodium hydroxide, or mixtures of the base and water. The mixture is refluxed and stirred until analysis indicates that the reaction is complete. After cooling, the oxime (1A) can be purified by techniques well known in the art, such as such as extraction, evaporation, trituration, chromatography, and recrystallization.

10 In Scheme A, step 2, the oxime (1A) is reacted with chloroacetyl chloride to provide the compound of formula (1B). For example, the oxime (1A) is dissolved in a suitable organic solvent such as acetone, a suitable buffer, such as potassium carbonate, is added and the mixture is cooled. Chloroacetyl chloride is then slowly added over a period of time ranging from about 5 to about 60 minutes. The mixture is then warmed to room temperature and stirred until analysis indicates that the reaction is complete. The compound of formula (1B) can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

15 In Scheme A, step 3, the compound of formula (1B) is refluxed in a suitable organic solvent to provide the 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C). For example, the compound of formula (1B) is refluxed with a Dean-Stark apparatus in a suitable organic solvent such as toluene until analysis indicates that the reaction is complete. The solution is then cooled and 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C) may be be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

20 In Scheme A, step 4, the benzyl oxadiazole of formula (3) is prepared by coupling the substituted cyclic amine of formula (2) with 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C). For example, substituted cyclic amine (2) and 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C) are dissolved in a suitable organic solvent such as ethanol and refluxed until analysis indicates that the reaction is complete. The benzyl

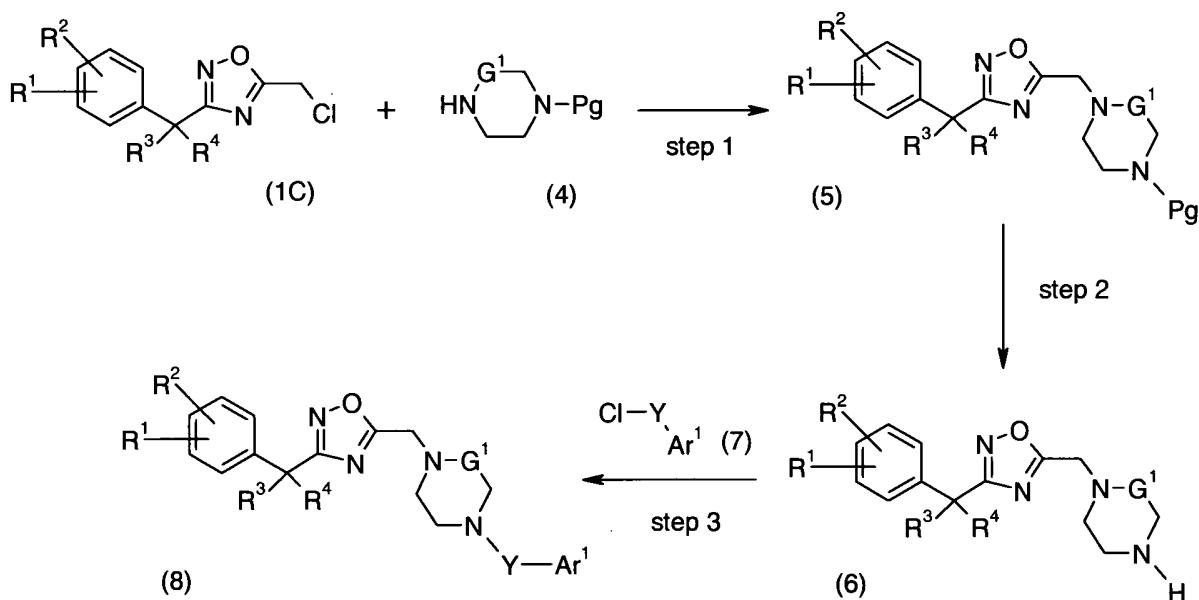
oxadiazole of formula (3) may be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

Many phenyl carbonitriles of formula (1) are commercially available or are well-known in the art such as 1-phenyl-cyclopropanecarbonitrile, 1-(4-methylphenyl)-1-cyclopropanecarbonitrile, 2-phenylbutyronitrile, 1-phenylcyclobutanecarbonitrile, p-chloro-alpha-methylphenyl acetonitrile, 1-(4-fluorophenyl)cyclopentanecarbonitrile, 1-phenylcyclohexane-1-carbonitrile, and the like. Alternatively, phenyl carbonitriles of formula (1) may be synthesized by techniques well known and appreciated by those of ordinary skill in the art. For example, 1-(4-fluoro-phenyl)-cyclopropanecarbonitrile may be prepared by reacting (4-fluoro-phenyl)-acetonitrile with bromochloroethane in an aqueous basic solution in the presence of triethylammonium chloride as set forth in the examples herein.

Additionally, many substituted cyclic amines of formula (2) are commercially available or are well-known in the art such as 1-phenylpiperazine, 1-(3-(trifluoromethyl)phenyl)piperazine, 1-(2,4-dichlorophenyl)piperazine, 1-(4-chloro-2-fluorophenyl)piperazine, 1-(p-tolyl)piperazine, 1-(3,4-difluorophenyl) piperazine, and the like. Alternatively, the substituted cyclic amines of formula (2) may be synthesized by techniques well known in the art. For example, 1-(3-methoxyphenyl)piperazine may be prepared by reacting bis(2-chloroethyl)amine hydrochloride, 3-methoxyaniline and diethylene glycol monomethyl ether at 150°C.

Scheme B provides a synthetic process for making benzyl oxadiazole piperazine aryl compounds of formula (8) which represent compounds of formula (I) wherein n is 1, G<sup>2</sup> is N, Pg is a suitable amino protecting group, such as t-Boc, and all of the remaining substituents are as defined in formula (I).

Scheme B



In Scheme B, step 1, the N-protected benzyl oxadiazole piperazine of formula (5) is prepared by coupling the N-protected piperazine of formula (4) with 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C) according to the procedure set forth in Scheme A, step 4.

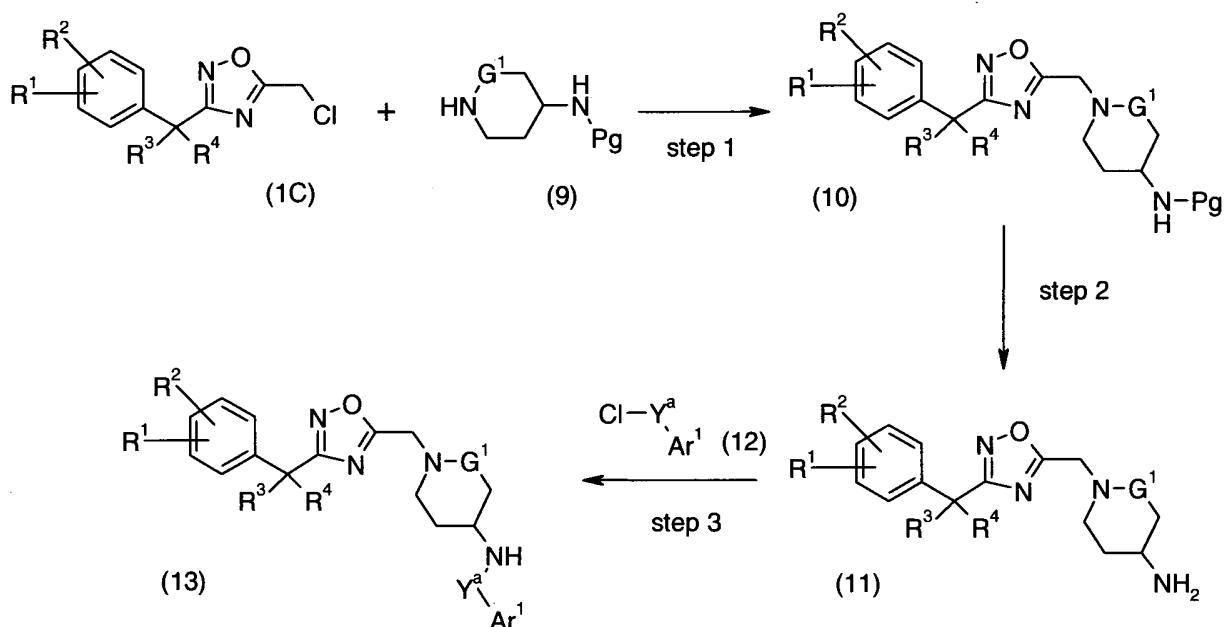
In Scheme B, step 2, the benzyl oxadiazole piperazine of formula (6) is prepared by deprotecting the N-protected benzyl oxadiazole piperazine of formula (5). Removal of amino protecting groups is well known and appreciated in the art and is described in *Protecting Groups in Organic Synthesis*, by T. Green, Wiley-Interscience (1981). For example, the N-protected benzyl oxadiazole piperazine of formula (5) is mixed with concentrated hydrochloric acid in methanol and heated to reflux until analysis indicates that the reaction is complete. The benzyl oxadiazole piperazine of formula (6) may be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Scheme B, step 3, the benzyl oxadiazole piperazine aryl of formula (8) is prepared by coupling the benzyl oxadiazole piperazine of formula (6) with the aryl chloride of formula (7). For example, benzyl oxadiazole piperazine (6) is contacted with Ar<sup>1</sup>-Y-Cl (7) in a suitable solvent such as methylene chloride in the presence of a suitable base such as triethylamine, diisopropylethylamine, N-methylmorpholine, Huniq's base, sodium carbonate, sodium bicarbonate, or potassium carbonate. The reaction is generally carried out at temperatures ranging from about ambient temperature to about 100°C for a period of time until analysis indicates that the reaction is complete. The benzyl oxadiazole piperazine aryl or formula (8) may be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

Many aryl chlorides of formula (7) are commercially available or are well-known in the art such as benzoyl chloride, 4-methoxybenzoyl chloride, 2-trifluoromethylbenzoyl chloride, 2,4-dichlorobenzoyl chloride, benzenesulfonyl chloride, 3-trifluoromethylbenzenesulfonyl chloride, 3-fluorobenzenesulfonyl chloride, and the like. Alternatively, the aryl chlorides of formula (7) may be synthesized by techniques well known in the art. For example, 2,5-dimethoxybenzenesulfonyl chloride may be prepared from the corresponding sulfonic acid by using thionyl chloride in dimethylformamide.

Scheme C provides a synthetic process for making benzyl oxadiazole piperidine aryl compounds of formula (13) which represent compounds of formula (I) wherein n is 1, G<sup>2</sup> is CH, Y is -NHC(O)-, -NHS(O)<sub>2</sub>-, or -NHC(O)CH(R<sup>7</sup>)-, and Pg is a suitable amino protecting group, such as t-Boc and all of the remaining substituents are as defined in formula (I).

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Scheme C

5 In Scheme C, step 1, the N-protected benzyl oxadiazole piperidine of formula (10) is prepared by coupling the N-protected piperidine of formula (9) with 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C) according to the procedure set forth in Scheme A, step 4.

In Scheme C, step 2, the benzyl oxadiazole piperidine of formula (11) is prepared by deprotecting the N-protected benzyl oxadiazole piperazine of formula (10) according to procedures set forth in Scheme 10 B, step 2.

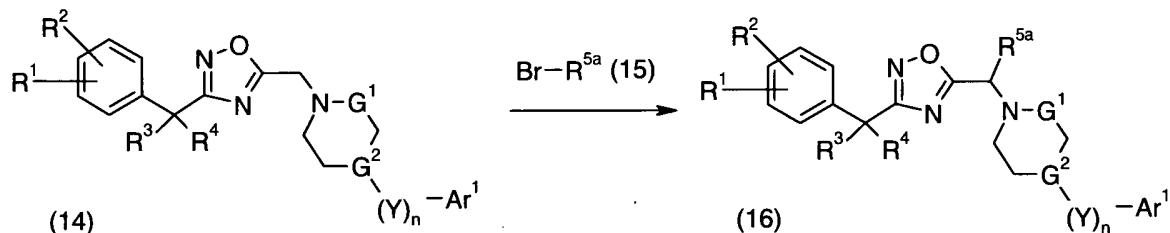
In Scheme C, step 3, the benzyl oxadiazole piperidine aryl of formula (13) is prepared by coupling the benzyl oxadiazole piperidine of formula (11) with the aryl chloride of formula (12) according to the procedures set forth in Scheme B, step 3.

Many aryl chlorides of formula (12) are commercially available or are well-known in the art such 15 as benzoyl chloride, 4-methoxybenzoyl chloride, 2-trifluoromethylbenzoyl chloride, 2,4-dichlorobenzoyl chloride, benzenesulfonyl chloride, 3-trifluoromethylbenzenesulfonyl chloride, 3-fluorobenzenesulfonyl chloride, and the like. Alternatively, the aryl chlorides of formula (12) may be synthesized by techniques well known in the art. For example, 2,5-dimethoxybenzenesulfonyl chloride may be prepared from the corresponding sulfonic acid by using thionyl chloride in dimethylformamide.

Scheme D provides a synthetic process for making benzyl oxadiazole piperidine aryl compounds 20 of formula (16) which represent compounds of formula (I) wherein  $\text{R}^5$  is  $\text{C}_1\text{-}\text{C}_6$  alkyl,  $\text{C}_1\text{-}\text{C}_6$  alkoxy, or  $\text{C}_1\text{-}\text{C}_6\text{-C(O)O-W}$ , wherein W is  $-\text{H}$  or  $\text{C}_1\text{-}\text{C}_6$  alkyl; and all of the remaining substituents are as defined in formula (I). The compound of formula (14) depicts compounds of formula (I) where  $\text{R}^5$  is  $-\text{H}$ . The substituent  $\text{R}^{5a}$  is used in compounds (15) and (16) below to depict compounds of formula (I) when  $\text{R}^5$  is 25 not  $-\text{H}$ .

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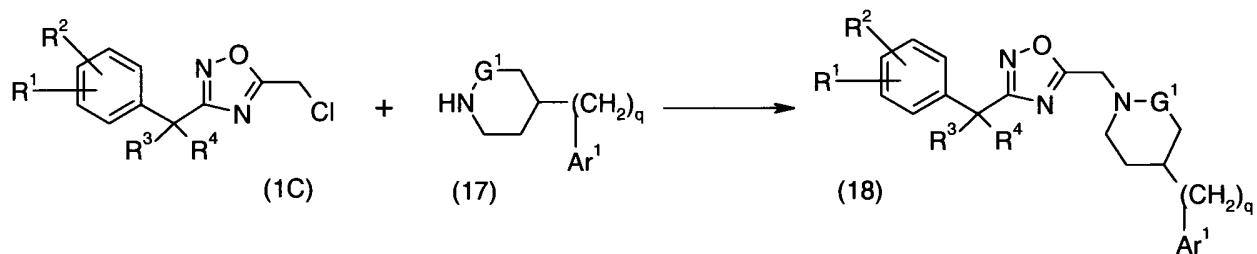
**Scheme D**



In Scheme D, the aryl oxadiazole of formula (14) is alkylated with an appropriate alkyl bromide (15) to provide alkylated aryl oxadiazole of formula (16). An appropriate alkylating agent of formula (15) is one in which R<sup>5a</sup> is as desired in the final product of formula (I). For example, the aryl oxadiazole of formula (14) is contacted with 2.0 to 3.0 molar equivalents of alkyl bromide (15). The reaction is carried out in the presence of a suitable base such as sodium bis(trimethylsilyl)amide or lithium diisopropylamide and in the presence of triethyl borane. The reaction is carried out in a suitable solvent such as tetrahydrofuran. The reaction is generally carried out at temperatures ranging from about -78°C to about 0°C. Generally the reactions require from about 1 to 72 hours. The product can be isolated and purified by techniques well known in the art such as extraction, evaporation, trituration, distillation, chromatography, and recrystallization.

Scheme E provides a synthetic process for making benzyl oxadiazole piperidine aryl compounds of formula (18) which represent compounds of formula (I) wherein G<sup>2</sup> is CH, n is 1 and Y is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; and all of the remaining substituents are as defined in formula (I). In formulae (17) and (18) below, q is 1, 2, or 3 to provide compounds of formula (I) where Y is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

### Scheme E

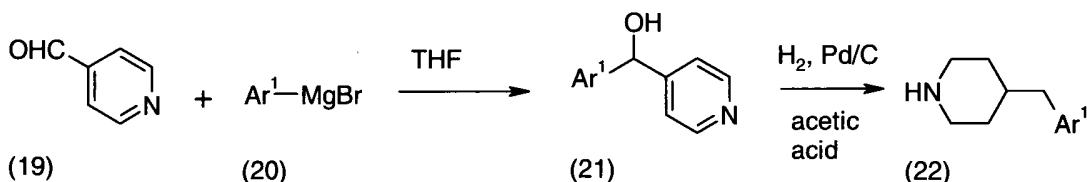


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In Scheme E, the benzyl oxadiazole piperidine of formula (18) is prepared by coupling the aryl piperidine of formula (17) with 5-chloromethyl-3-benzyl-[1,2,3]oxadiazole (1C) according to the procedure set forth in Scheme A, step 4.

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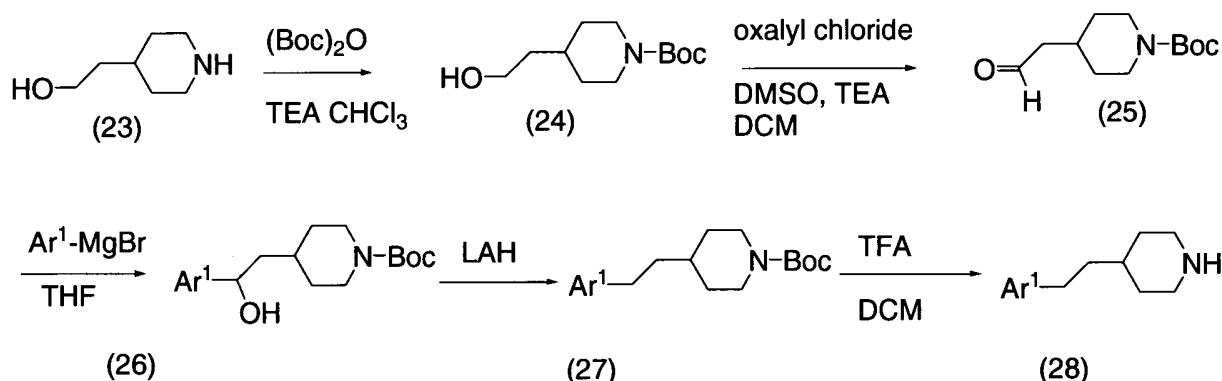
Many aryl piperidines of formula (17) are commercially available or are well-known in the art such as 4-benzylpiperidine, 4-(4-chlorobenzyl)piperidine, 4-(4-methoxybenzyl)piperidine, 4-(3-trifluoromethylbenzyl)piperidine, 4-(4-trifluoromethyl-benzyl)piperidine, 4-phenethyl-piperidine, 4-[2-(4-trifluorophenyl)-ethyl]piperidine, 4-[2-(3-methoxy-phenyl)-ethyl]piperidine, 4-(3-phenyl-propyl)piperidine and the like. Alternatively, the aryl piperidines of formula (17) may be synthesized by techniques well known in the art as set forth in Schemes E1, E2, and E3.

Scheme E1

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In Scheme E1, 4-pyridinecarboxaldehyde (19) is reacted with the aryl Grignard reactant in a suitable organic solvent such as tetrahydrofuran under standard Grignard conditions to provide the aryl-substituted pyridine of formula (21). The aryl-substituted piperidine of formula (22) is obtained by reducing the aryl-substituted pyridine of formula (21) according to standard palladium catalyzed reduction techniques in the presence of a suitable organic solvent such as acetic acid. The product may be isolated and purified according to art-known techniques such as extraction, evaporation, chromatography, and recrystallization.

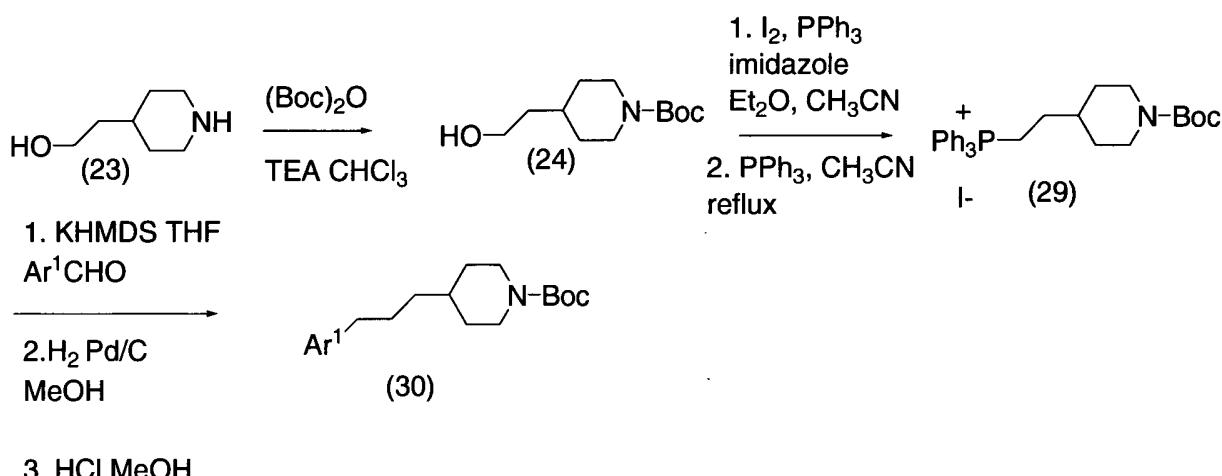
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Scheme E2

In Scheme E2, 4-piperidinethanol (23) is N-protected according to standard nitrogen protecting techniques. The selection and use of suitable amine protecting groups is described in *Protecting Groups in Organic Synthesis* by T. Greene and is well known and appreciated in the art. For example, the 4-piperidinethanol (23) may be N-protected using  $(\text{Boc})_2\text{O}$  in the presence of a tertiary amine, such as triethylamine and a suitable organic solvent such as chloroform to provide the Boc-protected 4-piperidinethanol (24). The N-protected aldehyde of formula (25) is obtained by oxidizing the Boc-protected 4-piperidinethanol (24) with a suitable oxidizing agent such as oxalyl chloride in the presence of a tertiary amine such as triethylamine and DMSO in a suitable solvent, such as dichloromethane. The N-protected aldehyde of formula (25) is then reacted with an aryl Grignard reactant in a suitable organic solvent such as tetrahydrofuran under standard Grignard conditions to provide the aryl-substituted N-protected piperidine of formula (26). The hydroxy moiety is then removed from the aryl-substituted N-protected piperidine of formula (26) using a suitable reducing agent such as lithium aluminum hydride to

provide the de-hydroxylated N-protected piperidine of formula (27). The aryl-substituted piperidine of formula (28) is obtained by deprotecting the de-hydroxylated N-protected piperidine of formula (27). The removal of amine protecting groups is well known and appreciated in the art and is described in *Protecting Groups in Organic Synthesis* by T. Greene. The product may be isolated and purified according to art-known techniques such as extraction, evaporation, chromatography, and recrystallization.

