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(54) **ETHERS, SECONDARY AMINES AND DERIVATIVES THEREOF AS MODULATORS OF THE 5-HT<sub>2A</sub> SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO**

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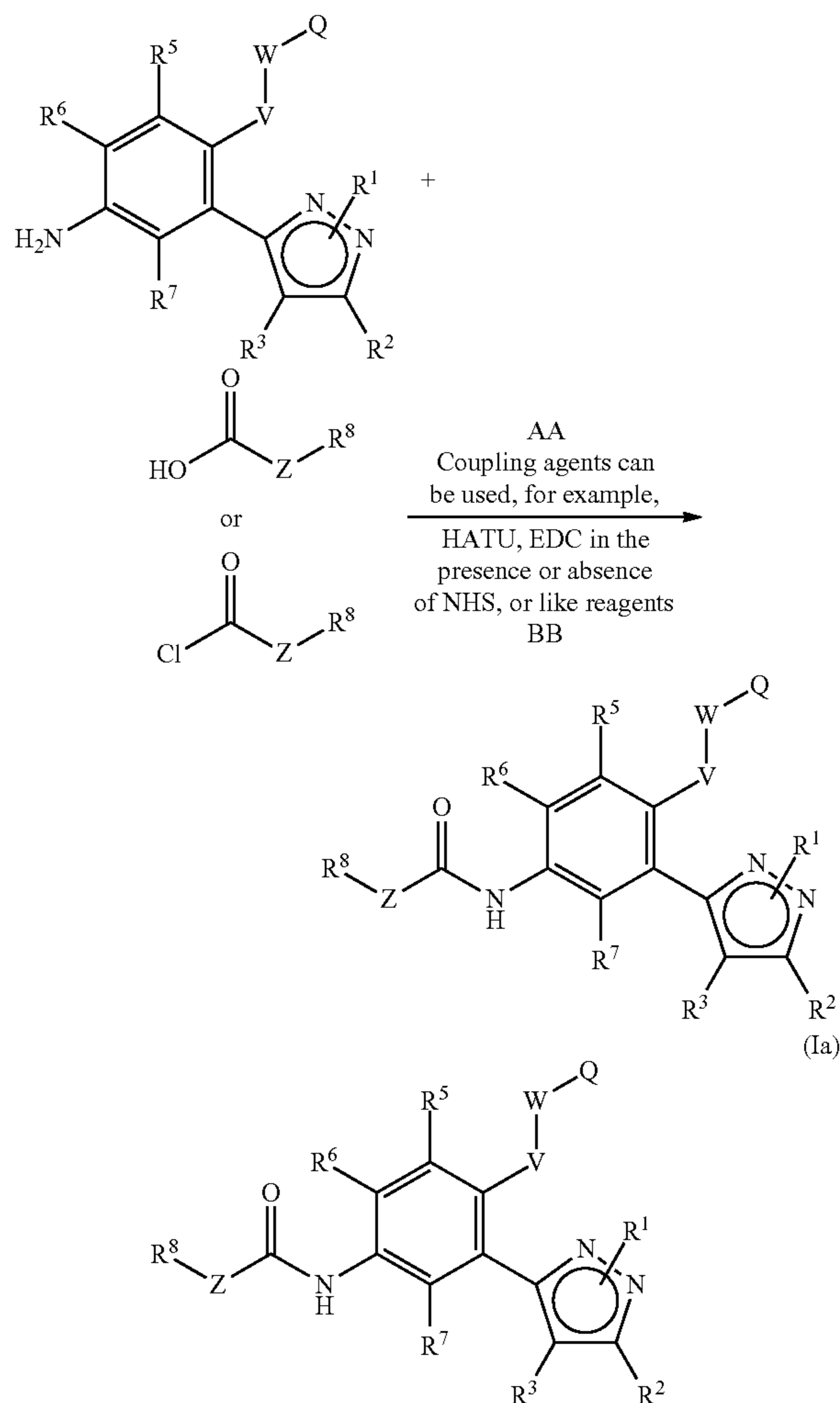
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(57) **ABSTRACT**

The present invention pertains to certain compounds of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT<sub>2A</sub> serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, and sleep disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy and the like. The present invention also relates to the methods for the treatment of 5-HT<sub>2A</sub> serotonin receptor associated disorders in combination with other pharmaceutical agents administered separately or together.