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Scheme E3

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In Scheme E3, 4-piperidinethanol (23) is N-protected according to standard nitrogen protecting techniques. The selection and use of suitable amine protecting groups is described in *Protecting Groups in Organic Synthesis* by T. Greene and is well known and appreciated in the art. For example, the 4-piperidinethanol (23) may be N-protected using  $(Boc)_2O$  in the presence of a tertiary amine, such as triethylamine and a suitable organic solvent such as chloroform to provide the Boc-protected 4-piperidinethanol (24). The phosphorus ylid (29) is obtained by treating the Boc-protected 4-piperidinethanol (24) with iodine in the presence of triphenylphosphine in a suitable solvent such as diethylether and acetonitrile. The resulting iodo intermediate is then treated *in situ* with triphenylphosphine in a suitable solvent such as acetonitrile, at reflux, to give the phosphorus ylid (29).

15 The reaction of an aldehyde with the phosphorus ylid (29) to give an alkene, under standard Wittig reaction conditions, is then carried out, using a suitable base such as potassium hexamethyldisilazamide (KHMDS), in a suitable solvent such as tetrahydrofuran. This is followed by reduction of the alkene according to standard palladium catalyzed reduction techniques, in the presence of a suitable organic solvent such as methanol, to give the aryl-substituted N-protected piperidine of formula (30).

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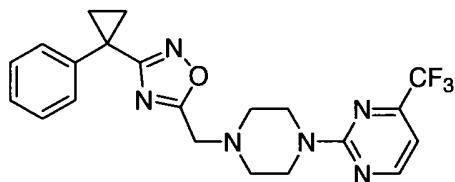
In the preparations and examples the following terms have the indicated meanings; "ng" refers to nanograms; " $\mu\text{g}$ " refers to micrograms; "mg" refers to milligrams; "g" refers to grams; "kg" refers to kilograms; "nmole" or "inmol" refers to nanomoles; "mmol" refers to millimoles; "mol" refers to moles; " $\mu\text{L}$ " refers to microliters; "mL" refers to milliliters; "L" refers to liters; "R<sub>f</sub>" refers to retention factor; " $^{\circ}\text{C}$ " refers to degrees Celsius; "bp" refers to boiling point; "mm of Hg" refers to pressure in millimeters of mercury; "mp" refers to melting point; "dec" refers to decomposition; "[ $\alpha$ ]<sub>D</sub><sup>20</sup>" refers to specific rotation of the D line of sodium at 20°C obtained in a 1 decimeter cell; "c" refers to concentration in g/mL; "nM" refers to nanomolar; " $\mu\text{M}$ " refers to micromolar; "mM" refers to millimolar; "M" refers to molar; "psi" refers to pounds per square inch; "rpm" refers to revolutions per minute; "HPLC" refers to high performance liquid chromatography; "RP-HPLC" refers to reverse phase high performance liquid chromatography; "HRMS" refers to high resolution mass spectrum; "DMSO" refers to dimethyl sulfoxide; "brine" refers to a saturated aqueous solution of sodium chloride; " $\mu\text{Ci}$ " refers to microcuries; "i.p." refers to intraperitoneally; "i.v." refers to intravenously; "Bn" refers to benzyl; "Boc" refers to *t*-butyloxycarbonyl; "DCC" refers to *N,N'*-dicyclohexylcarbodiimide; "DCM" refers to dichloromethane; "DIBAL-H" refers to diisobutylaluminum hydride; "DMF" refers to *N,N*-dimethylformamide; "DMSO" refers to dimethyl sulfoxide; "EtOH" refers to ethanol; "IPA" refers to isopropyl alcohol; "LDA" refers to lithium diisopropylamide; "LAH" refers to lithium aluminum hydride; "NaOtBu" refers to sodium t-butoxide; "TEA" refers to triethyl amine; "TFA" refers to trifluoroacetic acid; "THF" refers to tetrahydrofuran; "h" refers to hour or hours; "min" refers to minute or minutes; "s" refers to second or seconds; "Eq" refers to equivalent; or equivalents; N refers to normality (Eq/l); "soln" refers to solutions; "temp" refers to temperature; "conc" refers to concentrate; "vac" refers to vacuum.

#### Example 1

2-{4-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-4-trifluoromethyl-pyrimidine,

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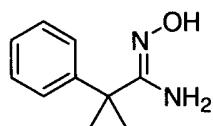
hydrochloride



1A

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N-Hydroxy-1-phenyl-cyclopropanecarboxamidine



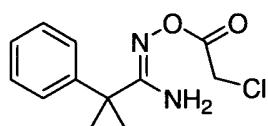
1-Phenyl-cyclopropanecarbonitrile (31 g, 0.22 mol) is dissolved in EtOH (1 L). Hydroxylamine hydrochloride (36 g, 0.52 mol) is added, followed by NaOEt (34 g, 0.51 mol) under rapid stirring. The

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mixture is heated to reflux for 6 hours, and cooled to RT. The solvent is removed and EtOAc is added. The organic solution is dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. The product is purified by column chromatography (SiO<sub>2</sub>) using 5% MeOH/CHCl<sub>3</sub>, to yield **1A** (36 g). MS (CI) *m/z* 177 [M+1].

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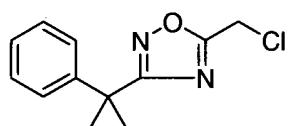
**1B**

The compound **1A** (36 g, 0.20 mol) is dissolved in acetone (400 mL). K<sub>2</sub>CO<sub>3</sub> (30 g, 0.216 mol) is added and the mixture is cooled on an ice bath. Chloroacetyl chloride (27 g, 0.235 mol) is added dropwise over 10 min. The mixture is warmed to RT, and stirred for 3 hr. The solvent is removed and water is added. The aqueous solution is extracted with EtOAc. The organic solution is dried with MgSO<sub>4</sub>, filtered and reduced in volume to ca. 300 mL. A similar volume of hexane is added, and the solution is left to stand at RT for 18 hr. A colorless solid is collected by filtration and dried in vacuo to yield **1B** (28.8 g). MS (CI) *m/z* 253 [M+1].

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**1C**5-Chloromethyl-3-(1-phenylcyclopropyl)-[1,2,4]oxadiazole

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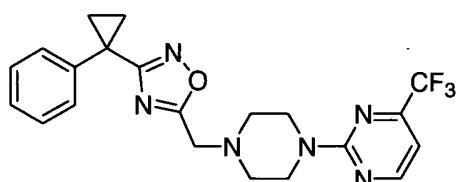
Compound **1B** (20 g, 79 mmol) is refluxed with a Dean-Stark apparatus in toluene (250 mL) for 3 hr. The solution is cooled and concentrated in vacuo. The product is purified by column chromatography (SiO<sub>2</sub>) using 5% MeOH/CHCl<sub>3</sub>, to yield **1C** (18.4 g) as a colorless liquid. MS (CI) *m/z* 235 [M+1]. Analysis Calcd

for C<sub>12</sub>H<sub>11</sub>Cl<sub>1</sub>N<sub>2</sub>O<sub>1</sub>; C, 61.42; H, 4.72; N, 11.94; Cl, 15.11. Found C: 61.35, H: 4.61, N: 11.84, Cl: 15.26.

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Example 12-[4-[3-(1-Phenylcyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl]-4-trifluoromethyl-pyrimidine hydrochloride

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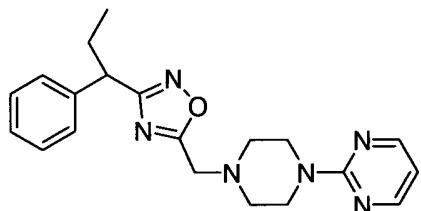
-33-

A solution of 2-piperazin-1-yl-4-trifluoromethyl-pyrimidine (2.0 g, 8.61 mmol) and compound **1C** (0.505 g, 2.15 mmol) in EtOH (200 mL) is refluxed, for 18 hr. The solution is cooled and concentrated in vacuo to yield an oil. The crude product is purified by an ISCO Sg 100C, with 3% MeOH/CHCl<sub>3</sub> for 5 minutes, 3 to 13% MeOH/CHCl<sub>3</sub> over 25 minutes, then hold at 13% MeOH/CHCl<sub>3</sub> for 30 minutes to give the desired product as an oil. The oil is suspended in acetone (20 mL) and 4M HCl (in dioxane) (2.15 mL) is added. Precipitation of the hydrochloride salt occurs and the solid is filtered, washed once with acetone and dried to yield **1** (0.662 g) as a white solid. MS (Cl) *m/z* 431 [M+1]. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 1.38 (q, *J*=4.4, 2H), 1.61 (q, *J*=4.1, 2H), 2.64 (t, *J*=4.6, 4H), 3.84 (s, 2H), 3.91(t, *J*=4.8, 4H), 6.75 (d, *J*=4.8, 2H), 7.29 (d, *J*=6.8, 2H), 7.34 (t, *J*=7.1, 1H), 7.45 (d, *J*=7.6, 1H), 8.47 (d, *J*=4.9, 1H). MS (Cl) *m/z* 431 [M+1]. Analysis Calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>6</sub>O x 0.92 HCl: C, 54.36; H, 4.76; N, 18.11. Found C: 53.97, H: 4.71, N: 17.76.

Example 2

2-[4-[3-(1-Phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl]-pyrimidine

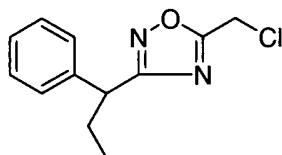
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2A

5-Chloromethyl-3-(1-phenyl-propyl)-[1,2,4]oxadiazole

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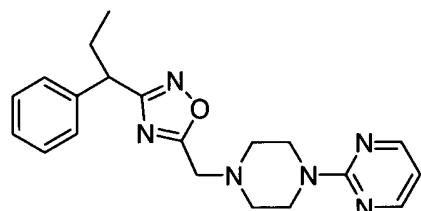


Compound **2A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 2-phenylbutyronitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) *m/z* 237 [M+1].

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Example 2

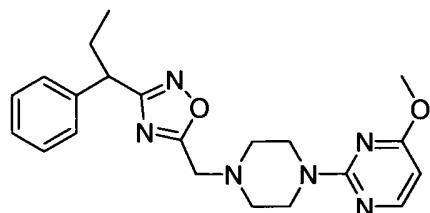
2-[4-[3-(1-Phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl]-pyrimidine



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Example 2 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-propyl)-[1,2,4]oxadiazole **2A** and 2-piperazin-1-yl-pyrimidine, omitting the treatment with HCl, to give the free base. LCMS - 100%, *m/z* 365 [M+1].

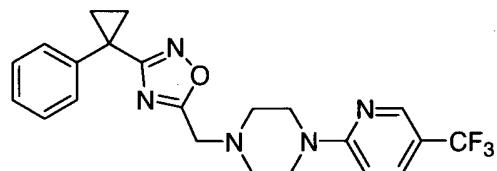
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Example 34-Methoxy-2-{4-[3-(1-phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine

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Example 3 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-propyl)-[1,2,4]oxadiazole **2A** and 4-methoxy-2-piperazin-1-yl-pyrimidine, omitting the treatment with HCl, to give the free base. LCMS - 100%, *m/z* 395 [M+1].

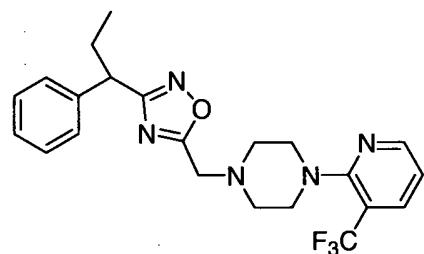
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Example 41-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

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Example 4 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazole **1C** and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. LCMS - 100%, *m/z* 430 [M+1].

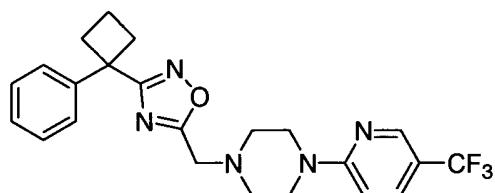
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Example 51-[3-(1-Phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(3-trifluoromethyl-pyridin-2-yl)-piperazine

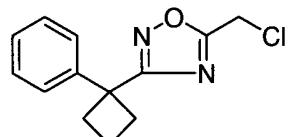
-35-

Example 5 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-propyl)-[1,2,4]oxadiazole **2A** and 1-(3-trifluoromethyl-pyridin-2-yl)-piperazine, omitting the treatment with HCl, to give the free base. LCMS - 100%, *m/z* 432 [M+1].

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Example 61-[3-(1-Phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine

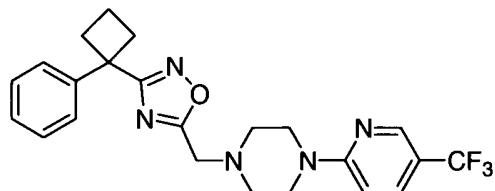
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6A5-Chloromethyl-3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazole

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Compound **6A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-phenylcyclobutanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) *m/z* 249 [M+1].

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Example 61-[3-(1-Phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine

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A solution of 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine (11.2 g, 48.2 mmol) and compound **6A** (3.0 g, 12.1 mmol) in EtOH (250 mL) is refluxed, for 18 hr. The solution is cooled and concentrated in vacuo to yield an oil. The crude product is purified by an ISCO Sg 100C, with 3% MeOH/CHCl<sub>3</sub> for 5 minutes, 3 to 13% MeOH/CHCl<sub>3</sub> over 25 minutes, then hold at 13% MeOH/CHCl<sub>3</sub> for 30 minutes to yield **6** (4.6 g) as an oil. MS (Cl) *m/z* 444 [M+1]. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 1.91-1.99 (m, 1H), 2.06-2.18 (m, 1H), 2.64 (t, J=

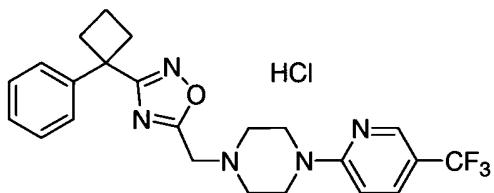
30

-36-

5.2, 4H), 2.71 (m, 2H), 2.88 (m, 2H), 3.65(t, J=4.6, 4H), 3.83 (s, 2H), 6.58 (d, J= 8.9, 1H), 7.19 (m, 1H), 7.30 (m, 4H), 7.59 (dd, J= 8.9, 1H), 8.35 (s, 1H).

Example 7

- 5 1-[3-(1-Phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

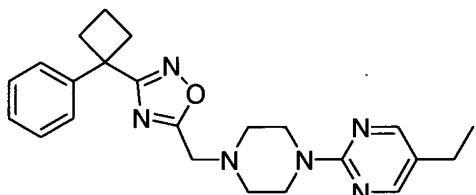


- 10 Example 6 (1.5 g, 3.38 mmol) is suspended in acetone (20 mL) and 4M HCl (in dioxane) (3.38 mL) is added. Precipitation of the hydrochloride salt occurs and the solid is filtered, washed once with acetone and dried to yield 7 (1.6 g) as a white solid. MS (Cl) *m/z* 444 [M+1]. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 1.91-1.99 (m, 1H), 2.06-2.18 (m, 1H), 2.64 (t, J= 5.2, 4H), 2.71 (m, 2H), 2.88 (m, 2H), 3.65(t, J=4.6, 4H), 3.83 (s, 2H), 6.58 (d, J= 8.9, 1H), 7.19 (m, 1H), 7.30 (m, 4H), 7.59 (dd, J= 8.9, 1H), 8.35 (s, 1H).

15

Example 8

- 5-Ethyl-2-{4-[3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine

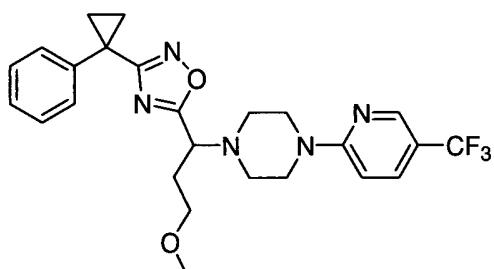


20

Example 8 is synthesized by the method described for example 6, using 5-chloromethyl-3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazole 6A and 5-ethyl-2-piperazin-1-yl-pyrimidine. LCMS - 100%, *m/z* 405 [M+1].

Example 9

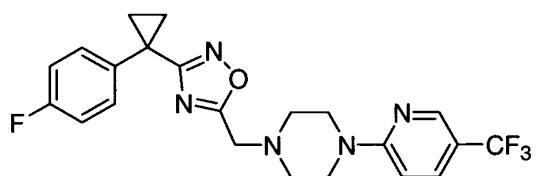
- 25 1-{3-Methoxy-1-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-propyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine



1-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, example 4,(0.20 g, 0.466 mmol) is dissolved in THF (2 ml) and cooled to -78°C. A solution of LDA (0.285 mL, 0.512 mmol) is added and the mixture stirred for 30 minutes. Triethyl borane (0.98 mL, 0.98 mmol) is added and the mixture stirred for 10 min, followed by the addition of bromoethyl methyl ether (0.092 mL, 0.978 mmol). After an additional 30 minutes at -78°C, the reaction is warmed to RT, and stirred for 18 hr. The reaction mixture is quenched with the slow addition of a solution of saturated ammonium chloride. The organic solution is separated and concentrated in vacuo to yield the crude product as an oil. The crude product is purified by an ISCO Sg 100C, with 20% EtOAc/hexanes for 5 minutes, 20 to 50% EtOAc/hexanes over 25 minutes, then hold at 50% EtOAc/hexanes for 30 minutes to give the desired product as an oil (8.0 mg). LCMS 100, *m/z* 488 [M+1].

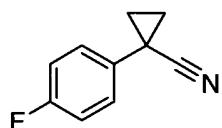
Example 10

1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



10A

1-(4-Fluoro-phenyl)-cyclopropanecarbonitrile

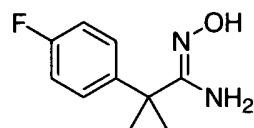


(4-Fluoro-phenyl)-acetonitrile (53 g, 0.39 mol), triethylbenzylammonium chloride (1.8 g, 7.8 mol) and bromochloroethane (112 g, 0.78 mol) are stirred and a solution of 50% aqueous sodium hydroxide (220mL) is added dropwise over 10 min, raising the temperature between 40-45°C. Once the addition was completed, the reaction was heated to maintain the temperature between 40-45°C, for 6 hr. Further portions of bromochloroethane (112 g, 0.78 mol) and 50% aqueous sodium hydroxide (220mL) are added and the reaction is stirred at 45°C, for 18 hr. The reaction was cooled, and the product extracted with methylene chloride. The organic solution is dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. The product is purified by column chromatography (SiO<sub>2</sub>) using 5% MeOH/CHCl<sub>3</sub>, to yield 10A (52 g) as a colorless solid. MS (Cl) *m/z* 162 [M+1].

10B

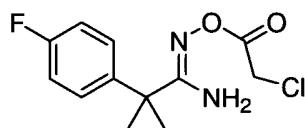
1-(4-Fluoro-phenyl)-N-hydroxy-cyclopropanecarboxamidine

-38-



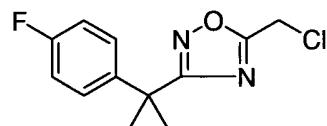
Compound **10A** (52 g, 0.32 mol) is dissolved in EtOH (1 L). Hydroxylamine hydrochloride (56 g, 0.81 mol) is added, followed by NaOEt (53 g, 0.78 mol) under rapid stirring. The mixture is heated to reflux for 6 hr. The reaction is cooled. The solvent is removed and EtOAc is added. The organic solution is dried with  $\text{MgSO}_4$ , filtered and concentrated in vacuo to give a waxy solid. This solid is dissolved in EtOAc (200 mL) and triturated with hexanes (1L). After 1 hr., a colorless solid is collected by filtration and dried in vacuo, to yield **10B** (51 g). MS (Cl)  $m/z$  195 [M+1].

10

10C

The compound **10B** (51 g, 0.26 mol) is dissolved in acetone (500 mL).  $\text{K}_2\text{CO}_3$  (40 g, 0.29 mol) is added and the mixture is cooled on an ice bath. Chloroacetyl chloride (36 g, 0.32 mol) is added dropwise over 10 min. The mixture is warmed to RT, and stirred for 3 hr. The solvent is removed and water is added. The aqueous solution is extracted with EtOAc. The organic solution is dried with  $\text{MgSO}_4$ , filtered and reduced in volume to ca. 300 mL. A similar volume of hexane is added, and the solution is left to stand at RT for 18 hr. A colorless solid is collected by filtration and dried in vacuo to yield **10C** (50 g). MS (Cl)  $m/z$  271 [M+1].

25

10D5-Chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazole

Compound **10C** (50 g, 0.185 mol) is refluxed with a Dean-Stark apparatus in toluene (800 mL) for 3 hr. The solution is cooled and concentrated in vacuo. The product is purified by column chromatography

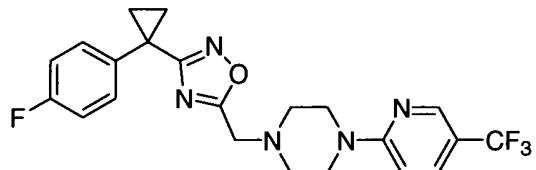
( $\text{SiO}_2$ ) using 5% MeOH/CHCl<sub>3</sub>, to yield **10D** (45.7 g) as a colorless solid. MS (Cl)  $m/z$  253 [M+1].

Analysis Calcd for C<sub>12</sub>H<sub>10</sub>Cl<sub>1</sub>F<sub>1</sub>N<sub>2</sub>O<sub>1</sub>: C, 57.04; H, 3.99; N, 11.09. Found C: 57.23, H: 3.95, N: 11.12.

Example 10

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1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



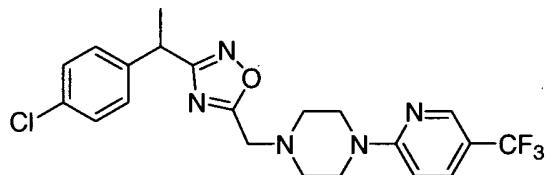
5

Example 10 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclopropyl]-[1,2,4]oxadiazole 10D and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. MS (Cl) *m/z* 448 [M+1]. <sup>1</sup>H NMR (400MHz, CD3OD) 1.40 (q, *J*= 4.7, 2H), 1.61 (q, *J*= 4.1, 2H), 3.58 (t, *J*= 5.2, 4H), 4.03 (brs, 4H), 4.79 (s, 2 H), 7.03 (t, *J*= 8.8, 2H), 7.13 (d, *J*= 9.3, 1H), 7.41 (d, *J*= 5.2, 1H), 7.43 (d, *J*= 5.2, 1H), 7.95 (dd, 1H), 8.40 (s, 1H). Analysis Calcd for C<sub>22</sub>H<sub>21</sub>F<sub>4</sub>N<sub>5</sub>O x 2.3 HCl: C, 49.63; H, 4.42; N, 12.76. Found C: 49.90, H: 4.47, N: 12.76.

10

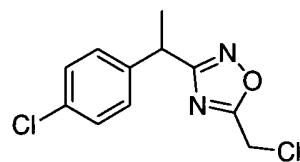
15

1-[3-[1-(4-Chloro-phenyl)-ethyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



20

5-Chloromethyl-3-[1-(4-chlorophenyl)-ethyl]-[1,2,4]oxadiazole

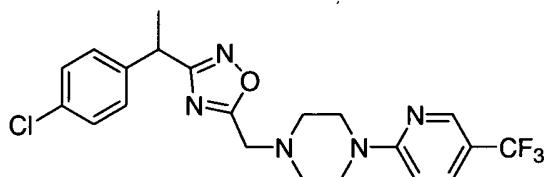


Compound 11A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using p-chloro- $\alpha$ -methylphenyl acetonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A. MS (Cl) *m/z* 258 [M+1].

30

Example 11  
1-[3-[1-(4-Chloro-phenyl)-ethyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

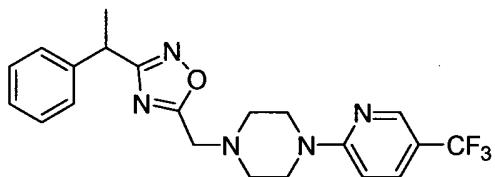
-40-



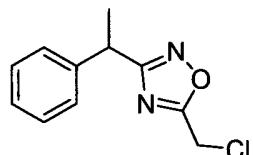
Example 11 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-ethyl]-[1,2,4]oxadiazole 11A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. MS (Cl) *m/z* 452 [M+1]. <sup>1</sup>H NMR (400MHz, DMSO) 1.55 (brs, 3H), 3.36 (brs, 2H), 3.75 (brs, 6 H), 4.39 (brs, 1H), 4.74 (brs, 2H), 7.04 (brs, 1H), 7.33 (brs, 4H), 7.87 (brs, 1H), 8.43 (brs, 1H). Analysis Calcd for C<sub>21</sub>H<sub>21</sub>ClF<sub>3</sub>N<sub>5</sub>O x 2.2 HCl: C, 47.40; H, 4.39; N, 13.16. Found C: 47.02, H: 4.45 N: 12.82.

Example 12

- 10      1-[3-(1-Phenyl-ethyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



- 15      12A  
5-Chloromethyl-3-(1-phenyl-ethyl)-[1,2,4]oxadiazole



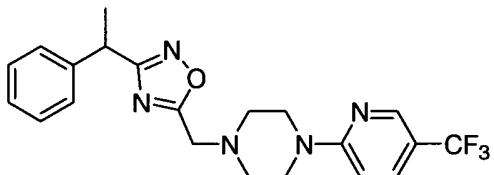
- 20      Compound 12A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using  $\alpha$ -methylbenzyl cyanide for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) *m/z* 223 [M+1].

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Example 12

1-[3-(1-Phenyl-ethyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine,  
hydrochloride

5

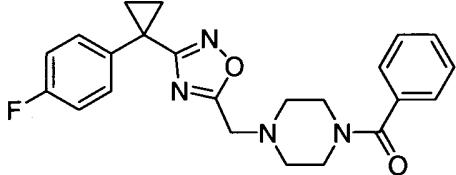


Example 12 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-ethyl)-[1,2,4]oxadiazole 12A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. MS (Cl)  $m/z$  418 [M+1].  $^1\text{H}$  NMR (400MHz, DMSO) 1.57 (d,  $J=7.2$ , 3H), 3.40 (brs, 2H), 4.06 (brs, 6H), 4.37 (brs, 1H), 4.77 (brs, 2H), 7.05 (d,  $J=9.1$ , 1H), 7.21 (m, 1H), 7.28 (m, 4H), 7.88 (dd,  $J=9.11$ H), 8.44 (brs, 1H). Analysis Calcd for  $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_5\text{O} \times 2.0 \text{ HCl}$ : C, 51.32; H, 4.93; N, 14.25. Found C: 50.94, H: 5.03 N: 13.92.

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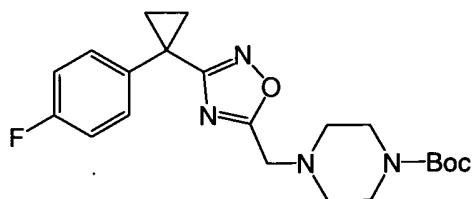
(4-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazin-1-yl)-phenyl-methanone



20

13A

4-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester



A mixture of 10D and tert-butyl-1-piperazine carboxylate (2.21 g, 11.87 mmol) in ethanol (300 mL) is heated to reflux and stirred for 16 h. The reaction mixture is concentrated to an oil and purified by an ISCO Sg 100C, with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> for 5 minute, 2 to 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub> over 20 minutes, then hold at 13% MeOH/CH<sub>2</sub>Cl<sub>2</sub> for 5 minutes. Fractions of interest are combined to give 13A MS (Cl)  $m/z$  403 [M+H].

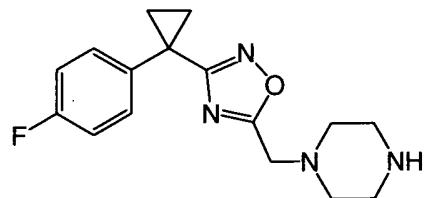
25

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13B

1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperazine

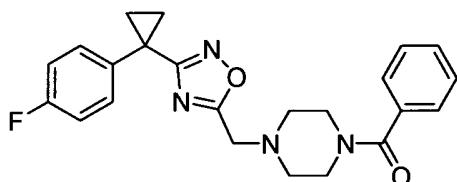
-42-



A mixture of **13A** (4.77 g, 11.85 mmol) and concentrated HCl (4.94 ml, 59.25 mmol) is combined in  
5 methanol (50 ml) and heated to reflux for 1h. The reaction mixture is concentrated to a solid. Ethyl acetate (50 ml) is added back and the solids collected by vacuum filtration, washed with ethyl acetate and dried in the vacuum oven overnight to give **13B** as the HCl salt (3.15 g). MS (Cl) *m/z* 303 [M+H].

#### Example 13

10 (4-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazin-1-yl)-phenyl-methanone

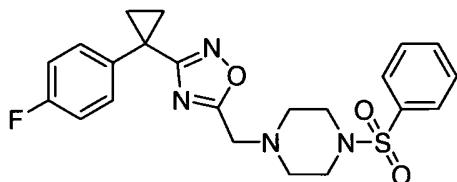


A solution of compound **13B** (50 mg, 0.165 mmol), benzoyl chloride (23.2 mg, 0.165 mmol) and Huniq's  
15 base (0.11 g, 0.83 mmol) in methylene chloride (1 mL) are stirred at RT, for 18 hr. The solution is concentrated in vacuo and the residue is purified by reversed phase HPLC (Column: Phenomenex Gemini 21x100 mm C18 5 micron; 20% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 1 minute, 20 to 100% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) over 7 minutes, then hold 100% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 2 minutes). LCMS - 100%, *m/z* 407 [M+1].

20

#### Example 14

1-Benzenesulfonyl-4-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazine



25

To a stirred solution of compound **13B** (50 mg, 0.165 mmol) in methylene chloride (1 mL) is added diisopropylethylamine (79 uL, 0.827 mmol) and benzene sulfonyl chloride (29 mg, 0.165 mmol). The resulting solution is stirred at RT for 16h. The solution is concentrated in vacuo and the residue is purified by reversed phase HPLC (Column: Phenomenex Gemini 21x100 mm C18 5 micron; 20% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 1 minute, 20 to 100% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 2 minutes).

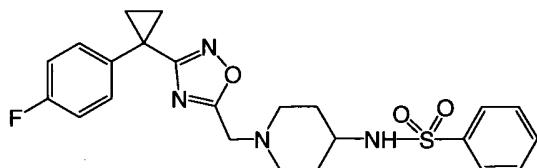
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-43-

$\text{NH}_4\text{OH}$ ) over 7 minutes, then hold 100% acetonitrile (0.2%  $\text{NH}_4\text{OH}$ )/ $\text{H}_2\text{O}$  (0.2%  $\text{NH}_4\text{OH}$ ) for 2 minutes). LCMS - 100%,  $m/z$  443 [M+1].

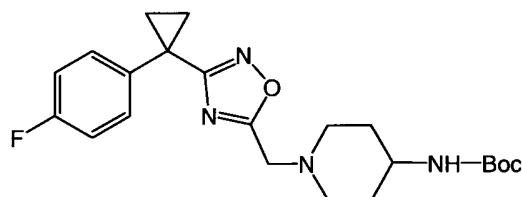
Example 15

5    N-(1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide



15A

10    (1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-carbamic acid tert-butyl ester

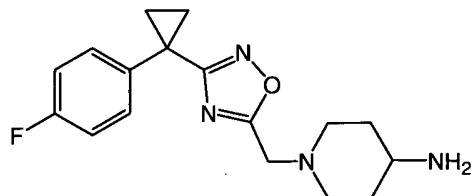


15    A mixture of **10D** (3.00 g, 11.87 mmol) and 4-N-boc-aminopiperidine (2.38 g, 11.87 mmol) in ethanol (300 mL) is heated to reflux and stirred for 16 hr. The reaction mixture is concentrated to an oil and purified by an ISCO Sg 100C, with 3% MeOH/  $\text{CH}_2\text{Cl}_2$  for 5 minute, 5 to 13% MeOH/ $\text{CH}_2\text{Cl}_2$  over 20 minutes, then a hold at 13% MeOH/ $\text{CH}_2\text{Cl}_2$  for 5 minutes. Fractions of interest are combined to give **15A** (3.35 g). MS (Cl)  $m/z$  417 [M+H].

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15B

1-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine

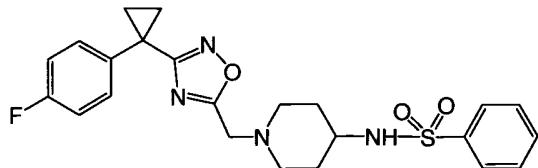


25

A mixture of **15A** (3.35 g, 8.04 mmol) and concentrated HCl (3.35 ml, 40.22 mmol) is combined in methanol (40 ml) and heated to reflux for 16 hr. The reaction mixture is concentrated to a solid. Ethyl acetate (40 ml) is added back and the solids collected by vacuum filtration, washed with ethyl acetate and dried in the vacuum oven overnight to give **15B** as the HCl salt (2.32 g). MS (Cl)  $m/z$  317 [M+H].

30

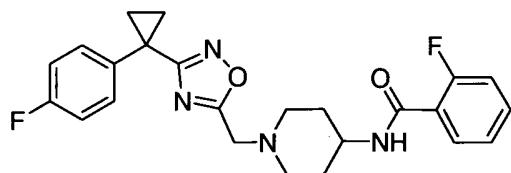
-44-

Example 15N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide

5

To a stirred solution of compound **15B** (50 mg, 0.158 mmol) in methylene chloride (1 mL) is added diisopropylethylamine (75 uL, 0.790 mmol) and benzene sulfonyl chloride (28 mg, 0.158 mmol). The resulting solution is stirred at RT for 16h. The solution is concentrated in vacuo and the residue is purified by reversed phase HPLC (Column: Phenomenex Gemini 21x100 mm C18 5 micron; 20% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 1 minute, 20 to 100% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) over 7 minutes, then hold 100% acetonitrile (0.2% NH<sub>4</sub>OH)/H<sub>2</sub>O (0.2% NH<sub>4</sub>OH) for 2 minutes). LCMS - 100%, *m/z* 457 [M+1].

10

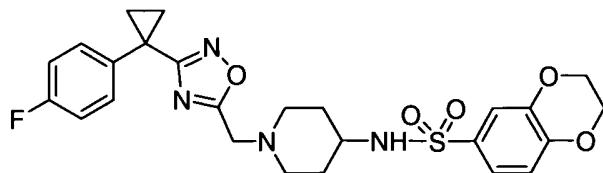
Example 16  
2-Fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzamide

Example **16** is synthesized by the method described for example **13**, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine **15B** and 2-fluoro-benzoyl chloride. LCMS - 95%, *m/z* 439 [M+1].

20

Example 17  
2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-

25

ylmethyl}-piperidin-4-yl)-amide

Example **17** is synthesized by the method described for example **15**, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine **15B** and 2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl chloride. LCMS - 100%, *m/z* 515 [M+1].

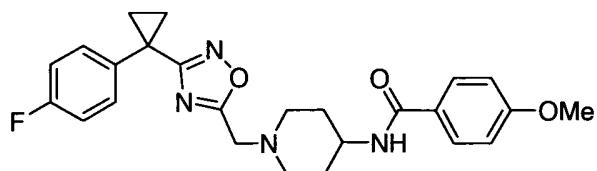
30

-45-

Example 18

N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-methoxybenzamide

5

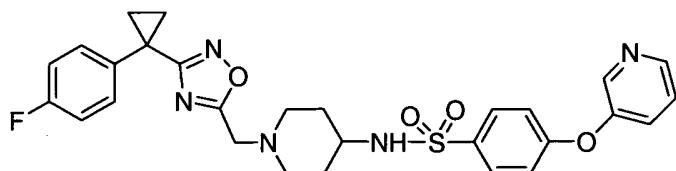


Example 18 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 4-methoxy-benzoyl chloride. LCMS - 100%,  $m/z$  451 [M+1].

Example 19

N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-(pyridin-3-yloxy)benzenesulfonamide

15

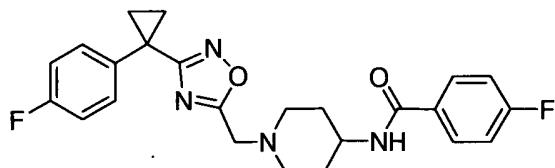


Example 19 is synthesized by the method described for example 15, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 4-(pyridin-3-yloxy)benzenesulfonyl chloride. LCMS - 98%,  $m/z$  550 [M+1].

Example 20

4-Fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzamide

25



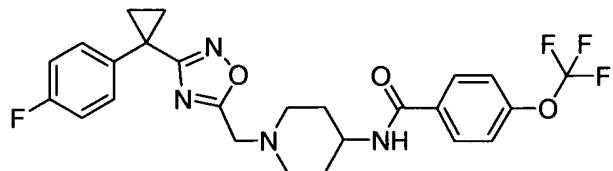
Example 20 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 4-fluoro-benzoyl chloride. LCMS - 100%,  $m/z$  439 [M+1].

30

Example 21

-46-

N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzamide



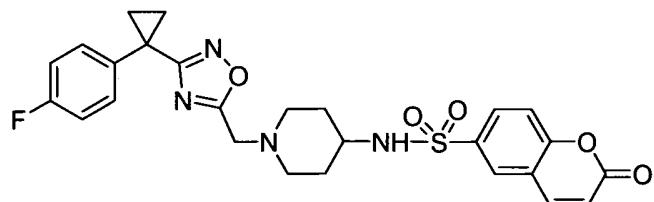
5

Example 21 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 4-trifluoromethoxy-benzoyl chloride. LCMS - 99%, *m/z* 505 [M+1].

10

Example 22

2-Oxo-2H-chromene-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide



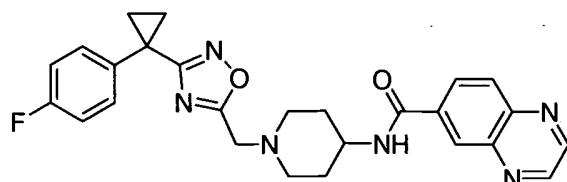
15

Example 22 is synthesized by the method described for example 15, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 2-oxo-2H-chromene-6-sulfonic acid. LCMS - 98%, *m/z* 525 [M+1].

20

Example 23

Quinoxaline-6-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide



25

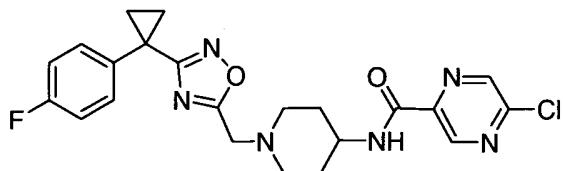
Example 23 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and quinoxaline-6-carboxylic acid. LCMS - 100%, *m/z* 473 [M+1].

30

Example 24

-47-

5-Chloro-pyrazine-2-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide



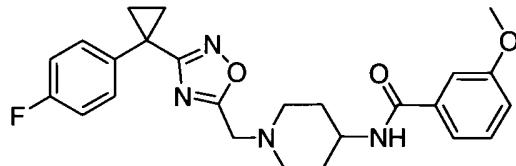
5

Example 24 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 5-chloro-pyrazine-2-carbonyl chloride. LCMS - 100%, *m/z* 457 [M+1].

10

Example 25

N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-3-methoxybenzamide



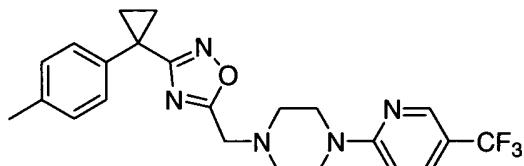
15

Example 25 is synthesized by the method described for example 13, using 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylamine 15B and 3-methoxy-benzoyl chloride. LCMS - 100%, *m/z* 451 [M+1].

20

Example 26

1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

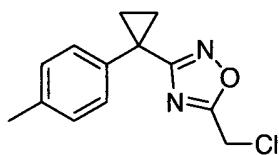


25

26A

5-Chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole

-48-

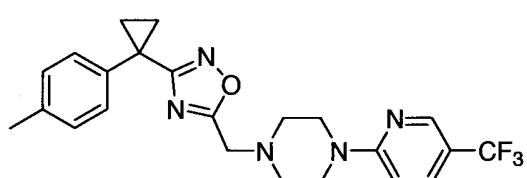


Compound **26A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-(4-methylphenyl)-1-cyclopropanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) 5 *m/z* 249 [M+H].

Example 26

1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

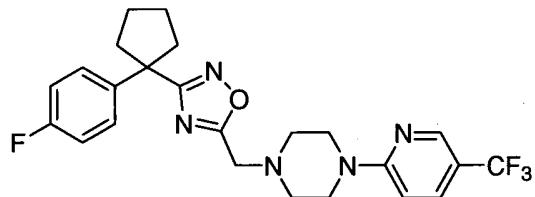
10



Example **26** is synthesized by the method described for example **1**, using 5-chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole **26A** and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. MS (Cl) *m/z* 444. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.43 (t, 2H), 1.63 (t, 2H), 2.34 (s, 3H), 3.61 (t, 4H), 4.09 (brs, 4H), 4.81 (s, 2H), 7.16 (m, 3H), 7.32 (d, 2H), 7.94 (d, 1H), 8.45 (s, 1H). Analysis Calcd for C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>N<sub>5</sub>O x 2HCl x 1H<sub>2</sub>O: C, 48.43; H, 5.65; N, 12.28; Cl, 12.43. Found C: 48.03, H: 4.72, N: 12.19, Cl: 11.14.

Example 27

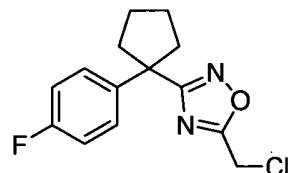
1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine



25

27A

5-Chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazole

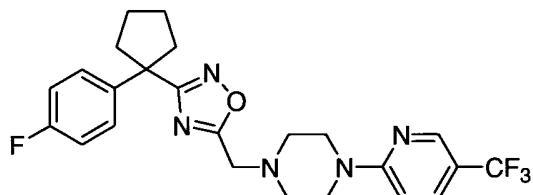


Compound **27A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-(4-fluorophenyl)cyclopentanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) *m/z* 281 [M+H].

5

Example 27

1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine



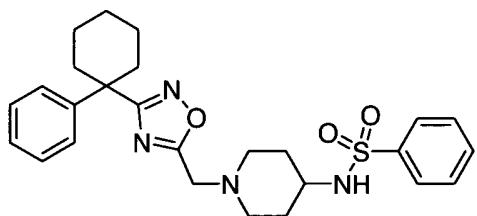
10

Example **27** is synthesized by the method described for example **1**, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclopentyl]-[1,2,4]oxadiazole **27A** and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine, omitting the treatment with HCl, to give the free base. MS (Cl) *m/z* 476. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) 1.71 (m, 2H), 1.80 (m, 2H), 2.14 (m, 2H), 2.64 (m, 4H), 2.73 (m, 2H), 3.66 (m, 4H), 3.84 (s, 2H), 6.62 (d, 1H), 6.97 (t, 2H), 7.35 (m, 2H), 7.62 (d, 1H), 8.39 (d, 1H). Analysis Calcd for C<sub>24</sub>H<sub>25</sub>F<sub>4</sub>N<sub>5</sub>O: C, 60.62; H, 5.30; N, 14.73; Found C: 60.39, H: 5.42, N: 14.57.

15

Example 28

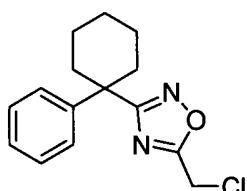
N-[1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide hydrochloride



25

28A

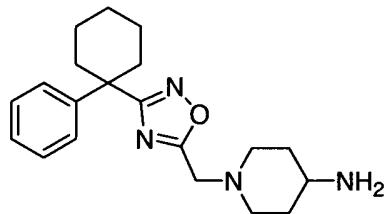
5-Chloromethyl-3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazole



-50-

Compound **28A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-phenylcyclohexane-1-carbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A**. MS (Cl) *m/z* 277 [M+H].

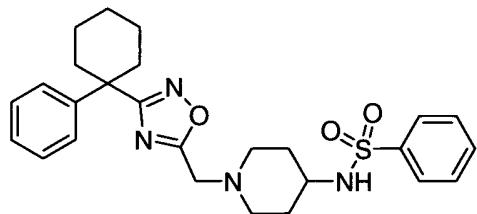
5

**28B**1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine

10 Compound **28B** is synthesized by the method described for example **15B** (Sequence **15A** to **15B**), using 5-chloromethyl-3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazole, **28A** for 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazole **10D** MS (Cl) *m/z* 341 [M+H].

**Example 28**

15 N-[1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide, hydrochloride



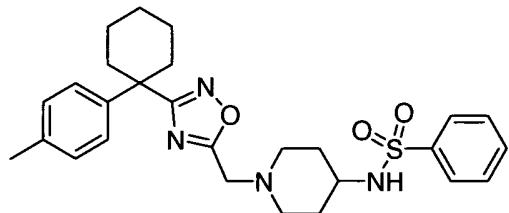
20 Example **28** is synthesized by the method described for example **15**, using 1-[3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine **28B** and benzenesulfonyl chloride, followed by treatment with HCl, as described in example 7. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.47-1.36 (m, 3H), 1.59-1.49 (m, 3H), 1.74 (m, 2H), 1.90 (m, 2H), 2.05 (s, 3H), 2.44 (m, 2H), 3.13 (m, 1H), 3.27 (m, 1H), 3.45 (m, 2H), 4.56 (s, 2H), 7.08 (t, 1H), 7.19 (t, 2H), 7.27 (d, 2H), 7.47 (t, 2H), 7.55 (t, 1H), 7.8 (d, 2H). Analysis Calcd for

25 C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>S x 1HCl x 1H<sub>2</sub>O: C, 58.36; H, 6.59; N, 10.47; Cl, 6.63. Found C: 58.98, H: 6.37, N: 10.36, Cl: 7.17.

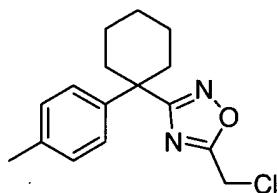
**Example 29**

30 N-[1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide, hydrochloride

-51-

29A5-Chloromethyl-3-(1-p-tolyl-cyclohexyl)-[1,2,4]oxadiazole

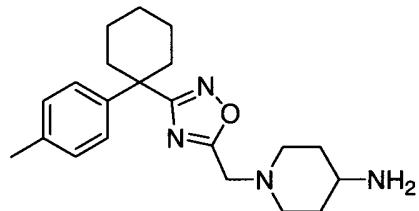
5



Compound **29A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-(4-methylphenyl)-1-cyclohexanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) 10  $m/z$  291 [M+H].