16 Claims, 8 Drawing Sheets



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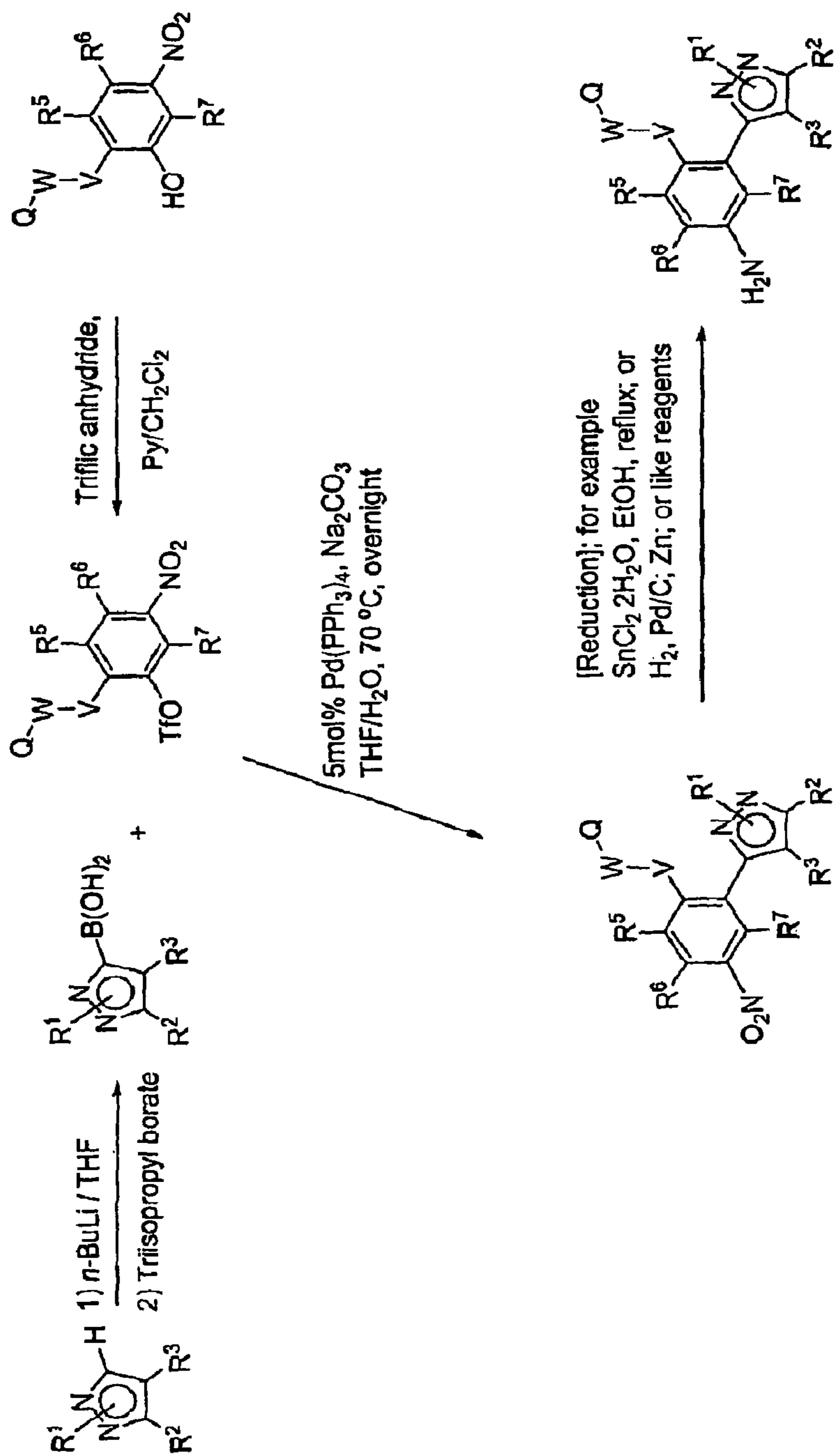