29B1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine

15

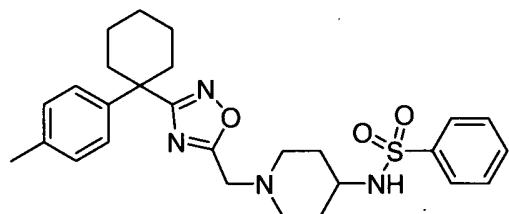


Compound **29B** is synthesized by the method described for example **15B** (Sequence **15A** to **15B**), using 5-chloromethyl-3-(1-p-tolyl-cyclohexyl)-[1,2,4]oxadiazole, **29A** for 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazole **10D** MS (Cl)  $m/z$  355 [M+H].

20

Example 29

N-{1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl}-benzenesulfonamide,  
hydrochloride

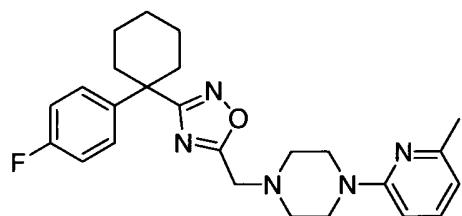


25

Example **29** is synthesized by the method described for example **15**, using 1-[3-(1-p-tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine **29B** and benzenesulfonyl chloride, followed by treatment with HCl, as described in example 7.  $^1\text{H-NMR}$  (500MHz, CD<sub>3</sub>OD) 1.45-1.35 (m, 3H), 1.54-1.49 (m, 3H), 1.74 (m, 2H), 1.89 (m, 2H), 2.00 (m, 2H), 2.17 (s, 3H), 2.44 (m, 2H), 3.13 (m, 1H), 3.27 (m, 1H), 3.45 (m, 2H), 4.56 (s, 2H), 7.00 (d, 1H), 7.13 (d, 1H), 7.47 (t, 2H), 7.55 (t, 1H), 7.8 (d, 2H). Analysis Calcd for C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>S x 1.3 HCl: C, 59.69; H, 6.56; N, 10.31; Cl, 8.70. Found C: 58.99, H: 6.65, N: 10.13, Cl: 8.28.

### Example 30

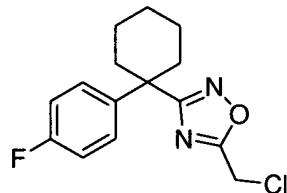
10 1-{3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(6-methyl-pyridin-2-yl)-piperazine, hydrochloride



15

30A

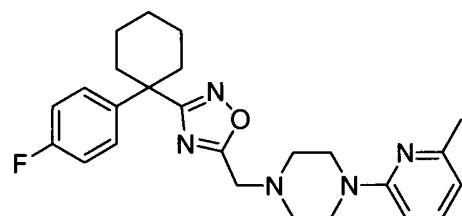
5-Chloromethyl-3-[1-(4-fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazole



20 Compound **30A** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 1-(4-fluorophenyl)cyclohexanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) *m/z* 295 [M+H].

### Example 30

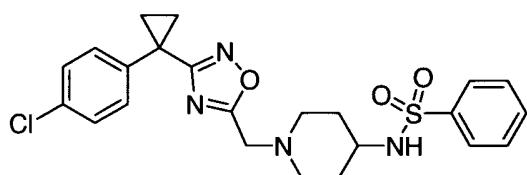
25 1-{3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(6-methyl-pyridin-2-yl)-piperazine, hydrochloride



Example 30 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclohexyl]-[1,2,4]oxadiazole 30A and 1-(6-methyl-pyridin-2-yl)-piperazine.  $^1\text{H-NMR}$  (500MHz, CD<sub>3</sub>OD) 1.48-1.32 (m, 3H), 1.60-1.50 (m, 3H), 2.01 (m, 2H), 2.48 (m, 2H), 2.54 (s, 3H), 3.36 (m, 4H), 3.91 (m, 4H), 4.55 (s, 2H), 6.89 (d, 1H), 6.93 (t, 2H), 7.13 (d, 1H), 7.30 (t, 2H), 7.93 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>30</sub>N<sub>5</sub>FO x 2HCl x 2H<sub>2</sub>O: C, 55.15; H, 6.66; N, 12.75; Cl, 13.02. Found C: 55.25, H: 6.40, N: 12.75, Cl: 13.10.

### Example 31

10 N-(1-{3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide, hydrochloride



15

### 31A

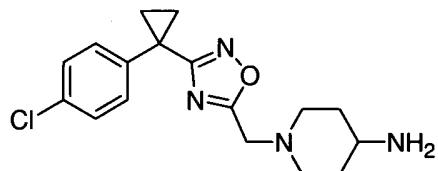
5-Chloromethyl-3-[1-(4-chlorophenyl)-cyclopropyl]-[1,2,4]oxadiazole



20 Compound 31A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using 1-(4-chlorophenyl)-1-cyclopropanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) m/z 270 [M+H].

### 31B

25 1-[3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine



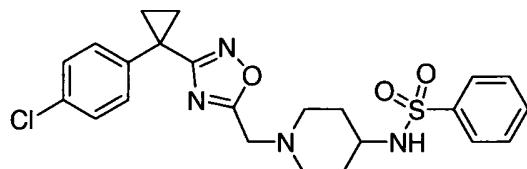
30 Compound 31B is synthesized by the method described for example 15B (Sequence 15A to 15B), using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclopropyl]-[1,2,4]oxadiazole 31A for 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclopropyl]-[1,2,4]oxadiazole 10D MS (Cl) m/z 333 [M+H].

-54-

Example 31

N-(1-[3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide, hydrochloride

5

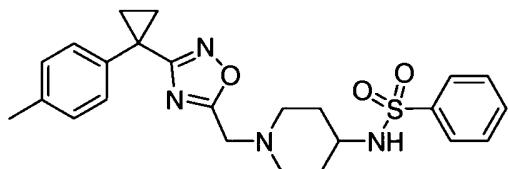


Example 31 is synthesized by the method described for example 15, using 1-[3-[1-(4-chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine 31B and benzenesulfonyl chloride, followed by treatment with HCl, as described in example 7. MS (Cl) m/z 473. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.45 (m, 2H), 1.66 (m, 2H), 1.89 (m, 2H), 2.05 (m, 2H), 3.30 (m, 2H), 3.41 (m, 1H), 3.61 (m, 2H), 4.70 (s, 2H), 7.36 (d, 2H), 7.40 (d, 2H), 7.62 (t, 2H), 7.66 (t, 1H), 7.91 (d, 2H). Analysis Calcd for C<sub>23</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub>S x 1HCl x 1H<sub>2</sub>O; C, 52.37; H, 5.35; N, 10.62; Cl, 13.44. Found C: 52.58, H: 5.03, N: 10.35, Cl: 13.54.

15

Example 32

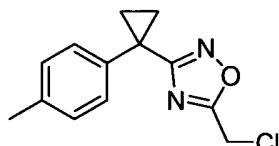
N-[1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide, hydrochloride



20

32A

5-Chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole



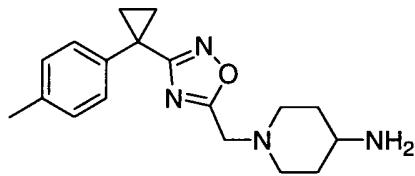
25

Compound 32A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using 1-(4-methylphenyl)-1-cyclopropanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) m/z 249 [M+H].

30

32B

1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine

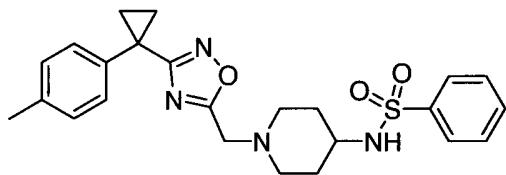


Compound 32B is synthesized by the method described for example 15B (Sequence 15A to 15B), using

5 5-chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole 32A for 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazole 10D. MS (Cl) *m/z* 313 [M+H].

Example 32.

N-[1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide,  
10 hydrochloride



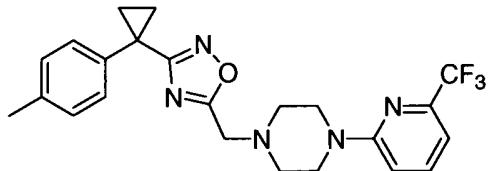
Example 32 is synthesized by the method described for example 15, using 1-[3-(1-p-tolyl-cyclopropyl)-

15 [1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylamine 32B and benzenesulfonyl chloride, followed by treatment with HCl, as described in example 7. MS (Cl) *m/z* 453. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.41 (m, 2H), 1.60 (m, 2H), 1.84 (m, 2H), 2.02 (m, 2H), 2.34 (s, 3H), 3.20 (brs, 2H), 3.39 (m, 1H), 3.53 (m, 2H), 4.60 (s, 2H), 7.16 (d, 2H), 7.31 (d, 2H), 7.60 (t, 2H), 7.66 (t, 1H), 7.92 (d, 2H). Analysis Calcd for C<sub>24</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>S x 1HCl x 1H<sub>2</sub>O: C, 56.85; H, 6.16; N, 11.05; Cl, 6.99. Found C: 57.36, H: 5.85, N: 11.01, Cl: 6.85.

20

Example 33

1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine,  
hydrochloride



25

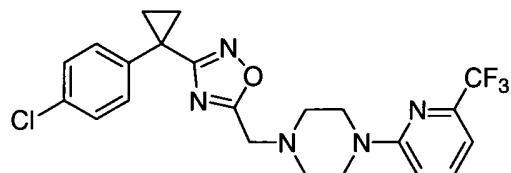
Example 33 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole 26A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.31 (t, 2H), 1.51 (t, 2H), 3.47 (m, 4H), 3.87 brs, 4H), 4.69 (s, 2H), 7.05 (m, 4H), 7.20 (d, 2H), 7.71 (t, 1H). Analysis Calcd for C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>N<sub>5</sub>O x 1.0 HCl: C, 57.56; H, 5.25; N, 14.59; Cl, 7.39. Found C:

30 C: 57.31, H: 5.24, N: 14.55, Cl: 7.33.

-56-

Example 34

1-[3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



5

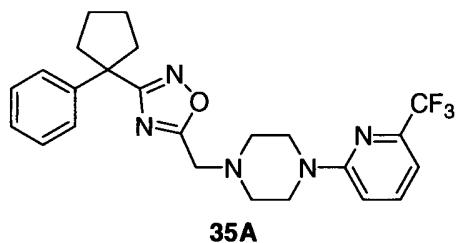
Example 34 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclopropyl]-[1,2,4]oxadiazole 31A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.48 (t, 2H), 1.68 (t, 2H), 3.57 (m, 4H), 3.99 (brs, 4H), 4.80 (s, 2H), 7.16 (d, 2H), 7.37 (d, 2H), 7.45 (d, 2H), 7.83 (t, 1H). Analysis Calcd for C<sub>22</sub>H<sub>21</sub>ClF<sub>3</sub>N<sub>5</sub>O x 1.0 HCl: C, 52.81; H, 4.43; N, 14.00; Cl, 14.17. Found C: 52.67, H: 4.44, N: 13.91, Cl: 14.57.

10

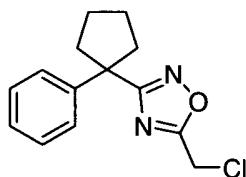
15

Example 35

1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

35A5-Chloromethyl-3-(1-phenyl-cyclopentyl)-[1,2,4]oxadiazole

20



Compound 35A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using 1-phenyl-cyclopentanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) *m/z* 263

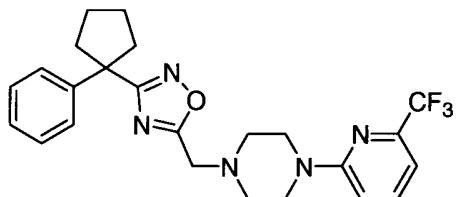
25 [M+H].

Example 35

1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

30

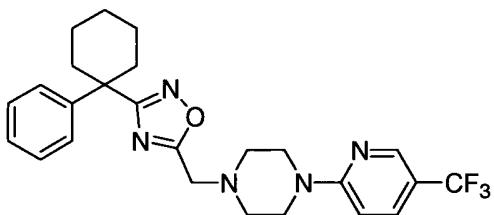
-57-



Example 35 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclopentyl)-[1,2,4]oxadiazole 35A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.64 (m, 2H), 1.75 (m, 2H), 2.13 (m, 2H), 2.64 (m, 2H), 3.40 (m, 4H), 3.83 (brs, 4H), 4.65 (s, 2H), 7.03 (m, 2H), 7.11 (t, 1H), 7.19 (t, 2H), 7.29 (d, 2H), 7.69 (t, 1H). Analysis Calcd for C<sub>24</sub>H<sub>26</sub>F<sub>3</sub>N<sub>5</sub>O x 1.0 HCl: C, 58.36; H, 5.51; N, 14.18; Cl, 7.18. Found C: 58.00, H: 5.50, N: 14.04, Cl: 7.01.

#### Example 36

10 1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine

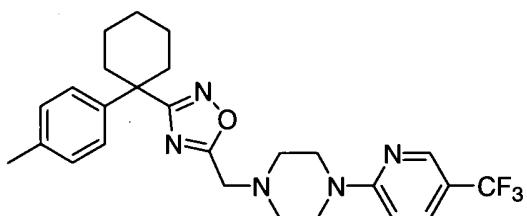


Example 36 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclohexyl)-[1,2,4]oxadiazole 28A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.28-1.42 (m, 3H), 1.44-1.60 (m, 3H), 1.92 (m, 2H), 2.48 (m, 2H), 2.54 (t, 4H), 3.57 (t, 4H), 3.81 (s, 2H), 6.74 (d, 1H), 7.07 (t, 1H), 7.15 (t, 2H), 7.24 (d, 2H), 7.60 (d, 1H), 8.23 (s, 1H). Analysis Calcd for C<sub>25</sub>H<sub>28</sub>F<sub>3</sub>N<sub>5</sub>O: C, 63.68; H, 5.99; N, 14.85. Found C: 63.62, H: 5.98, N: 14.89.

20

#### Example 37

1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



25

Example 37 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolylcyclohexyl)-[1,2,4]oxadiazole 29A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz,

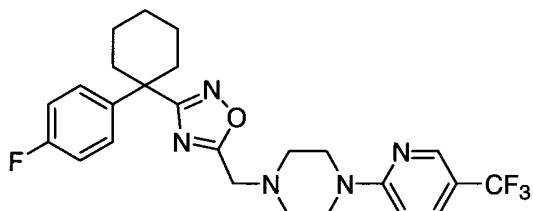
-58-

$\text{CD}_3\text{OD}$ ) 1.28-1.42 (m, 3H), 1.39-1.61 (m, 6H), 2.00 (m, 2H), 2.17 (s, 3H), 2.45 (m, 2H), 3.91 (m, 4H), 4.41 (m, 4H), 4.69 (s, 2H), 6.95 (d, 1H), 7.01 (d, 2H), 7.15 (d, 2H), 7.78 (d, 1H), 8.33 (s, 1H). Analysis Calcd for  $\text{C}_{26}\text{H}_{30}\text{F}_3\text{N}_5\text{O} \times 1.5 \text{ HCl}$ : C, 57.80; H, 5.88; N, 12.96; Cl, 9.84. Found C: 58.24, H: 6.00, N: 12.96, Cl: 8.88.

5

Example 38

1-[3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine



10

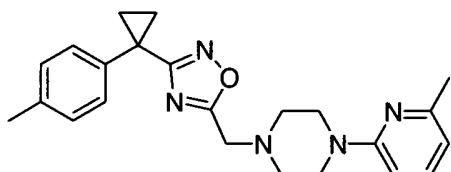
Example 38 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclohexyl]-[1,2,4]oxadiazole 30A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine.  $^1\text{H-NMR}$  (500MHz,  $\text{CD}_3\text{OD}$ ) 1.36-1.60 (m, 6H), 1.90 (m, 2H), 2.49 (m, 2H), 2.55 (t, 4H), 3.57 (t, 4H), 3.81 (s, 2H), 6.73 (d, 1H), 6.89 (t, 2H), 7.25 (t, 2H), 7.60 (d, 1H), 8.23 (s, 1H). Analysis Calcd for  $\text{C}_{25}\text{H}_{27}\text{F}_4\text{N}_5\text{O}$ : C, 61.34; H, 5.56; N, 14.31. Found C: 61.42, H: 5.60, N: 14.28.

15

Example 39

1-(6-Methyl-pyridin-2-yl)-4-[3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine, hydrochloride

20



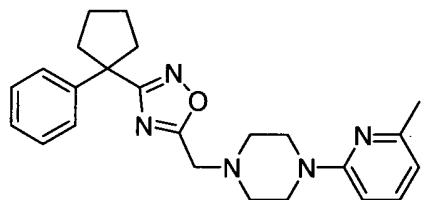
25

Example 39 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolylcyclopropyl)-[1,2,4]oxadiazole 26A and 1-(6-methyl-pyridin-2-yl)-piperazine.  $^1\text{H-NMR}$  (500MHz,  $\text{CD}_3\text{OD}$ ) 1.41 (t, 2H), 1.61 (t, 2H), 2.35 (s, 3H), 2.63 (s, 3H), 3.29 (m, 4H), 3.95 (m, 4H), 4.45 (s, 2H), 6.97 (d, 1H), 7.17 (d, 2H), 7.26 (d, 1H), 7.31 (d, 2H), 8.03 (dd, 1H). Analysis Calcd for  $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O} \times 1.67 \text{ HCl} \times 0.67 \text{ H}_2\text{O}$ : C, 59.76; H, 6.54; N, 15.15; Cl, 12.78. Found C: 59.51, H: 6.50, N: 15.21, Cl: 12.65.

30

Example 40

1-(6-Methyl-pyridin-2-yl)-4-[3-(1-phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine

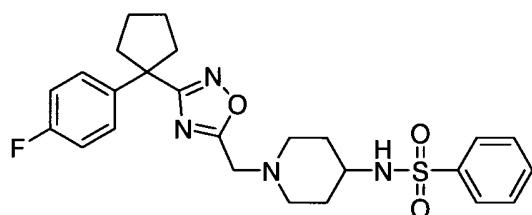


Example 40 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclopentyl)-[1,2,4]oxadiazole 35A and 1-(6-methyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>)

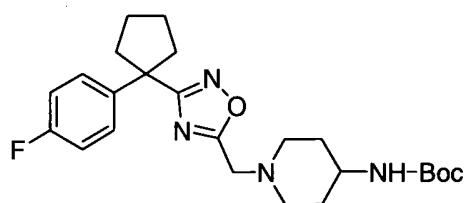
5 1.72 (m, 2H), 1.81 (m, 2H), 2.18 (m, 2H), 2.38 (s, 3H), 2.75 (m, 2H), 3.55 (m, 4H), 3.83 (s, 2H), 6.41 (d, 1H), 6.50 (d, 1H), 7.21 (t, 1H), 7.29 (t, 2H), 7.38 (m, 3H). Analysis Calcd for C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O: C, 71.44; H, 7.24; N, 17.36. Found C: 70.69, H: 7.13, N: 17.12.

#### Example 41

10 N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-yl}methyl)-piperidin-4-yl)-benzenesulfonamide, hydrochloride



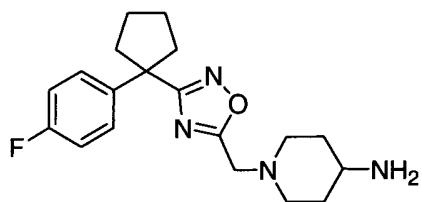
15 41A  
(1-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-yl}methyl)-piperidin-4-yl) carbamic acid tert-butyl ester



20 A mixture of 27A and 4-N-boc-aminopiperidine in ethanol is heated to reflux and stirred for 16 hr. The reaction mixture is concentrated to an oil and purified by an ISCO Sg 100C, with 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub> for 5 minute, 5 to 13% MeOH/CH<sub>2</sub>Cl<sub>2</sub> over 20 minutes, then a hold at 13% MeOH/CH<sub>2</sub>Cl<sub>2</sub> for 5 minutes. Fractions of interest are combined to give 41A. MS (Cl) m/z 445 [M+H].

25 41B  
1-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-yl}methyl)-piperidin-4-ylamine

-60-

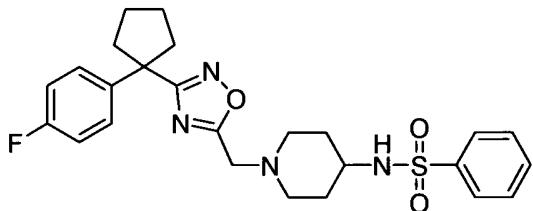


A mixture of **41A** and concentrated HCl is combined in methanol and heated to reflux for 16 hr. The reaction mixture is concentrated to a solid. Ethyl acetate is added back and the solids collected by  
5 vacuum filtration, washed with ethyl acetate and dried in the vacuum oven overnight to give **41B** as the HCl salt (2.32 g). MS (Cl) *m/z* 345 [M+H].

Example 41

N-(1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide,

10 hydrochloride

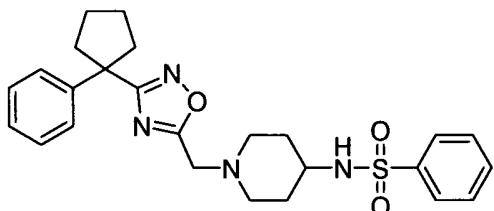


To a stirred solution of compound **41B** in methylene chloride is added diisopropylethylamine and benzene 15 sulfonyl chloride. The resulting solution is stirred at RT for 16h. The product is purified by column chromatography (SiO<sub>2</sub>) using 0-80% EtOAc/Hexanes. The product is suspended in anhydrous diethyl ether and 1M HCl (in diethyl ether) is added. Precipitation of the hydrochloride salt occurs and the solid is filtered, washed once with acetone and dried to yield **41** as a white solid. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.74 (m, 2H), 1.87 (m, 4H), 2.02 (m, 2H), 2.21 (m, 2H), 2.74 (m, 2H), 3.25 (m, 2H), 3.40 (m, 1H), 3.57 (m, 2H), 4.66 (s, 2H), 7.04 (t, 2H), 7.42 (m, 2H), 7.60 (t, 2H), 7.66 (t, 1H), 7.91 (d, 2H). Analysis Calcd for  
20 C<sub>25</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>3</sub>S x HCl: C, 57.63; H, 5.80; N, 10.75; Cl, 6.80. Found C: 57.14, H: 5.78, N: 10.55, Cl: 6.78.

Example 42

N-(1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide,

25 hydrochloride



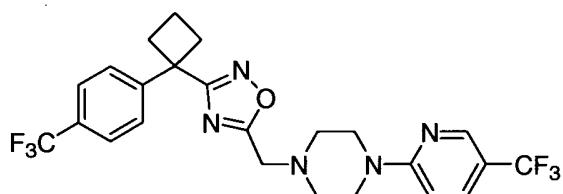
-61-

Example 42 is synthesized by the method described for example 41, using 5-chloromethyl-3-(1-phenylcyclopentyl)-[1,2,4]oxadiazole 35A. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.76 (m, 2H), 1.85 (m, 4H), 2.01 (m, 2H), 2.24 (m, 2H), 2.74 (m, 2H), 3.23 (m, 2H), 3.38 (m, 1H), 3.63 (m, 2H), 7.22 (t, 1H), 7.31 (t, 2H), 7.39 (d, 2H), 7.60 (t, 2H), 7.67 (t, 1H), 7.91 (d, 2H). Analysis Calcd for C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>S x HCl: C, 59.69; H, 6.21; N, 11.14; Cl, 7.05. Found C: 59.41, H: 6.09, N: 11.08, Cl: 7.25.

### Example 43

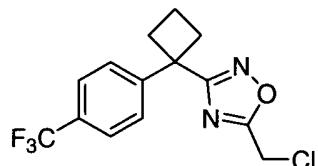
1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

10

**43A**

5-Chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole

15

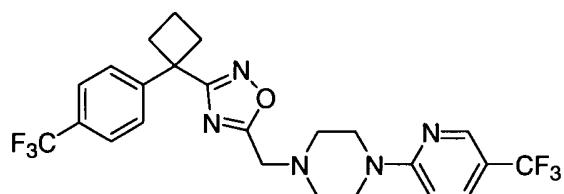


Compound 43A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C), using 1-(4-trifluoromethyl-phenyl)-cyclobutanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) *m/z* 317 [M+H].

### Example 43.

1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

25



Example 43 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole 43A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine.

30 <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 2.06 (m, 1H), 2.27 (m, 1H), 2.82 (m, 2H), 2.98 (m, 2H), 3.59 (m, 4H), 4.05

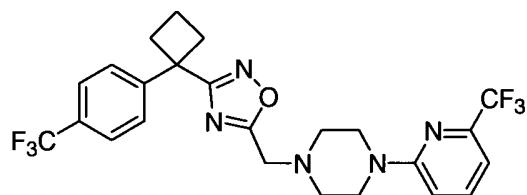
-62-

(bm, 4H), 4.83 (s, 2H), 7.13 (d, 1H), 7.55 (d, 2H), 7.67 (d, 2H), 7.92 (d, 1H), 8.45 (s, 1H). Analysis Calcd for  $C_{24}H_{23}F_6N_5O \times 1.5 HCl \times 0.5 H_2O$ : C, 50.12; H, 4.47; N, 12.18; Cl, 9.25. Found C: 50.11, H: 4.31, N: 12.06, Cl: 10.02.

5

Example 44

1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



10

Example 44 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole 43A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine.

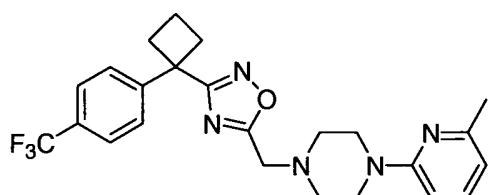
$^1H$ -NMR (500MHz, CD<sub>3</sub>OD) 1.98 (m, 1H), 2.15 (m, 1H), 2.71 (m, 2H), 2.88 (m, 2H), 3.45 (m, 4H), 3.86 (bm, 4H), 4.70 (s, 2H), 7.03 (d, 2H), 7.44 (d, 2H), 7.55 (d, 2H), 7.71 (t, 1H). Analysis Calcd for  $C_{24}H_{23}F_6N_5O \times 1 HCl \times 1 H_2O$ : C, 50.94; H, 4.63; N, 12.37; Cl, 6.26. Found C: 51.23, H: 4.18, N: 12.24, Cl: 6.38.

15

Example 45

1-(6-Methyl-pyridin-2-yl)-4-{3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazine, hydrochloride

20



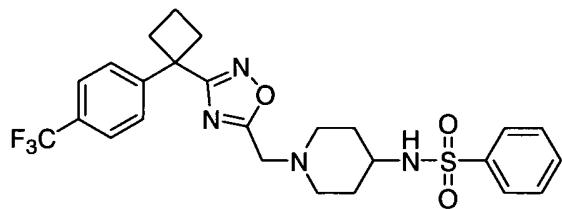
25

Example 45 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole 43A and 1-(6-methyl-pyridin-2-yl)-piperazine.  $^1H$ -NMR (500MHz, CD<sub>3</sub>OD) 2.07 (m, 2H), 2.24 (m, 1H), 2.65 (s, 3H), 2.83 (m, 2H), 3.01 (m, 2H), 3.48 (m, 4H), 4.00 (m, 4H), 4.65 (s, 2H), 7.27 (d, 1H), 7.57 (d, 2H), 7.66 (d, 2H), 8.05 (t, 1H). Analysis Calcd for  $C_{24}H_{26}F_3N_5O \times 2.5 HCl \times 0.5 H_2O$ : C, 53.44; H, 5.42; N, 12.98; Cl, 13.14. Found C: 53.17, H: 5.46, N: 12.87, Cl: 12.90.

30

Example 46

N-(1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide, hydrochloride

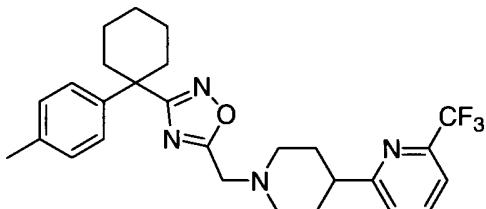


Example 46 is synthesized by the method described for example 41, using 5-chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole 43A. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.82 (bm, 2H), 2.17 (m, 3H), 2.28 (m, 1H), 2.83 (m, 2H), 2.96 (m, 2H), 3.33 (bm, 2H), 3.42 (m, 1H), 3.60 (m, 2H), 4.72 (s, 2H), 7.53-7.68 (m, 7H), 7.92 (d, 2H). Analysis Calcd for C<sub>25</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>S x 1 HCl x 1 H<sub>2</sub>O: C, 52.22; H, 5.26; N, 9.74; Cl, 6.17. Found C: 51.81, H: 4.91, N: 9.55, Cl: 6.29.

10

Example 47

1'-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride



15

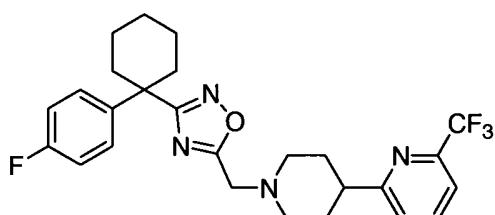
Example 47 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolyl-cyclohexyl)-[1,2,4]oxadiazole 29A and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.56-1.74 (m, 6H), 2.15 (m, 2H), 2.26 (m, 4H), 2.31 (s, 3H), 2.60 (m, 2H), 3.21 (m, 1H), 3.43 (m, 2H), 3.76 (m, 2H), 4.77 (s, 2H), 7.14 (d, 2H), 7.29 (d, 2H), 7.58 (d, 1H), 7.67 (d, 1H), 8.01 (t, 1H). Analysis Calcd for C<sub>27</sub>H<sub>31</sub>F<sub>3</sub>N<sub>4</sub>O x 1 HCl: C, 62.24; H, 6.19; N, 10.94; Cl, 6.80. Found C: 62.08, H: 6.18, N: 10.57, Cl: 6.67.

20

25

Example 48

1'-[3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride



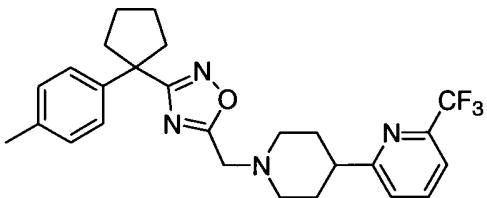
Example 48 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclohexyl]-[1,2,4]oxadiazole 30A and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl.  
<sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.56-1.75 (m, 6H), 2.15 (m, 2H), 2.26 (m, 4H), 2.63 (m, 2H), 3.21 (m, 1H), 3.43 (m, 2H), 3.76 (m, 2H), 4.79 (s, 2H), 7.04 (t, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.68 (d, 1H), 8.01 (t, 1H).

5 Analysis Calcd for C<sub>26</sub>H<sub>28</sub>F<sub>4</sub>N<sub>4</sub>O x 1 HCl: C, 59.48; H, 5.57; N, 10.67; Cl, 6.75. Found C: 59.01, H: 5.53, N: 10.47, Cl: 6.66.

#### Example 49

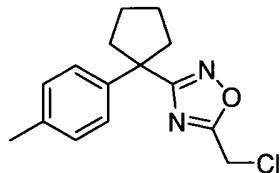
1'-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

10

**49A**

15

5-Chloromethyl-3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazole

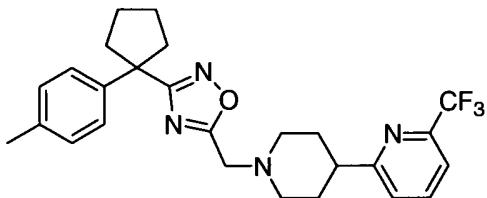


Compound 49A is synthesized by the method described for example 1C (Sequences 1A to 1B to 1C),  
20 using 1-p-tolyl-cyclopentanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in 1A MS (Cl) *m/z* 277 [M+H].

#### Example 49

1'-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

25



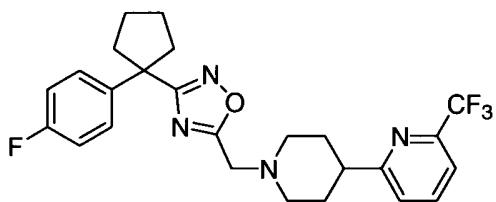
-65-

Example **49** is synthesized by the method described for example **1**, using 5-chloromethyl-3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazole **49A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.78 (m, 2H), 1.88 (m, 2H), 2.26 (m, 6H), 2.31 (s, 3H), 3.21 (m, 1H), 3.43 (m, 2H), 3.76 (m, 2H), 4.76 (s, 2H), 7.12 (d, 2H), 7.28 (d, 2H), 7.58 (d, 1H), 7.68 (d, 1H), 8.01 (t, 1H).

**5** Analysis Calcd for C<sub>26</sub>H<sub>29</sub>F<sub>3</sub>N<sub>4</sub>O x 1.0 HCl: C, 61.60; H, 5.96; N, 11.05; Cl, 6.99. Found C: 60.70, H: 5.83, N: 10.77, Cl: 6.81.

#### Example 50

**10** 1'-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride



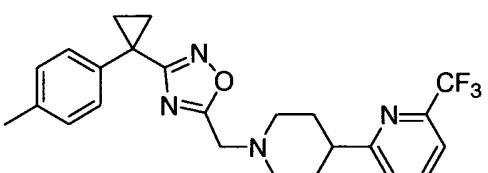
Example **50** is synthesized by the method described for example **1**, using 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazole **27A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.78 (m, 2H), 1.88 (m, 2H), 2.25 (m, 6H), 2.75 (m, 2H), 3.21 (m, 1H), 3.33 (m, 2H), 3.76 (m, 2H), 4.75 (s, 2H), 7.03 (t, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.68 (d, 1H), 8.01 (t, 1H).

**15** Analysis Calcd for C<sub>25</sub>H<sub>26</sub>F<sub>4</sub>N<sub>4</sub>O x 1.0 HCl: C, 58.77; H, 5.33; N, 10.96; Cl, 6.94. Found C: 57.24, H: 5.15, N: 10.60, Cl: 6.76.

**20**

#### Example 51

**25** 1'-{3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

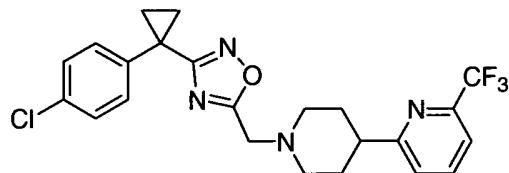


Example **51** is synthesized by the method described for example **1**, using 5-chloromethyl-3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazole **26A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.41 (m, 2H), 1.61 (m, 2H), 2.22 (m, 4H), 2.32 (s, 3H), 3.22 (m, 1H), 3.37 (m, 2H), 3.77 (m, 2H), 4.70 (s, 2H), 7.11 (t, 2H), 7.32 (d, 2H), 7.63 (d, 1H), 7.70 (d, 1H), 8.02 (t, 1H).

**30** Analysis Calcd for C<sub>24</sub>H<sub>25</sub>F<sub>3</sub>N<sub>4</sub>O x 1.0 HCl: C, 60.19; H, 5.47; N, 11.70; Cl, 7.40. Found C: 59.75, H: 5.42, N: 11.50, Cl: 7.32.

Example 52

1'-{3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

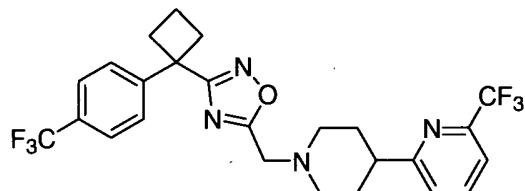


5

Example 52 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclopropyl]-[1,2,4]oxadiazole **31A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.42 (m, 2H), 1.61 (m, 2H), 2.26 (m, 4H), 3.22 (m, 1H), 3.37 (m, 2H), 3.74 (m, 2H), 4.70 (s, 2H), 7.31 (d, 2H), 7.42 (d, 2H), 7.50 (d, 1H), 7.60 (t, 1H), 8.00 (t, 1H). Analysis Calcd for C<sub>23</sub>H<sub>22</sub>ClF<sub>3</sub>N<sub>4</sub>O x 1.0 HCl: C, 55.32; H, 4.64; N, 11.22; Cl, 14.20. Found C: 54.93, H: 4.60, N: 10.95, Cl: 14.22.

Example 53

15 6-Trifluoromethyl-1'-{3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl}-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

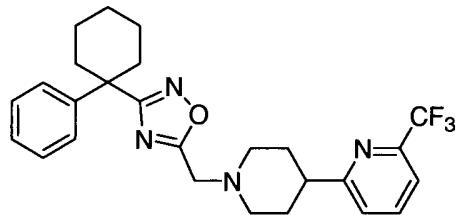


20 Example 53 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazole **43A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 2.07 (m, 1H), 2.22 (m, 4H), 2.83 (m, 2H), 2.91 (m, 2H), 3.22 (m, 1H), 3.37 (m, 2H), 3.77 (m, 2H), 4.70 (s, 2H), 7.51 (m, 3H), 7.62 (m, 3H), 8.02 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>24</sub>F<sub>6</sub>N<sub>4</sub>O x 1. HCl: C, 54.90; H, 4.61; N, 10.24; Cl, 6.48. Found C: 54.56, H: 4.58, N: 10.00, Cl: 25 6.11.

Example 54

1'-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

30

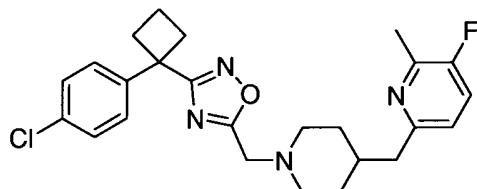


Example 54 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclohexyl)-[1,2,4]oxadiazole **28A** and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.48-1.76 (m, 6H), 2.15-2.26 (m, 6H), 2.62 (m, 2H), 3.22 (m, 1H), 3.47 (m, 2H), 3.77 (m, 2H), 4.80 (s, 2H), 7.24 (t, 2H), 7.31 (t, 2H), 7.42 (d, 2H), 7.63 (d, 1H), 7.70 (d, 1H), 8.02 (t, 1H). Analysis Calcd for C<sub>26</sub>H<sub>29</sub>F<sub>3</sub>N<sub>4</sub>O x HCl x 3 H<sub>2</sub>O: C, 55.66; H, 6.47; N, 9.99; Cl, 6.32. Found C: 55.99, H: 5.40, N: 9.86, Cl: 6.85.

10

Example 55

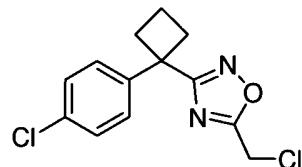
6-(1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylmethyl)-3-fluoro-2-methyl-pyridine, hydrochloride



15

55A

5-Chloromethyl-3-[1-(4-chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazole



20

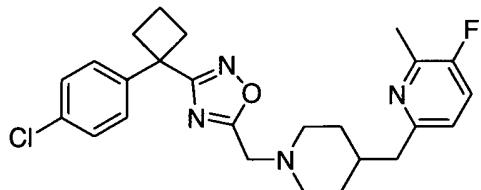
Compound 55A is synthesized by the method described for example 1C (Sequences **1A** to **1B** to **1C**), using 1-(4-chloro-phenyl)-cyclobutanecarbonitrile for 1-phenyl-cyclopropanecarbonitrile, in **1A** MS (Cl) *m/z* 284 [M+H].

25

Example 55

6-(1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-ylmethyl)-3-fluoro-2-methyl-pyridine, hydrochloride

-68-



Example 55 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclobutyl]-[1,2,4]oxadiazole 55A and 3-fluoro-2-methyl-6-piperidin-4-ylmethyl-pyridine. <sup>1</sup>H-NMR

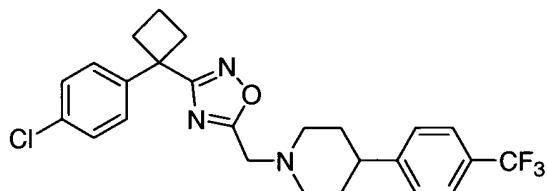
5 (500MHz, CD<sub>3</sub>OD) 1.76 (brs, 2H), 2.03 (m, 3H), 2.21 (m, 2H), 2.77 (m, 5H), 2.94 (m, 2H), 3.06 (brs, 2H), 3.25 (brs, 2H), 3.75 (brs, 2H), 4.79 (brs, 2H), 7.35 (m, 4H), 7.82 (m, 1H), 8.30 (m, 1H). Analysis Calcd for C<sub>25</sub>H<sub>28</sub>ClFN<sub>4</sub>O x 2 HCl: C, 56.88; H, 5.73; N, 10.61; Cl, 20.15. Found C: 56.31, H: 5.69, N: 10.38, Cl: 20.04.

10

Example 56

1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(4-trifluoromethyl-phenyl)-piperidine, hydrochloride

15



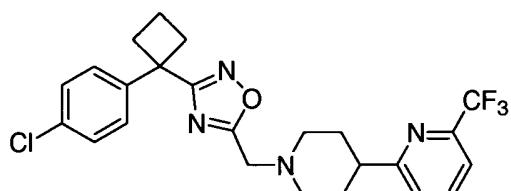
Example 56 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclobutyl]-[1,2,4]oxadiazole 55A and 4-(4-trifluoromethyl-phenyl)-piperidine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 2.07 (m, 3H), 2.22 (m, 3H), 2.78 (m, 2H), 2.96 (m, 2H), 3.06 (m, 1H), 3.40 (m, 2H), 3.85 (m, 2H),

20 4.86 (s, 2H), 7.36 (s, 4H), 7.51 (d, 2H), 7.67 (d, 2H). Analysis Calcd for C<sub>25</sub>H<sub>25</sub>ClF<sub>3</sub>N<sub>3</sub>O x 1 HCl: C, 58.60; H, 5.11; N, 8.20; Cl, 13.84. Found C: 58.36, H: 5.16, N: 8.05, Cl: 13.68.

25

Example 57

1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4'bipyridinyl, hydrochloride

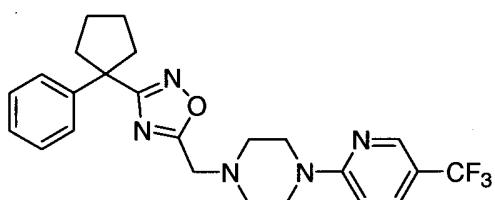


Example 57 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclobutyl]-[1,2,4]oxadiazole 55A and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 2.06 (m, 1H), 2.26 (m, 5H), 2.78 (m, 2H), 2.96 (m, 2H), 3.23 (m, 1H), 3.41 (m, 2H), 3.83 (brs, 2H), 4.83 (s, 2H), 7.36 (s, 4H), 7.63 (d, 1H), 7.71 (d, 1H), 8.02 (t, 1H). Analysis Calcd for C<sub>24</sub>H<sub>24</sub>ClF<sub>3</sub>N<sub>4</sub>O x 1 HCl: C, 56.15; H, 4.91; N, 10.91; Cl, 13.81. Found C: 55.41, H: 4.86, N: 10.67, Cl: 13.78.

#### Example 58

##### 1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine

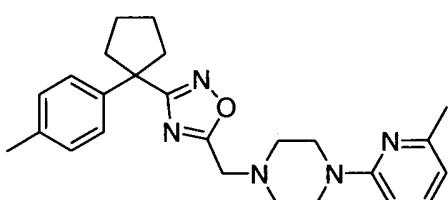
10



Example 58 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-cyclopentyl)-[1,2,4]oxadiazole 35A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) 1.71 (m, 2H), 1.81 (m, 2H), 2.18 (m, 2H), 2.63 (m, 4H), 2.74 (m, 2H), 3.66 (m, 4H), 3.83 (s, 2H), 6.61 (d, 2H), 7.20 (t, 1H), 7.29 (t, 2H), 7.38 (d, 2H), 7.62 (m, 1H), 8.38 (s, 1H). Analysis Calcd for C<sub>24</sub>H<sub>26</sub>F<sub>3</sub>N<sub>5</sub>O: C, 63.01; H, 5.73; N, 15.31. Found C: 62.87, H: 5.79, N: 15.26.

#### Example 59

##### 1-(6-Methyl-pyridin-2-yl)-4-[3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine, hydrochloride



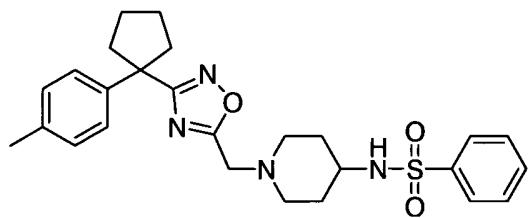
Example 59 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazole 49A and 1-(6-methyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.73 (m, 2H), 1.85 (m, 2H), 2.20 (m, 2H), 2.29 (s, 3H), 2.58 (s, 3H), 2.65 (m, 2H), 3.33 (m, 4H), 3.99 (m, 4H), 4.61 (s, 2H), 6.99 (d, 1H), 7.11 (d, 2H), 7.24 (d, 1H), 7.27 (d, 2H), 8.03 (t, 1H). Analysis Calcd for C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O x 2.5 HCl x 3 H<sub>2</sub>O: C, 53.36; H, 7.07; N, 12.44; Cl, 15.77. Found C: 52.73, H: 7.14, N: 12.17, Cl: 14.83.

30

#### Example 60

##### N-[1-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide, hydrochloride

-70-



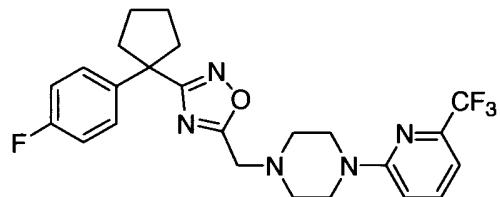
Example 60 is synthesized by the method described for example 41, using 5-chloromethyl-3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazole 49A. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.70-1.87 (m, 6H), 2.04 (m, 2H), 2.20 (m, 2H), 2.29 (s, 3H), 2.69 (m, 2H), 3.33 (m, 2H), 3.36 (m, 1H), 3.54 (m, 2H), 4.66 (s, 2H), 7.12 (d, 2H), 7.27 (d, 2H), 7.59 (t, 2H), 7.66 (t, 1H), 7.91 (d, 2H). Analysis Calcd for C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>S x 1 HCl: C, 60.39; H, 6.43; N, 10.83; Cl, 6.86. Found C: 60.27, H: 6.50, N: 10.55, Cl: 6.93.