Figure 1

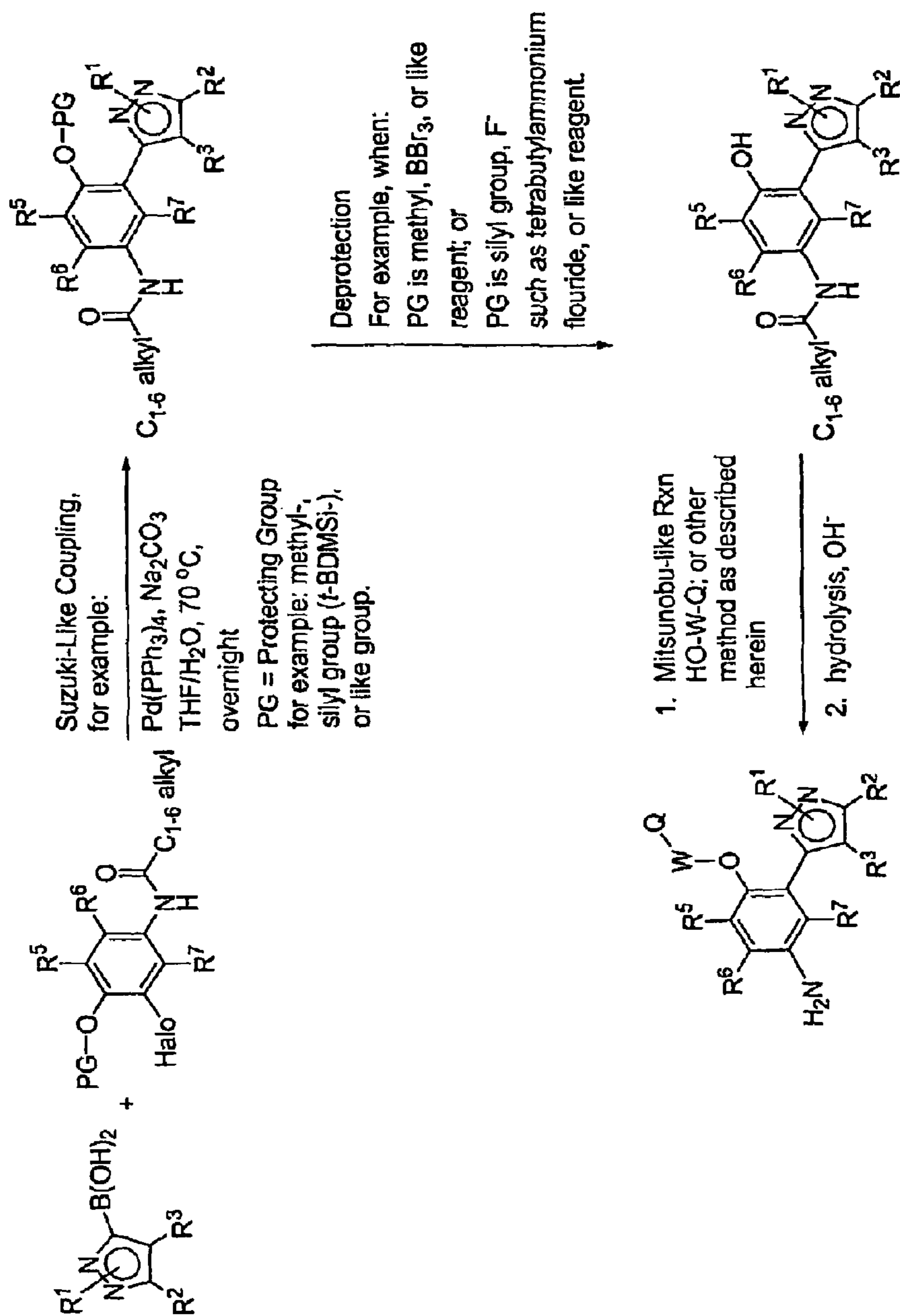


Figure 2

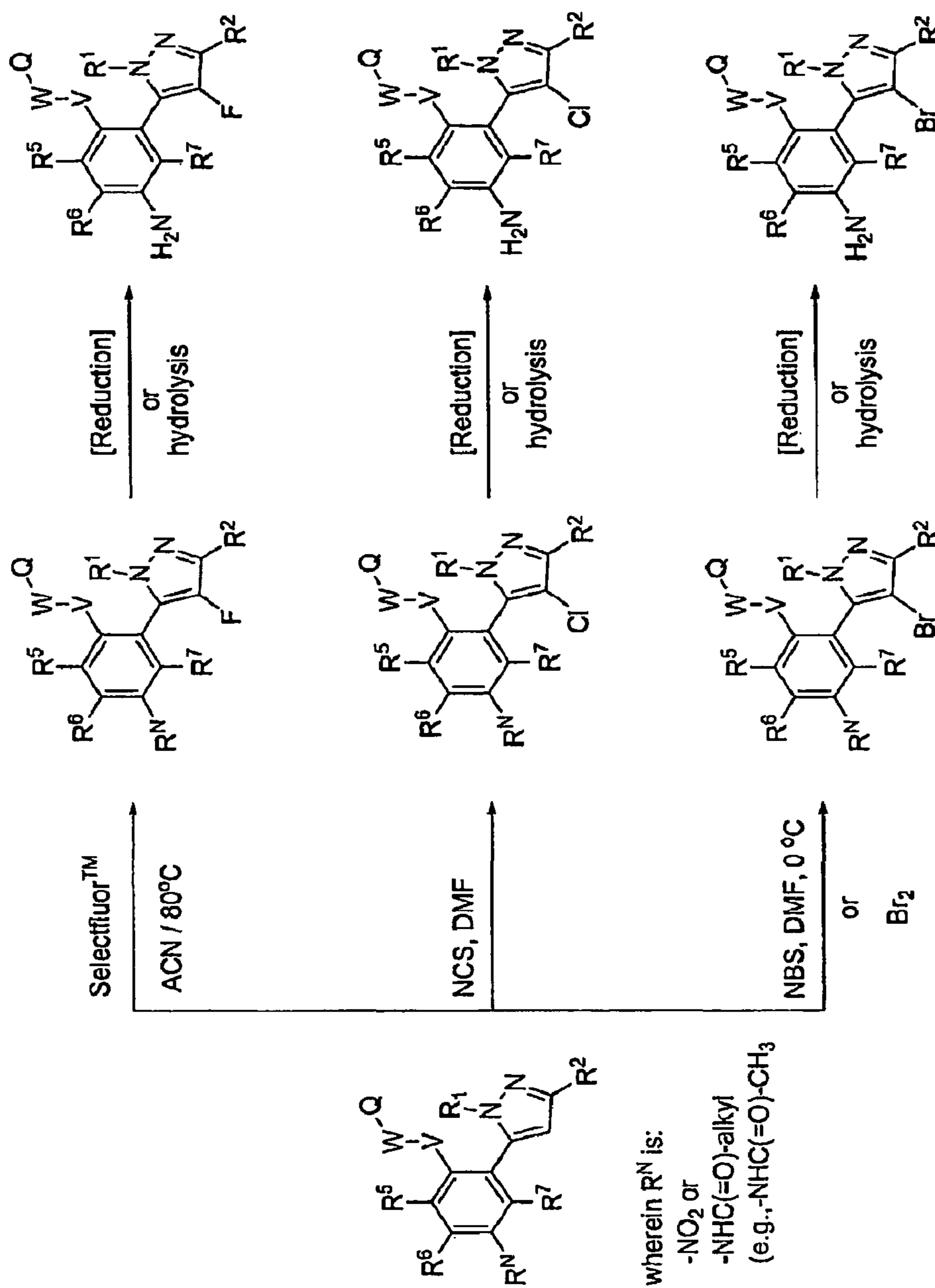