10

Example 61

1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

15



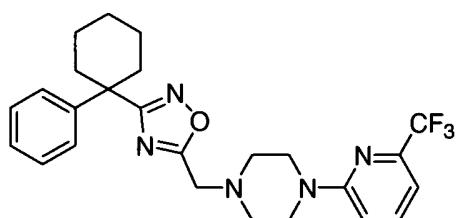
Example 61 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazole 27A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.76 (m, 2H), 1.87 (m, 2H), 2.22 (m, 2H), 2.75 (m, 2H), 3.53 (m, 4H), 3.97 (brs, 4H),

20 4.80 (s, 2H), 7.04 (t, 2H), 7.15 (d, 2H), 7.43 (m, 2H), 7.82 (t, 1H). Analysis Calcd for C<sub>24</sub>H<sub>26</sub>F<sub>3</sub>N<sub>5</sub>O x 1.0 HCl: C, 56.31; H, 5.12; N, 13.68; Cl, 6.93. Found C: 55.81, H: 5.07, N: 13.52, Cl: 7.00.

25

Example 62

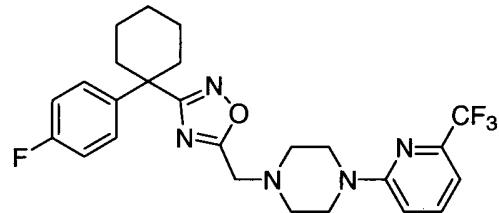
1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



Example 62 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazole 28A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.33-1.63 (m, 6H), 2.04 (m, 2H), 2.49 (m, 2H), 3.22 (m, 4H), 3.82 (bm, 4H), 4.64 (s, 2H), 7.07 (d, 1H), 7.09 (d, 1H), 7.10 (t, 1H), 7.17 (t, 2H), 7.28 (d, 2H), 7.70 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>28</sub>F<sub>3</sub>N<sub>5</sub>O x HCl: C, 59.11; H, 5.75; N, 13.79; Cl, 6.98. Found C: 59.00, H: 5.75, N: 13.89, Cl: 6.72.

Example 63

1-[3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



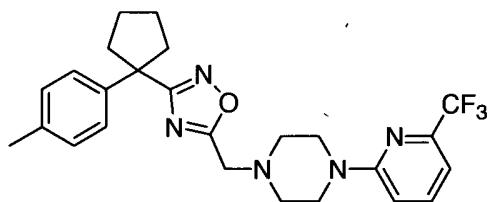
Example 63 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazole 30A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.36-1.62 (m, 6H), 2.01 (m, 2H), 2.48 (m, 2H), 3.22 (m, 4H), 3.84 (m, 4H), 4.65 (s, 2H), 6.90 (t, 2H), 7.01 (d, 2H), 7.29 (t, 2H), 7.71 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>27</sub>F<sub>4</sub>N<sub>5</sub>O x HCl: C, 57.09; H, 5.37; N, 13.31; Cl, 6.74. Found C: 57.19, H: 5.45, N: 13.20, Cl: 6.49.

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Example 64

1-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

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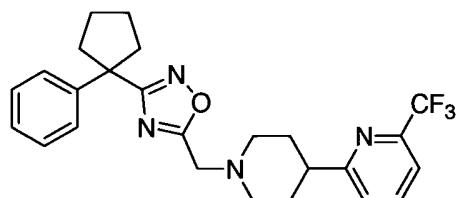


Example 64 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazole 49A and 1-(6-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.75 (m, 2H), 1.87 (m, 2H), 2.21 (m, 2H), 2.30 (s, 3H), 2.74 (m, 2H), 3.55 (m, 4H), 3.97 (bm, 4H), 4.80 (s, 2H), 7.12-7.17 (m, 4H), 7.27 (d, 2H), 7.82 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>28</sub>F<sub>3</sub>N<sub>5</sub>O x 1.0 HCl x 0.5 H<sub>2</sub>O: C, 58.08; H, 5.85; N, 13.55; Cl, 6.86. Found C: 58.07, H: 5.52, N: 13.39, Cl: 6.55.

Example 65

1'-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride

5



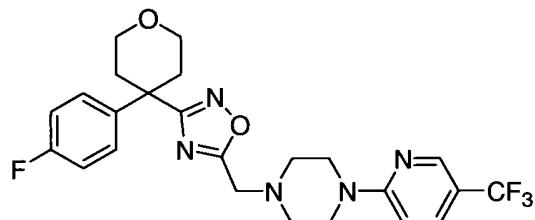
Example 65 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclopentyl)-[1,2,4]oxadiazole 35A and 6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.78 (m, 2H), 1.88 (m, 2H), 2.22 (m, 6H), 2.75 (m, 2H), 3.21 (m, 1H), 3.33 (m, 2H), 3.77 (m, 2H), 4.74 (s, 2H), 7.21 (t, 1H), 7.31 (t, 2H), 7.42 (d, 2H), 7.59 (d, 1H), 7.68 (d, 1H), 8.01 (t, 1H). Analysis Calcd for C<sub>25</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O x 1.0 HCl: C, 60.91; H, 5.73; N, 11.37; Cl, 7.19. Found C: 60.54, H: 5.71, N: 11.11, Cl: 6.42.

15

Example 66

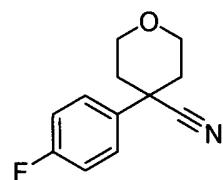
1-[3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

20

66A

4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-carbonitrile

25



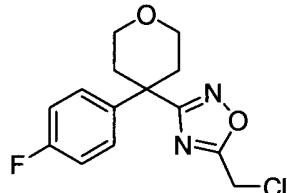
Sodium hydride (10g, 0.24mol) is added portionwise to DMSO (150ml) at ~5°C. The mixture is mechanically stirred for a further 5 minutes and allowed to warm to room temperature. An ether solution

of (4-fluoromethyl-phenyl)-acetonitrile (15g, 0.11moles) and dichloroethyl ether (14.3ml 0.12mol) is then added dropwise to the sodium hydride DMSO mixture over 30 minutes at a temperature of 25-30°C. The resulting thick slurry is stirred overnight. TLC analysis using 70:30 EtOAc:Hexane shows no starting material. The reaction is poured onto ice water (300ml) and extracted with ether (2x250ml). The ether is dried, filtered and evaporated to dryness yielding a yellow oil, **66A** (22g, 96%) MS (Cl) *m/z* 206 [M+H].

5

**66B****5-Chloromethyl-3-[4-(4-fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazole**

10

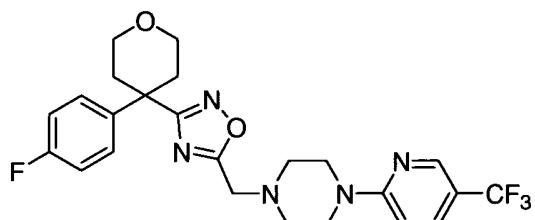


Compound **66B** is synthesized by the method described for example **1C** (Sequences **1A** to **1B** to **1C**), using 4-(4-fluoro-phenyl)-tetrahydro-pyran-4-carbonitrile, **66A**, in **1A** MS (Cl) *m/z* 297 [M+H].

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**Example 66****1-[3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride**

20



25

Example **66** is synthesized by the method described for example **1**, using 5-chloromethyl-3-[4-(4-fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazole, **66B**, and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine.

<sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 2.33 (m, 2H), 2.68 (m, 2H), 3.55 (m, 4H), 3.65 (m, 2H), 3.85 (m, 2H), 4.00

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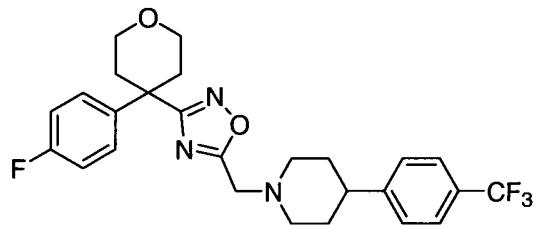
(bm, 4H), 4.85 (s, 2H), 7.14 (t, 2H), 7.18 (d, 2H), 7.42 (m, 2H), 7.82 (t, 1H). Analysis Calcd for

C<sub>24</sub>H<sub>25</sub>F<sub>4</sub>N<sub>5</sub>O<sub>2</sub>: C, 54.60; H, 4.96; N, 13.27; Cl, 6.72. Found C: 54.63, H: 4.95, N: 12.93, Cl: 6.50.

30

**Example 67****1-[3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(4-trifluoromethyl-phenyl)-piperidine, hydrochloride**

-74-

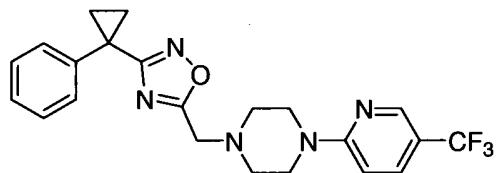


Example 67 is synthesized by the method described for example 1, using 5-chloromethyl-3-[4-(4-fluorophenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazole, 66B, and 4-(4-trifluoromethyl-phenyl)-piperidine.

<sup>5</sup> <sup>1</sup>H NMR (500MHz, CD<sub>3</sub>OD) 2.33 (m, 2H), 2.68 (m, 2H), 3.55 (m, 4H), 3.65 (m, 2H), 3.85 (m, 2H), 4.00 (bm, 4H), 4.85 (s, 2H), 7.14 (t, 2H), 7.18 (d, 2H), 7.42 (m, 2H), 7.82 (t, 1H). Analysis Calcd for C<sub>26</sub>H<sub>27</sub>F<sub>4</sub>N<sub>3</sub>O<sub>2</sub>: C, 54.60; H, 4.96; N, 13.27; Cl, 6.72. Found C: 54.63, H: 4.95, N: 12.93, Cl: 6.50.

#### Example 68

<sup>10</sup> 1-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride



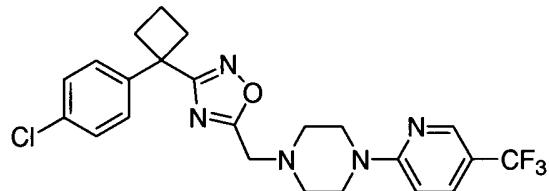
<sup>15</sup> Example 68 is synthesized by the method described for example 1, using 5-chloromethyl-3-(1-phenylcyclopropyl)-[1,2,4]oxadiazole 1C and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 1.35 (q, 2H), 1.58 (q, 2H), 2.65 (t, 4H), 3.65 (t, 4H), 3.18 (s, 2H), 6.59 (d, 1H), 7.33 (m, 1H), 7.41 (m, 2H), 7.58 (d, 2H), 7.60 (d, 1H), 8.35 (s, 1H). Analysis Calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>6</sub>O x 1.96 HCl: C, 52.75; H, 4.82; N, 13.98. Found C: 52.38, H: 4.73, N: 13.85.

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#### Example 69

1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride

25



Example 69 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-chlorophenyl)-cyclobutyl]-[1,2,4]oxadiazole 55A and 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine. <sup>1</sup>H NMR

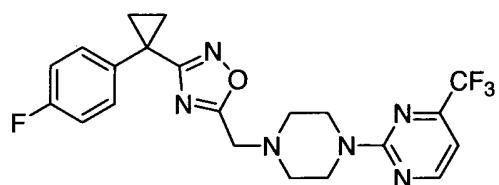
-75-

(400MHz, CDCl<sub>3</sub>) 1.90 (m, 1H), 2.14 (m, 1H), 2.69 (m, 2H), 2.88 (m, 2H), 3.27(s, 2H), 3.65 (t, 4H), 4.09 (brs, 4H), 7.29 (s, 5H), 8.03 (dd, 1H), 8.40 (brs, 1H). Analysis Calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>6</sub>O x 2.41 HCl: C, 48.83; H, 4.53; N, 12.38. Found C: 49.21, H: 4.79, N: 11.95.

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Example 70

2-(4-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl)-4-trifluoromethyl-pyrimidine



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Example 70 is synthesized by the method described for example 1, using 5-chloromethyl-3-[1-(4-fluorophenyl)-cyclopropyl]-[1,2,4]oxadiazole 10D and 2-piperazin-1-yl-4-trifluoromethyl-pyrimidine. <sup>1</sup>H-NMR (500MHz, CD<sub>3</sub>OD) 1.38 (t, 2H), 1.60 (t, 2H), 3.35 (s, 4H), 4.78 (s, 2H), 4.82 (s, 4H), 7.02 (m, 3H), 7.42 (m, 2H), 8.65 (d, 1H). LCMS - 98%, m/z 449 [M+1]. Analytical HPLC 97%.

15

## METHODS AND FORMULATIONS

In some situations, compounds of the invention may exist in isomeric form; for example, as tautomers, enantiomers, or diasteromers. Some compounds may exhibit polymorphism. All enantiomers, and diasteromers are incorporated within the definition of the compounds of the invention. It is further to 5 be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary 10 phase) and how to determine activity or cytotoxicity using the standard tests described herein, or using other similar tests which are well known in the art.

Certain of the compounds of the present invention can exist in unsolvated forms as well as 15 solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

In one embodiment, the present invention provides a method for causing vasodilation in a patient in need thereof comprising administering a compound of formulae (I), (II), or (III). For the sake of brevity, all of the sub-formulae of formula (II), i.e. formulae (IIA), (IIB), (IIC), and (IID), are included when mentioning compounds of formula (II).

20 In another embodiment, the present invention provides a method of blocking calcium channels, the method comprising of administering to a patient in need of calcium channel blocking a therapeutically effective amount of a compound of formulae (I) or (II) to block calcium channels. In a preferred embodiment of this method, the calcium channels are T-type calcium channels. In another preferred embodiment of this method, the calcium channels are N-type, T-type, and L-type calcium channels.

25 In a further embodiment, the present invention provides a method of treating a disease selected from hypertension, congestive heart failure, stroke, ischaemic heart disease, and angina pectoris comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formulae (I), (II), or (III). It is also recognized that one skilled in the art may affect the associated diseases and conditions by treating a patient presently afflicted with the diseases or conditions or by 30 prophylactically treating a patient afflicted with the diseases or conditions with a therapeutically effective amount of the compounds of formulae (I), (II), or (III).

Another aspect of this invention is directed to methods of reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) during surgery (e.g., coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary 35 angioplasty (PTCA) or any percutaneous transluminal coronary intervention (PTCI), organ transplantation, or other non-cardiac surgeries) comprising administering to a mammal (e.g., a female or male human) a therapeutically effective amount of a compound of formulae (I), (II), or (III), or a pharmaceutically acceptable salt of said compound.

The compounds of formula (I), (II), and (III), which are N-type calcium channel antagonists, are potentially useful in the treatment of a range of disorders. The treatment of pain, particularly neuropathic pain, is a preferred use.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, *Prog. Neurobiol.*, 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, *Science*, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, *Textbook of Pain*, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36,

679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

5 Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

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It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

20 Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardial infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredema and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

25 As used herein, the term "patient" refers to a warm-blooded animal such as a mammal which is (1) in need of vasodilation, (2) in need of blocking calcium channels, (3) afflicted with or at risk of developing hypertension, congestive heart failure, stroke, ischaemic heart disease, or angina pectoris, or (4) afflicted with pain or a sub-category of pain as described above. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of animals within the scope of the meaning of the term. A patient is in need of treatment for hypertension, congestive heart failure, stroke, ischaemic heart disease, angina pectoris, or pain when the patient is afflicted within one or more of the diseases or conditions described herein or is at a recognized risk of developing one or more of the diseases or conditions described herein as diagnosed by an attending physician or clinician.

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The identification of those patients who are in need of treatment for hypertension, congestive heart failure, stroke, ischaemic heart disease, angina pectoris, or pain is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are in need of such treatment.

5 As used herein, the term "therapeutically effective amount" of a compound of formulae (I), (II), or (III) refers to an amount which is effective in (1) causing vasodilation in the patient in need thereof, (2) blocking calcium channels, (3) treating hypertension, congestive heart failure, stroke, ischaemic heart disease, or angina pectoris, or (4) treating pain. The term "treating" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and  
10 conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment of the hypertension, congestive heart failure, stroke, ischaemic heart disease, angina pectoris, or pain.

A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under  
15 analogous circumstances. In determining the therapeutically effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen  
20 selected; the use of concomitant medication; and other relevant circumstances.

The compounds of the invention intended for pharmaceutical use may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe  
25 any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and  
30 methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

35 Formulations suitable for oral administration include solid formulations, such as tablets, capsules containing particulates, liquids, or powders; lozenges (including liquid-filled), chews; multi- and nanoparticulates; gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

40 Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol,

polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage

5 forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight% to 80 weight% of the dosage form, more typically from 5 weight% to 60 weight% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch 10 glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight% to 25 weight%, preferably from 5 weight% to 20 weight% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders 15 include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

20 Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight% of the tablet, and glidants may comprise from 0.2 weight% to 1 weight% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc 25 stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight% to 10 weight%, preferably from 0.5 weight% to 3 weight% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavoring agents, preservatives and taste-masking agents.

30 Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H.

35 Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

The foregoing formulations for the various types of administration discussed above may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

5 The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

10 Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

15 The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

20 The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

25 Formulations for parenteral administration may be formulated to be immediate and/or modified release. Thus, compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

30 The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

35 Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

40 The compounds of the invention may also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

5       The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

10      Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

15      Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

20      A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1 $\mu$ g to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1 $\mu$ l to 100 $\mu$ l. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

25      Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

30      Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

35      In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" of the compound of formula (I). The overall daily may be administered in a single dose or, more usually, as divided doses throughout the day.

40      The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various well known alternatives may be used as appropriate.

45      The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid; a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose; or a heteropolysaccharide

polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

5 The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

10 Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

15 A calcium channel blocker of the present invention, particularly those showing N-type calcium channel antagonism, may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of pain. For example, a compound of formulae (I), (II), or (III), or a pharmaceutically acceptable salt thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- 20 (i) opioid analgesics, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;
- 25 (ii) nonsteroidal antiinflammatory drugs (NSAIDs), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and their pharmaceutically acceptable salts;
- 30 (iii) barbiturate sedatives, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts;
- (iv) benzodiazepines having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts,
- 35 (v) H<sub>1</sub> antagonists having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their pharmaceutically acceptable salts;
- (vi) miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts;
- (vii) skeletal muscle relaxants, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, orphenadrine and their pharmaceutically acceptable salts,

- (viii) NMDA receptor antagonists, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid and their pharmaceutically acceptable salts;
- 5 (ix) alpha-adrenergic active compounds, e.g. doxazosin, tamsulosin, clonidine and 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- (x) tricyclic antidepressants, e.g. desipramine, imipramine, amitriptiline and nortriptiline;
- (xi) anticonvulsants, e.g. carbamazepine and valproate;
- (xii) Tachykinin (NK) antagonists, particularly NK-3, NK-2 and NK-1 e.g.
- 10 antagonists, ( $\alpha R,9R$ )-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S)
- 15 (xiii) Muscarinic antagonists, e.g oxybutin, tolterodine, propiverine, tropsium chloride and darifenacin;
- (xiv) COX-2 inhibitors, e.g. celecoxib, rofecoxib and valdecoxib;
- (xv) Non-selective COX inhibitors (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);
- (xvi) coal-tar analgesics, in particular, paracetamol;
- (xvii) neuroleptics, such as droperidol;
- 20 (xviii) Vanilloid receptor agonists, e.g. resiniferatoxin;
- (xix) Beta-adrenergic compounds such as propranolol;
- (xx) Local anaesthetics, such as mexiletine;
- (xxi) Corticosteroids, such as dexamethasone
- (xxii) serotonin receptor agonists and antagonists;
- 25 (xxiii) cholinergic (nicotinic) analgesics;
- (xxiv) miscellaneous agents such as Tramadol®;
- (xxv) PDEV inhibitors, such as sildenafil, vardenafil or taladafil;
- (xxvi) serotonin reuptake inhibitors, e.g. fluoxetine, paroxetine, citalopram and sertraline;
- (xxvii) mixed serotonin-noradrenaline reuptake inhibitors, e.g. milnacipran, venlafaxine and duloxetine;
- 30 (xxviii) noradrenaline reuptake inhibitors, e.g. reboxetine;
- (xxix) alpha-2-delta ligands, e.g. gabapentin and pregabalin.

The compounds of the invention may be usefully combined with one or more agents for reducing the risk of a cardiovascular disorder including anti-inflammatory agents, such as alclofenac, algestone acetonide, alpha arylase, amcinafal, amcinafide, amfenac sodium, amiprilose hydrochloride, anakinra, anirolac, apazone, balsalazide disodium, bendazac, benoxaprofen, benzylamine hydrochloride, bromelains, broperamole, budesonide, carprofen, cicloprofen, cintazone, cliprofen, clobetasol propionate, clobetasone butyrate, clopirac, cloticasone propionate, cortodoxone, deflazacort, desonide, desoximetasone, dexamethasone dipropionate, diclofenac potassium, diclofenac sodium, diflumidone sodium, diflunisal, difluprednate, diftalone, drocinonide, enlimomab, enolicam sodium, epirizole, etodolac,

etofenamate, felbinac, fenamole, fensufen, fenclofenac, fenclorac, fendosal, fenipalone, fentiazac, flazalone, fluazacort, flufenamic acid, flumizole, flunisolide acetate, flunixin, flunixin meglumine, fluocortin butyl, fluorometholone acetate, fluquazone, flurbiprofen, fluretofen, fluticasone propionate, furaprofen, furobufen, ibufenac, ibuprofen, ibuprofen aluminum, ilonidap, indomethacin, indomethacin sodium, 5 indoprofen, indoxole, intrazole, isoflupredone acetate, isoxepac, isoxicam, ketoprofen, lofemizole hydrochloride, lornoxicam, meclofenamate sodium, meclofenamic acid, mefenamic acid, mesalamine, meseclazone, methylprednisolone suleptanate, morniflumate, nabumetone, naproxen, naproxen sodium, 10 naproxol, nimazone, olsalazine sodium, orgotein, orpanoxin, oxaprozin, oxyphenbutazone, paranyline hydrochloride, pentosan polysulfate sodium, phenbutazone sodium glycerate, pirfenidone, piroxicam, 15 piroxicam cinnamate, piroxicam olamine, pirprofen, prednazate, prifelone, proolic acid, proquazone, proxazole, proxazole citrate, rimexolone, romazarit, salcolex, salsalate, salycilates, sanguinarium chloride, seclazone, sermetacin, sudoxicam, sulindac, suprofen, talmetacin, talniflumate, talosalate, tebufelone, tenidap, tenidap sodium, tenoxicam, tesicam, tesimide, tetrydamine, tiopinac, tolmetin, tolmetin sodium, 20 triconide, triflumidate, zidometacin, zomepirac sodium; anti-thrombotic and/or fibrinolytic agents, such as plasminogen (to plasmin via interactions of prekallikrein, kininogens, Factors XII, XIIIa, plasminogen proactivator, and tissue plasminogen activator[TPA]) streptokinase, urokinase: anisoylated plasminogen-streptokinase activator complex; pro-urokinase, (Pro-UK); rTPA (alteplase or activase; r denotes recombinant), rPro-UK, abbokinase, eminase, septase anagrelide hydrochloride, bivalirudin, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, ifetroban, 25 ifetroban sodium, tinzaparin sodium, retapulse, trifeneagrel, warfarin, dextrans; anti-platelet agents, such as clopidogrel, sulfipyrazone, aspirin; dipyridamole, clofibrate, pyridinol carbamate, PGE, glucagon, antiserotonin drugs, caffeine, theophyllin pentoxifyllin, ticlopidine, anagrelide; lipid reducing agents, such as gemfibrozil, cholystyramine, colestipol, nicotinic acid, probucol, lovastatin, fluvastatin, simvastatin, atorvastatin, pravastatin, cirivastatin; and direct thrombin inhibitors, such as hirudin, hirugen, hirulog, agatroban, PPACK, and thrombin aptamers.

Useful dosages of the compounds of the invention can be determined by comparing their in vitro activity, and in vivo activity in animal models. The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

The compounds of the present invention can be administered to a human patient at dosage levels in the range of about 1 to about 2,000 mg per day, preferably from about 1 to about 1,000 mg per day, more preferably from about 5 to about 600 mg per day, even more preferably from about 10 to 300 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 10 mg per kilogram of body weight per day is preferable. However, the specific dosage used can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75  $\mu$ M, preferably, about 1 to 50  $\mu$ M, most preferably, about 0.1 to about 5  $\mu$ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 10-500 mg of the active ingredient. Desirable blood levels may be maintained by multiple oral dosing, or continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The 10 sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The ability of a compound of the present invention to modulate the T-type calcium channel is demonstrated using pharmacological models that are well known to the art, for example, using models such as the tests described below.

15

#### T-type Calcium Channel FLIPR Assay

A stable tetracycline-inducible TREx-293 cell line is generated expressing recombinant mouse  $\alpha$ 1H.

The coding sequence for mouse  $\alpha$ 1H T-type calcium channel cDNA (accession number 20 NM\_021415) is cloned using standard cloning techniques (e.g. *Molecular Cloning A Laboratory Manual*, 2nd Edition, J. Sambrook, E. F. Fritsch, T. Maniatis; Cold Spring Harbor Laboratory Press; Cold Spring Harbor, N.Y., 1989) and is subcloned into the mammalian expression vector pcDNA4/TO (Invitrogen, Carlsbad CA). This expression vector has a CMV promoter to drive expression of the  $\alpha$ 1H gene. This plasmid construct is used to stably transfect TREx-293 cells (Invitrogen, Carlsbad CA), a human embryonic kidney cell line stably expressing the tetracycline repressor protein.

Cells are maintained at 37° C and 5% CO<sub>2</sub> in Dulbecco's Modified Eagle Media supplemented with 10% fetal bovine serum, 200  $\mu$ g/ml Zeocin, and 5  $\mu$ g/ml Blasticidin. Cells are induced with 1  $\mu$ g/ml tetracycline and plated onto black-sided 384 well Poly-D Lysine coated plates at 12,000 cells/well for at least twenty-four hours. The cells are incubated with the fluorescent Ca<sup>2+</sup> indicator Fluo-4 AM (50  $\mu$ g, 30 Molecular Devices, Sunnyvale, CA) dissolved in pluronic acid and DMEM supplemented with 2.6 mM probenecid for 1 hour at 37°C and 5% CO<sub>2</sub>. Cells are then rinsed with assay buffer (consisting of 0.34 mM Na<sub>2</sub>HPO<sub>4</sub>, 4.2 mM NaHCO<sub>3</sub>, 0.44 mM KH<sub>2</sub>PO<sub>4</sub>, 0.41 mM MgSO<sub>4</sub>, 0.49 mM MgCl<sub>2</sub>, 20 mM HEPES, 5.5 mM d-Glucose, 0.1% BSA, 137 mM NaCl, and 2.6 mM probenecid) and incubated at 37°C and 5% CO<sub>2</sub> for 10 minutes. Cells are pretreated with putative antagonists for 5 minutes followed by a rapid increase 35 of 4.8 mM extracellular Ca<sup>2+</sup>. The increase in intracellular calcium as determined by an increase in fluorescence is then measured for 5 minutes following the extracellular Ca<sup>2+</sup> addition on a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, Calif.). Fluorescence increase in response to Ca<sup>2+</sup> in the presence of test compounds is compared to control responses in the same plate and the IC<sub>50</sub> for each compound is determined using Prism 4.0 (GraphPad Software, Inc., San Diego CA). The 40 results of this evaluation are shown in Table 2.

L-Type Calcium Channel FLIPR A10 Assay

FLIPR Instrumentation: FLIPR (fluorometric imaging plate reader) is Molecular Devices's rapid throughput system for cell-based fluorescence assays. In this application, it is used specifically for measuring changes in intracellular calcium flux. The basic principal involves illumination of 384-well microplate with the simultaneous measurement of emitted fluorescence using a CCD camera. The cell plate wells contain cells that have been loaded with a fluorescent dye, whose emission characteristics change upon binding with a particular ion ( $\text{Ca}^{2+}$  in this case). As a result, changes in fluorescence can be quantified and thus extrapolated to represent some specific pharmacologic effect (or lack thereof).

Cell Culture and Dye Loading: The A10 smooth muscle cell line derived from embryonic thoracic aorta of the DBIX rat (ATCC, CRL-1476); which endogenously expresses L-type calcium channels; is used for this assay. The growth media for A10 cells is Ham's F12/DME high glucose (Irvine Scientific, 9052), supplemented with 20% fetal bovine serum (HyClone Labs, SH30071.02), and 1% each of L-glutamine (Gibco BRL, 25030-032) and antibiotic-antimycotic (Gibco BRL, 15240-096).

Cells are grown to confluence and replated on black-sided 384-well plates (Falcon, 35 3962) at 12K cells/well for use in FLIPR. Forty-eight hours after replating, growth media is removed and cells are loaded at 37°C with 50 $\mu\text{l}$  media containing 1 $\mu\text{M}$  Fluo-4 dye (Molecular Probes, F-14201) for 1 hour. The dye-containing media is then washed away six times with buffer (composition in mM: 1.25  $\text{CaCl}_2$ , 1.2  $\text{MgSO}_4$ , 11 glucose, 10 HEPES, 3.0 KCl, 137.0 NaCl, pH 7.4 with Tris base) in an Embla384 (Molecular Devices, 0200-3906). The residual buffer volume is adjusted to 20 $\mu\text{l}$  and allowed to incubate at room temp for an additional hour.

FLIPR protocol: A five minute drug-pre-incubation period is initiated when 20 $\mu\text{l}$  of drug-containing buffer is pipetted into the cell plate with the 384-well pipettor integrated in the FLIPR apparatus. Fluorescent counts are monitored at two second intervals for 960 seconds, beginning 60 seconds prior to the delivery of drug-containing buffer. Following drug addition, 20 $\mu\text{l}$  aliquots of a high K+, depolarizing stimulus (composition in mM: 1.25  $\text{CaCl}_2$ , 1.2  $\text{MgSO}_4$ , 11 glucose, 10 HEPES, 140.0 KCl, pH 7.4 with Tris base) are added to each well and fluorescence is monitored at one second intervals for 120 secibds, beginning ten seconds prior to the stimulus addition. CCD camera exposure time is 0.4 seconds, laser excitation is at 488 nm with a power of 0.6W, and a 510 to 560nm bandpass interference filter preceded the camera.

Data Analysis: Data are analyzed as a summation of fluorescent counts above basal during the stimulation period (an approximation of area under the curve), after normalizing the data with a spatial uniformity correction (for variations in laser illumination and cell density), a negative control correction and a bias subtraction (a bias subtraction subtracts the fluorescence value measured at a specific sample point from all the other time points in each well and allows for all data on the y-axis to be zeroed). Drug effects are expressed as percent inhibition of fluorescence from an average of 8 K+-stimulated wells that were pre-treated in the drug incubation period with buffer only. Data are analyzed using FLIPR software, Microsoft Excel and Origin. The IC50 calculations are performed and graphed in Origin.

N-type Calcium Channel FDSS6000 Assay

A stable cell line is generated expressing recombinant rat  $\alpha_{1B}$ . The coding sequence for rat  $\alpha_{1B}$  cDNA (accession number AF055477) is cloned using standard cloning techniques (e.g. *Molecular Cloning A Laboratory Manual*, 2nd Edition, J. Sambrook, E. F. Fritsch, T. Maniatis; Cold Spring Harbor Laboratory Press; Cold Spring Harbor, N.Y., 1989) and is subcloned into the mammalian expression vector pcDNA 6/V5 (Invitrogen, Carlsbad CA). This plasmid construct is used to stably transfect HEK-tsA201 cells.

Cells are maintained at 37° C and 5% CO<sub>2</sub> in Dulbecco's Modified Eagle Media supplemented with 10% fetal bovine serum, 25 µg/ml Zeocin, and 5 µg/ml Blasticidin and 25 µg/ml Hygromycin. Cells are plated onto black-sided 384 well Poly-D Lysine coated plates at 5,000 cells/well and incubate for 24 hours. The cells are incubated with the fluorescent Ca<sup>2+</sup> indicator Fluo-4 AM (50 µg, Molecular Probes, Eugene, OR) dissolved in pluronic acid for 1 hour at 37°C and 5% CO<sub>2</sub>. Cells are then rinsed with assay buffer (consisting of 1 mM Na<sub>2</sub>HPO<sub>4</sub>, 26 mM NaHCO<sub>3</sub>, 1.8 mM CaCl<sub>2</sub>, 0.8 mM MgCl<sub>2</sub>, 117 mM NaCl, 20 mM HEPES, 5.6 mM d-Glucose) and incubated at 37°C for 10 minutes. Cells are pretreated with putative antagonists for 5 minutes followed by an addition of KCl (30 mM). The influx of intracellular calcium as determined by an increase in fluorescence is then measured for 5 minutes following the extracellular K<sup>+</sup> addition on a plate reader (FDSS6000, HAMAMATSU, Japan). Fluorescence increase in response to K<sup>+</sup> in the presence of test compounds is compared to control responses in the same plate and the IC<sub>50</sub> for each compound is determined using Excel Fit™ (Sigmoidal-600, Microsoft). The results of this evaluation are shown in Table 2.

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TABLE 2  
Calcium Channel Functional Activity

<u>Compound</u>	<u>Exmpl. No.</u>	<u>T-Type Calcium Channel IC<sub>50</sub> µM<sup>a</sup></u>	<u>L-Type Calcium Channel IC<sub>50</sub> µM<sup>a</sup></u>	<u>N-Type Calcium Channel IC<sub>50</sub> µM<sup>a</sup></u>
2-{4-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-4-trifluoromethyl-pyrimidine hydrochloride	1	0.771	0.754	<3.0
2-{4-[3-(1-Phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine	2	0.739	6.90	>1.0
4-Methoxy-2-{4-[3-(1-phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine	3	0.229	2.60	>1.0
1-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	4	0.945	>10.0	0.835
1-[3-(1-Phenyl-propyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(3-trifluoromethyl-pyridin-2-yl)-piperazine	5	0.275	1.00	>1.0
1-[3-(1-Phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-	6	0.301 <sup>b</sup>	0.675	1.19

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piperazine				
1-[3-(1-Phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	7	0.650	0.772 <sup>b</sup>	1.55
5-Ethyl-2-{4-[3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine	8	0.192	1.70	>1.0
1-{3-Methoxy-1-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-propyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine	9	0.696		
1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	10	0.428	0.720	<3.0
1-{3-[1-(4-Chloro-phenyl)-ethyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	11	0.596	2.30	<3.0
1-[3-(1-Phenyl-ethyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	12	0.236	0.751	<3.0
(4-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazin-1-yl)-phenyl-methanone	13	0.485	>10.0	>3.0
1-Benzenesulfonyl-4-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazine	14	0.262	>10.0	0.546 <sup>b</sup>
N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide	15	0.330	>10.0	
2-Fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzamide	16	0.257	>10.0	<3.0
2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide	17	0.469	>10.0	
N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-methoxy-benzamide	18	0.162	>10.0 <sup>b</sup>	
N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-(pyridin-3-yloxy)-benzenesulfonamide	19	0.891	>10.0	
4-Fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-	20	0.119	>7.63 <sup>b</sup>	<3.0

[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzamide				
N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzamide	21	0.106	>10.0 <sup>b</sup>	0.263
2-Oxo-2H-chromene-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide	22	0.479	>10.0	
Quinoxaline-6-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide	23	0.115	>10.0	
5-Chloro-pyrazine-2-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide	24	0.078	>10.0	<3.0
N-(1-{3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-3-methoxy-benzamide	25	0.0872	>4.32 <sup>b</sup>	<3.0
1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	26	0.472	0.292	
1-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine	27	0.890	0.390	
N-{1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl}-benzenesulfonamide, hydrochloride	28	0.237	1.41	0.577 <sup>b</sup>
N-{1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl}-benzenesulfonamide, hydrochloride	29	0.794	1.43	0.636
1-{3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(6-methyl-pyridin-2-yl)-piperazine, hydrochloride	30	0.453	>10.0	<3.0
N-(1-{3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide, hydrochloride	31	0.809	0.314	
N-{1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl}-benzenesulfonamide, hydrochloride	32	0.087	1.91	<3.0
1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	33	0.130	>10.0	<3.0

1-[3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	34	0.128	0.258	<3.0
1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	35	0.108	0.388	0.431 <sup>b</sup>
1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine	36	0.744	0.422	0.790
1-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	37	0.426	1.58	<3.0
1-[3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine	38	0.285	0.474	<3.0
1-(6-Methyl-pyridin-2-yl)-4-[3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine, hydrochloride	39	0.942	>10.0	<3.0
1-(6-Methyl-pyridin-2-yl)-4-[3-(1-phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine	40	0.800	0.328	2.05
N-(1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide, hydrochloride	41	0.078	9.49	0.459 <sup>b</sup>
N-[1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl]-benzenesulfonamide, hydrochloride	42	0.073	0.023	0.366
1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	43	0.134	0.413	<3.0
1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	44	0.161	0.155	<3.0
1-(6-Methyl-pyridin-2-yl)-4-[3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperazine, hydrochloride	45	0.426	0.343	1.87
N-(1-[3-[1-(4-Trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl)-benzenesulfonamide,	46	0.708	0.547	0.310

hydrochloride				
1'-[3-(1-p-Tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	47	0.671	0.537	<3.0
1'-{3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	48	0.167	4.99	0.657
1'-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	49	0.059	0.355	0.854
1'-{3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	50	0.098	0.285	0.608
1'-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	51	0.019	0.582	0.816
1'-{3-[1-(4-Chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	52	0.575	0.337	1.53
6-Trifluoromethyl-1'-[3-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	53	0.139	1.11	0.354
1'-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	54	0.441	0.594	<3.0
6-(1-{3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-ylmethyl)-3-fluoro-2-methyl-pyridine, hydrochloride	55	0.464	0.736	0.711
1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(4-trifluoromethyl-phenyl)-piperidine, hydrochloride	56	0.485	>10.0	>3.0
1'-{3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl}-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	57	0.481	1.30	<3.0
1-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-	58	1.48	0.178 <sup>b</sup>	

(5-trifluoromethyl-pyridin-2-yl)-piperazine				
1-(6-Methyl-pyridin-2-yl)-4-[3-(1-p-tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazine, hydrochloride	59	1.10	0.082	<3.0
N-{1-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-4-yl}-benzenesulfonamide, hydrochloride	60	1.03	0.083	
1-[3-[1-(4-Fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	61	1.28	0.156	0.551
1-[3-(1-Phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	62	1.16	0.440	<3.0
1-[3-[1-(4-Fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	63	2.13	0.685	>3.0
1-[3-(1-p-Tolyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(6-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	64	3.47	0.208 <sup>b</sup>	>3.0
1'-[3-(1-Phenyl-cyclopentyl)-[1,2,4]oxadiazol-5-ylmethyl]-6-trifluoromethyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl, hydrochloride	65	2.03	0.167	0.902 <sup>b</sup>
1-[3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	66	4.58	0.409	<3.0
1-[3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(4-trifluoromethyl-phenyl)-piperidine, hydrochloride	67	1.05	0.754	<3.0
1-[3-(1-Phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	68	1.87	0.331	0.832
1-[3-[1-(4-Chloro-phenyl)-cyclobutyl]-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine, hydrochloride	69	1.10	0.175	<3.0
2-(4-[3-[1-(4-Fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl)-4-trifluoromethyl-pyrimidine	70	1.96 <sup>b</sup>	0.902	0.626

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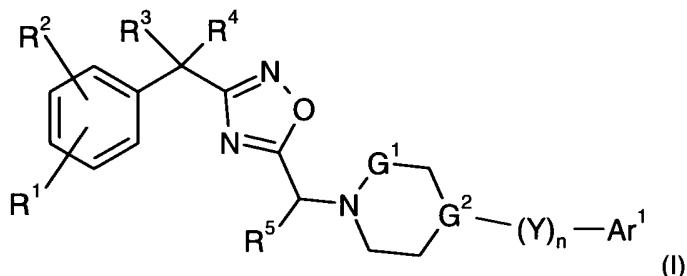
Notes: a: The biological values are from a n=1, unless otherwise noted; b: biological values are from a n=2.

The foregoing biological tests establish that the compounds of the present invention are potent calcium

5 channel antagonists.

## WHAT IS CLAIMED IS:

## 1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are each independently -H, -OH, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or substituted C<sub>1</sub>-C<sub>6</sub> alkoxy;

10 R<sup>3</sup> and R<sup>4</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl or R<sup>3</sup> and R<sup>4</sup> taken together with the carbon atom to which they are attached form C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or cycloheteroalkyl, provided that if one of R<sup>3</sup> and R<sup>4</sup> is -H, then the other is C<sub>1</sub>-C<sub>6</sub> alkyl;

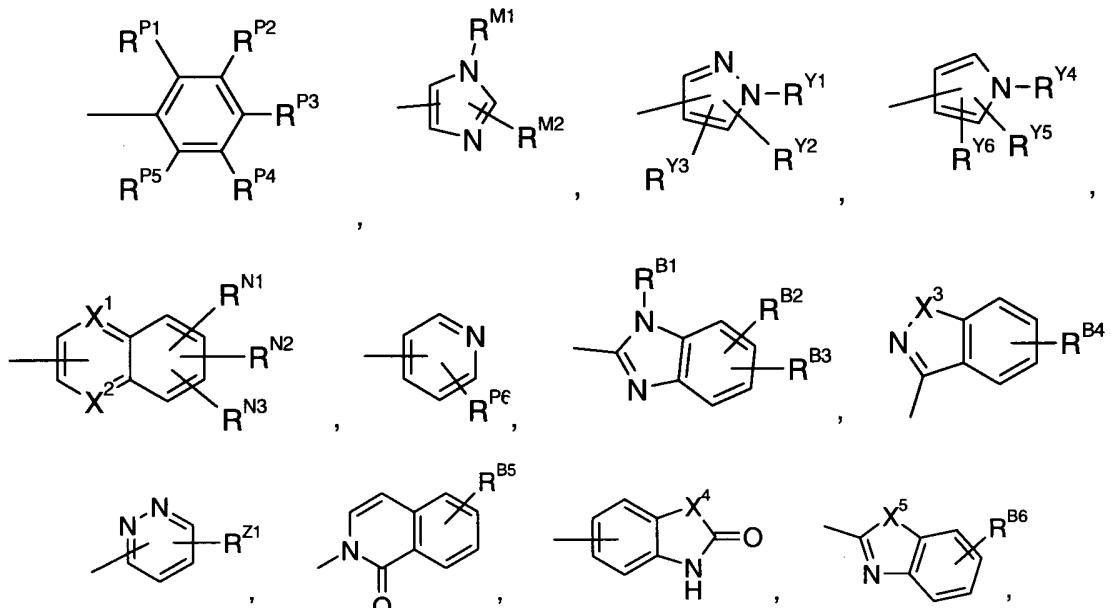
R<sup>5</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -(CH<sub>2</sub>)<sub>q</sub>-C(O)O-W, wherein W is -H or C<sub>1</sub>-C<sub>6</sub> alkyl and q is 1-6;

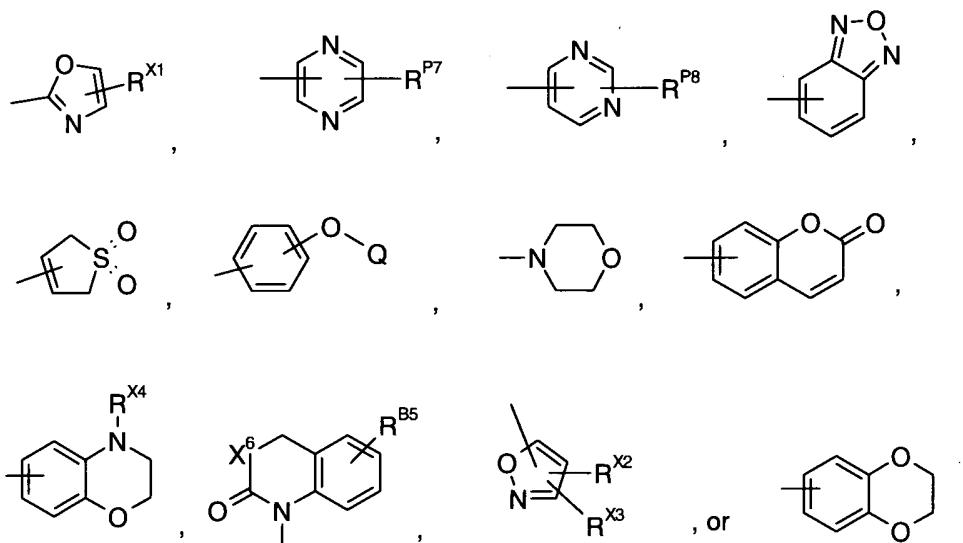
G<sup>1</sup> is methylene or ethylene;

15 G<sup>2</sup> is C(R<sup>6</sup>) or N, wherein R<sup>6</sup> is -H, -OH or C<sub>1</sub>-C<sub>6</sub> alkyl;

Y is -CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- , -O- , -C(O)- , -C(O)CH<sub>2</sub>- , -S- , -S(O)- , -S(O)<sub>2</sub>- , -NHC(O)- , -NHC(O)CH(R<sup>7</sup>)- , or -NHS(O)<sub>2</sub>- , wherein R<sup>7</sup> is -H or C<sub>1</sub>-C<sub>4</sub> alkyl;

Ar<sup>1</sup> is a radical of the formulae





wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>P7</sup>, R<sup>P8</sup>, R<sup>N1</sup>, R<sup>N2</sup>, R<sup>N3</sup>, and R<sup>Z1</sup> are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or -NR<sup>8</sup>R<sup>9</sup>, wherein R<sup>8</sup> and R<sup>9</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>M1</sup>, R<sup>M2</sup>, R<sup>B1</sup>, R<sup>B2</sup>, R<sup>B3</sup>, R<sup>B4</sup>, R<sup>B5</sup>, R<sup>B6</sup>, R<sup>X1</sup>, R<sup>X2</sup>, R<sup>X3</sup>, R<sup>X4</sup>, R<sup>Y1</sup>, R<sup>Y2</sup>, R<sup>Y3</sup>, R<sup>Y4</sup>, R<sup>Y5</sup>, and R<sup>Y6</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; X<sup>1</sup> and X<sup>2</sup> are independently CH or N; X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> are each independently NH, O, or S; X<sup>6</sup> is CH<sub>2</sub> or O; Q is substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, napthyl, 2-pyridyl, or 3-pyridyl; and

n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

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2. A compound according to claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo, -CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically acceptable salt thereof.

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3. A compound according to either claim 1 or claim 2 where R<sup>3</sup> and R<sup>4</sup> taken together with the carbon atom to which they are attached form C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or a pharmaceutically acceptable salt thereof.

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4. A compound according to either claim 1 or 2 where R<sup>3</sup> and R<sup>4</sup> taken together with the carbon atom to which they are attached form cycloheteroalkyl; or a pharmaceutically acceptable salt thereof.

5. A compound according to any of claims 1 to 4 wherein R<sup>5</sup> is -H; or a pharmaceutically acceptable salt thereof.

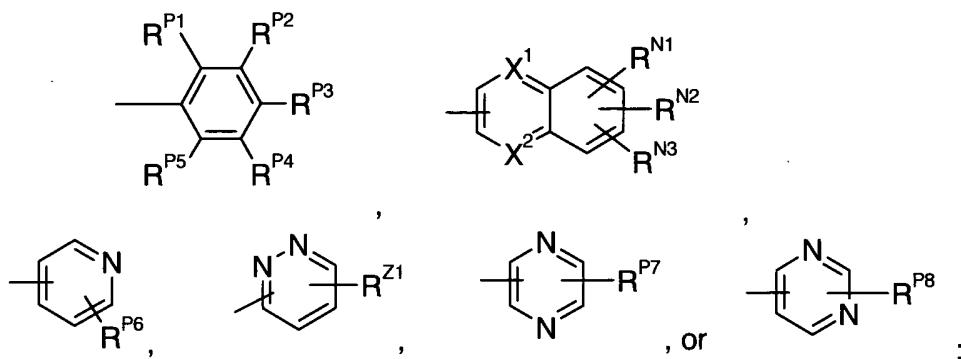
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6. A compound according to any of claims 1 to 5 wherein G<sup>1</sup> is methylene; or a pharmaceutically acceptable salt thereof.

7. A compound according to any of claims 1 to 6 wherein n is 0; or a pharmaceutically acceptable salt thereof.

5 8. A compound according to any of claims 1 to 6 wherein n is 1 and Y is  $-C(O)-$ ,  $-S(O)_2-$ ,  $-NHS(O)_2-$ ,  $-NHC(O)-$ ; or a pharmaceutically acceptable salt thereof.

9. A compound according to any of claims 1 to 8 wherein Ar<sup>1</sup> is

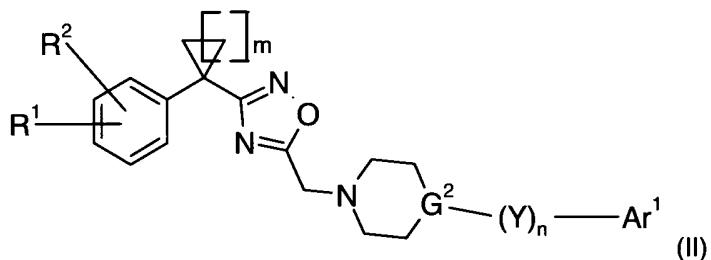


10 or a pharmaceutically acceptable salt thereof.

10. A compound according to any of claims 1 to 9 wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>Z1</sup>, R<sup>P7</sup> and R<sup>P8</sup> are each independently  $-H$ , halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or  $-CF_3$ ; or a pharmaceutically acceptable salt thereof.

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11. A compound of the formula



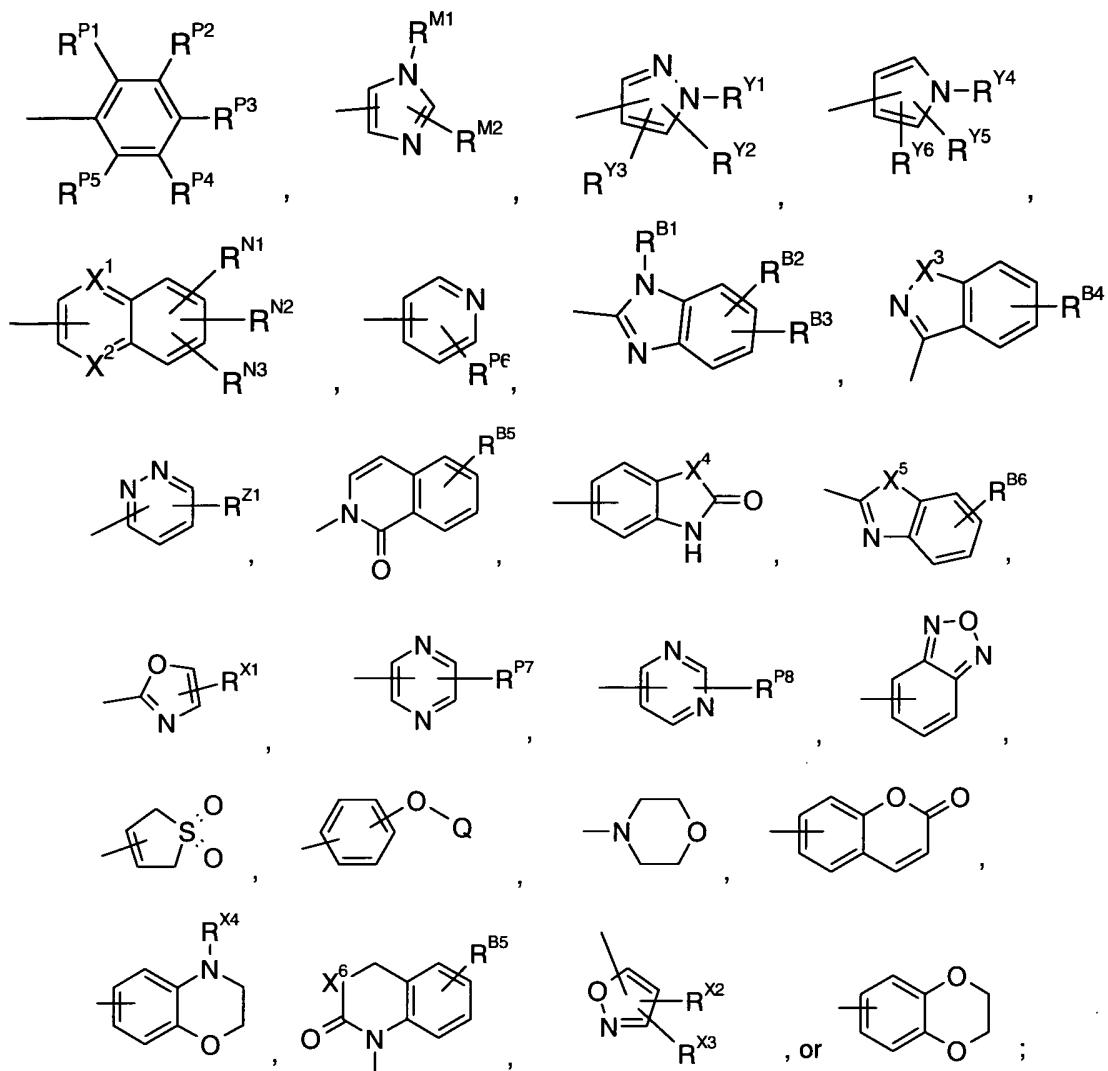
or a pharmaceutically acceptable salt thereof, wherein

20 R<sup>1</sup> and R<sup>2</sup> are each independently  $-H$ ,  $-OH$ , halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,  $-CF_3$  or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

G<sup>2</sup> is C(R<sup>6</sup>) or N, wherein R<sup>6</sup> is  $-H$ ,  $-OH$  or C<sub>1</sub>-C<sub>6</sub> alkyl;

Y is  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-O-$ ,  $-C(O)-$ ,  $-C(O)CH_2-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-NHC(O)-$ ,  $-NHC(O)CH(R^7)-$ , or  $-NHS(O)_2-$ , wherein R<sup>7</sup> is  $-H$  or C<sub>1</sub>-C<sub>4</sub> alkyl;

Ar<sup>1</sup> is a radical of the formulae



wherein R<sup>P1</sup>, R<sup>P2</sup>, R<sup>P3</sup>, R<sup>P4</sup>, R<sup>P5</sup>, R<sup>P6</sup>, R<sup>P7</sup>, R<sup>P8</sup>, R<sup>N1</sup>, R<sup>N2</sup>, R<sup>N3</sup>, and R<sup>Z1</sup> are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or -NR<sup>B8</sup>R<sup>B9</sup>, wherein R<sup>B8</sup> and R<sup>B9</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>M1</sup>, R<sup>M2</sup>, R<sup>B1</sup>, R<sup>B2</sup>, R<sup>B3</sup>, R<sup>B4</sup>, R<sup>B5</sup>, R<sup>B6</sup>, R<sup>X1</sup>, R<sup>X2</sup>, R<sup>X3</sup>, R<sup>X4</sup>, R<sup>Y1</sup>, R<sup>Y2</sup>, R<sup>Y3</sup>, R<sup>Y4</sup>, R<sup>Y5</sup>, and R<sup>Y6</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; X<sup>1</sup> and X<sup>2</sup> are independently CH or N; X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> are each independently NH, O, or S; X<sup>6</sup> is CH<sub>2</sub> or O; Q is -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, naphyl, 2-pyridyl, or 3-pyridyl;

10 m is 1, 2, 3, or 4; and

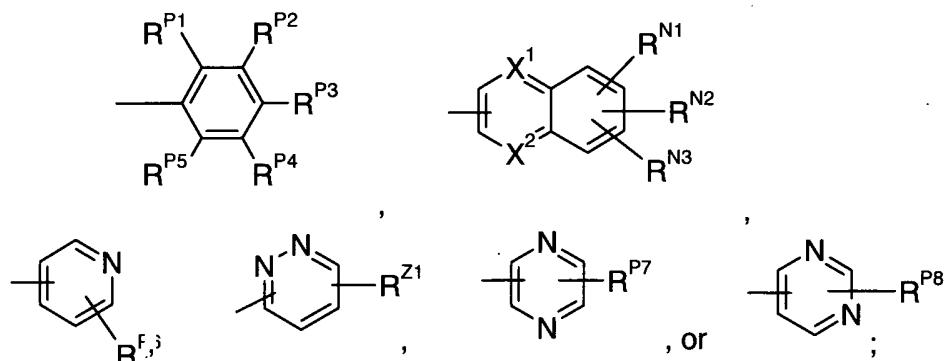
n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

12. A compound according to claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo, -CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub> alkyl and n is 0; or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo, -CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub> alkyl; n is 1; Y is -C(O)-, -S(O)<sub>2</sub>-, -NHS(O)<sub>2</sub>-, -NHC(O)-; and Ar<sup>1</sup> is

-100-



or a pharmaceutically acceptable salt thereof.

14. A compound according to any of claims 11 to 13 wherein m is 1; or a pharmaceutically

5 acceptable salt thereof.

15. A compound according to any of claims 11 to 13 wherein m is 2; or a pharmaceutically acceptable salt thereof.

10 16. A compound according to any of claims 11 to 13 wherein m is 3; or a pharmaceutically acceptable salt thereof.

15 17. A compound according to any of claims 11 to 13 wherein m is 4; or a pharmaceutically acceptable salt thereof.

18. A compound selected from the group consisting of:

20 2-{4-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-4-trifluoromethyl-pyrimidine;

1-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-

20 piperazine;

1-[3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine;

5-ethyl-2-{4-[3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-pyrimidine;

1-{3-methoxy-1-[3-(1-phenyl-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-propyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine;

25 1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine;

(4-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazin-1-yl)-phenyl-methanone;

1-benzenesulfonyl-4-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperazine;

30 N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide;

2-fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzamide;

2,3-dihydro-benzo[1,4]dioxine-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide;

5 N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-methoxy-benzamide;

N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-(pyridin-3-yloxy)-benzenesulfonamide;

10 4-fluoro-N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzamide;

N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzamide;

2-oxo-2H-chromene-6-sulfonic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide;

15 quinoxaline-6-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide;

5-chloro-pyrazine-2-carboxylic acid (1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-amide;

20 N-(1-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-3-methoxy-benzamide;

1-[3-(1-p-tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl]-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine;

1-{3-[1-(4-fluoro-phenyl)-cyclopentyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyridin-2-yl)-piperazine;

25 N-{1-[3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl}-benzenesulfonamide;

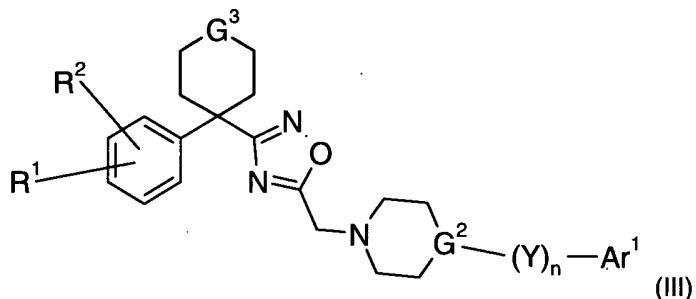
N-{1-[3-(1-p-tolyl-cyclohexyl)-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl}-benzenesulfonamide;

1-{3-[1-(4-fluoro-phenyl)-cyclohexyl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(6-methyl-pyridin-2-yl)-piperazine;

30 N-(1-{3-[1-(4-chloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl)-benzenesulfonamide;

N-{1-[3-(1-p-Tolyl-cyclopropyl)-[1,2,4]oxadiazol-5-ylmethyl}-piperidin-4-yl}-benzenesulfonamide; or a pharmaceutically acceptable salt thereof.

19. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

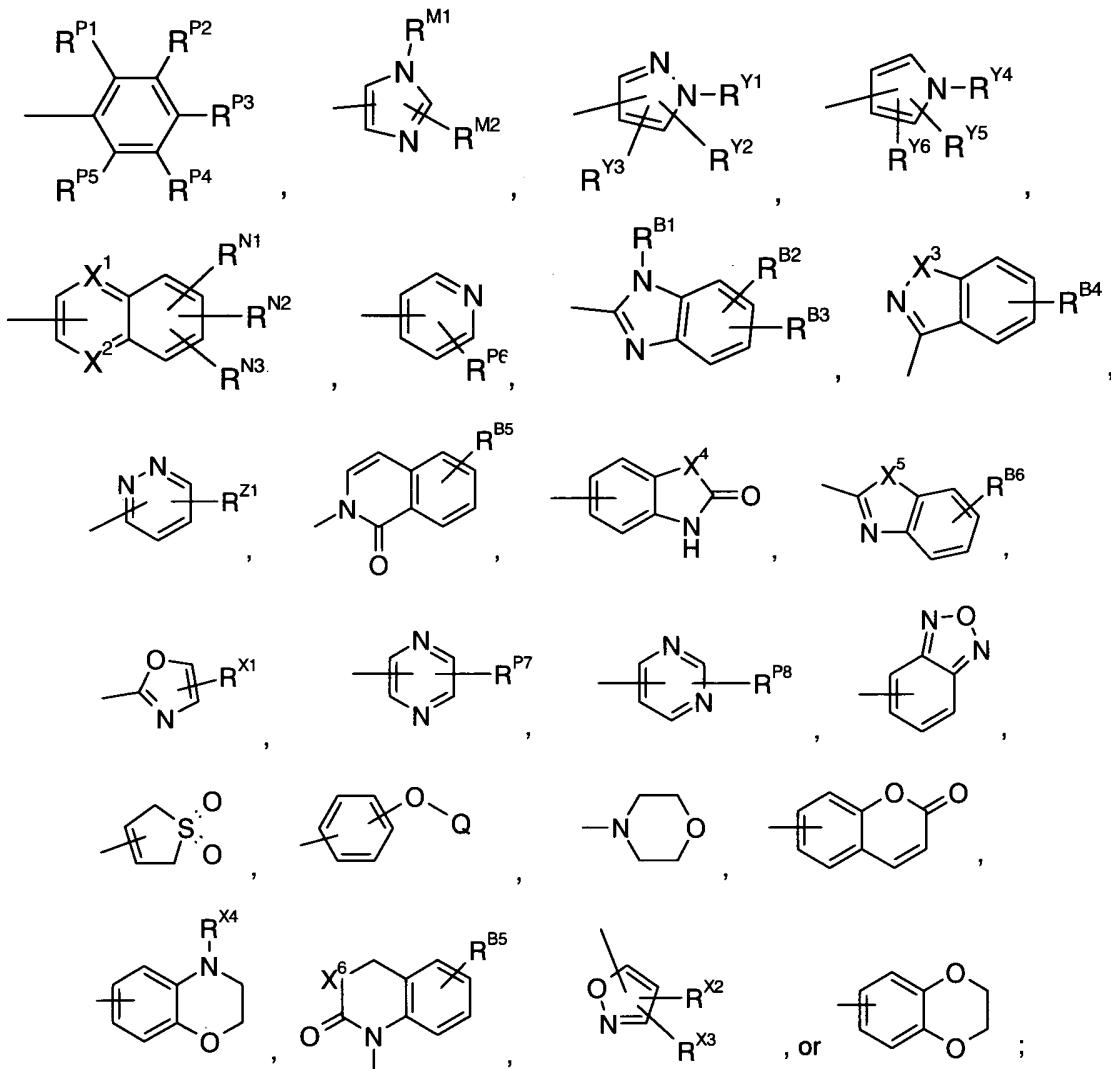
R<sup>1</sup> and R<sup>2</sup> are each independently -H, -OH, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

G<sup>2</sup> is C(R<sup>6</sup>) or N, wherein R<sup>6</sup> is -H, -OH or C<sub>1</sub>-C<sub>6</sub> alkyl;

G<sup>3</sup> is -O- or -N(R<sup>H1</sup>), wherein R<sup>H1</sup> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl;

Y is -CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>- , -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- , -O- , -C(O)- , -C(O)CH<sub>2</sub>- , -S- , -S(O)- , -S(O)<sub>2</sub>- , -NHC(O)- , -NHC(O)CH(R<sup>7</sup>)- , or -NHS(O)<sub>2</sub>- , wherein R<sup>7</sup> is -H or C<sub>1</sub>-C<sub>4</sub> alkyl;

Ar<sup>1</sup> is a radical of the formulae



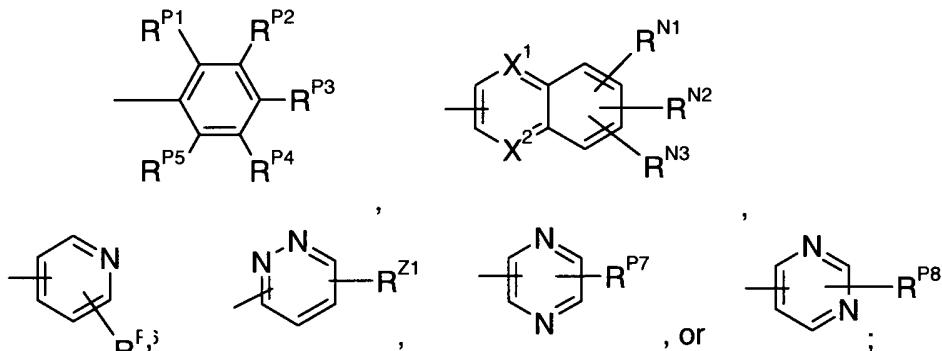
wherein  $R^{P1}$ ,  $R^{P2}$ ,  $R^{P3}$ ,  $R^{P4}$ ,  $R^{P5}$ ,  $R^{P6}$ ,  $R^{P7}$ ,  $R^{P8}$ ,  $R^{N1}$ ,  $R^{N2}$ ,  $R^{N3}$ , and  $R^{Z1}$  are each independently -H, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, -CN, -CF<sub>3</sub>, or -NR<sup>8</sup>R<sup>9</sup>, wherein R<sup>8</sup> and R<sup>9</sup> are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl;  $R^{M1}$ ,  $R^{M2}$ ,  $R^{B1}$ ,  $R^{B2}$ ,  $R^{B3}$ ,  $R^{B4}$ ,  $R^{B5}$ ,  $R^{B6}$ ,  $R^{X1}$ ,  $R^{X2}$ ,  $R^{X3}$ ,  $R^{X4}$ ,  $R^{Y1}$ ,  $R^{Y2}$ ,  $R^{Y3}$ ,  $R^{Y4}$ ,  $R^{Y5}$ , and  $R^{Y6}$  are each independently -H or C<sub>1</sub>-C<sub>6</sub> alkyl; X<sup>1</sup> and X<sup>2</sup> are independently CH or N; X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> are each independently NH, O, or S; X<sup>6</sup> is CH<sub>2</sub> or O; Q is -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, napthyl, 2-pyridyl, or 3-pyridyl; and

5 n is 0 or 1;

provided that when Y is O, S, NHC(O), NHS(O)<sub>2</sub>, NHC(O)CH(R<sup>7</sup>), or NHS(O)<sub>2</sub>, then G<sup>2</sup> is CH.

10 20. A compound according to claim 19 wherein R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo, -CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub> alkyl and n is 0; or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 19 wherein R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo, -CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub> alkyl; n is 1; Y is -C(O)-, -S(O)<sub>2</sub>-, -NHS(O)<sub>2</sub>-, -NHC(O)-; and Ar<sup>1</sup> is



15

or a pharmaceutically acceptable salt thereof.

22. A compound selected from the group consisting of

20 1-{3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(5-trifluoromethyl-pyrin-2-yl)-piperazine; and

1-{3-[4-(4-Fluoro-phenyl)-tetrahydro-pyran-4-yl]-[1,2,4]oxadiazol-5-ylmethyl}-4-(4-trifluoromethyl-phenyl)-piperidine;

or a pharmaceutically acceptable salt thereof.

25 23. A pharmaceutical composition comprising a compound according to any of claims 1 to 22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30 24. A method of causing vasodilation in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound according to any of claims 1 to 22, or a pharmaceutically acceptable salt thereof.

25. A method of treating a disease or condition selected from hypertension, congestive heart failure, stroke, ischaemic heart disease, or angina pectoris in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound according to any of claims 1 to 22, or a pharmaceutically acceptable salt thereof.

5

26. A method of treating a disease or condition selected from the group consisting of chronic pain, inflammatory pain, neuropathic pain, visceral pain, nociceptive pain, multiple sclerosis, neurodegenerative disorder, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, sciatica, fibromyalgia and causalgia.

10

27. A method according to claim 26 wherein said disease or condition is neuropathic pain.

# INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2007/003107

A. CLASSIFICATION OF SUBJECT MATTER	INV.	C07D271/06	C07D413/06	C07D413/12	C07D413/14	A61K31/4245
		A61P9/08	A61P25/28	A61P25/06		

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, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/014370 A (ASTRAZENECA AB [SE]; NPS PHARMA INC [US]; MCLEOD DONALD A [US]; KERS A) 19 February 2004 (2004-02-19) claims 1,23-25 example 186 -----	1-27
A	WO 2005/021523 A (NEUROMED TECH INC [CA]; SNUTCH TERRANCE P [CA]; ZAMPONI GERALD W [CA];) 10 March 2005 (2005-03-10) page 34; example P46 claims 17,18 -----	1-27



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

5 February 2008

Date of mailing of the international search report

15/02/2008

Name and mailing address of the ISA/

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Authorized officer

Seitner, Irmgard

## INTERNATIONAL SEARCH REPORT

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 24–27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

<b>International application No</b> <b>PCT/IB2007/003107</b>
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Patent document cited in search report	Publication date	Patent family member(s)			Publication date
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					26-01-2007
					22-02-2006
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WO 2005021523	A 10-03-2005	AU 2004268711 A1	BR P10414094 A	CA 2537487 A1	10-03-2005
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					29-11-2006
					21-06-2006
					01-03-2007
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