Figure 3

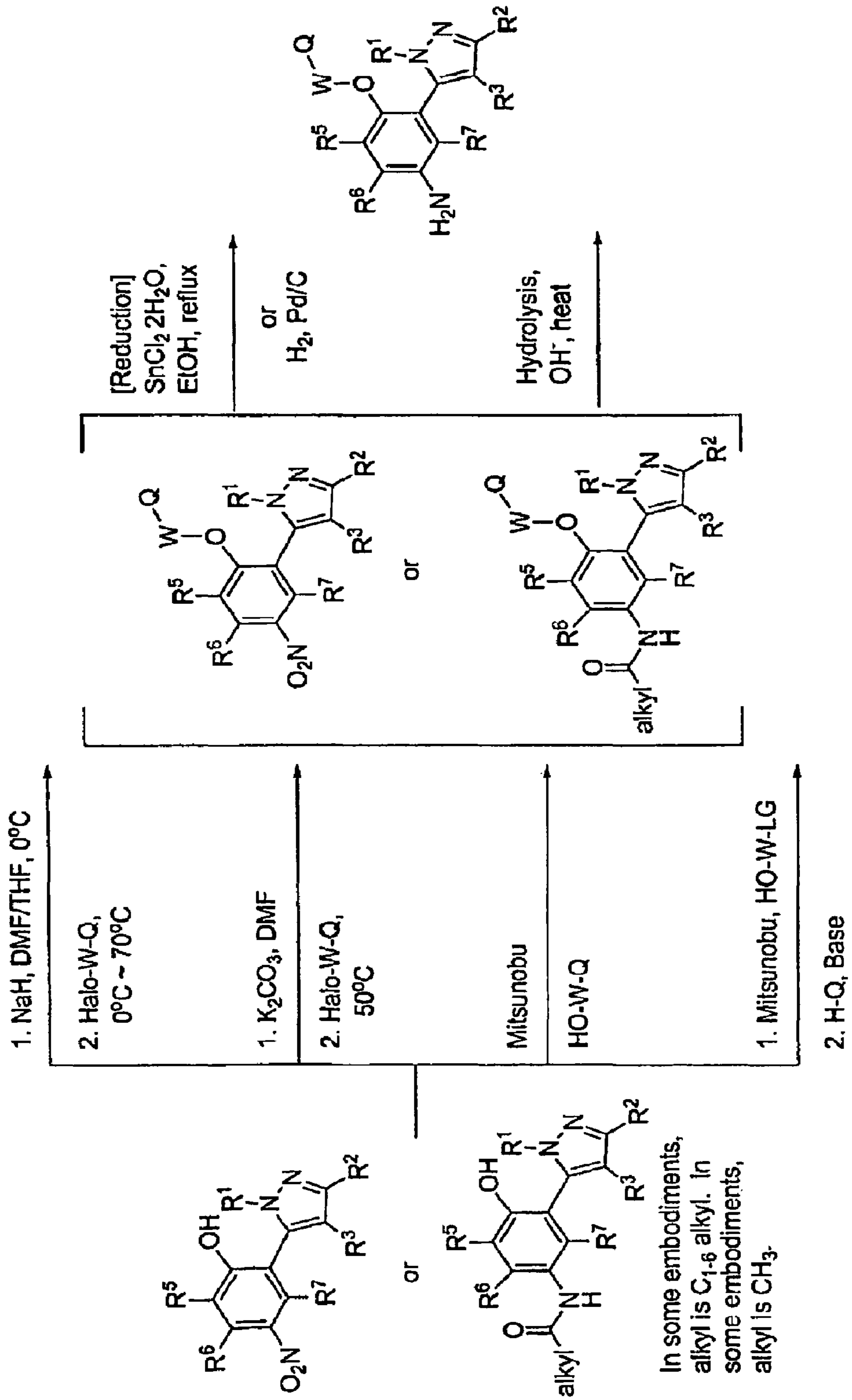
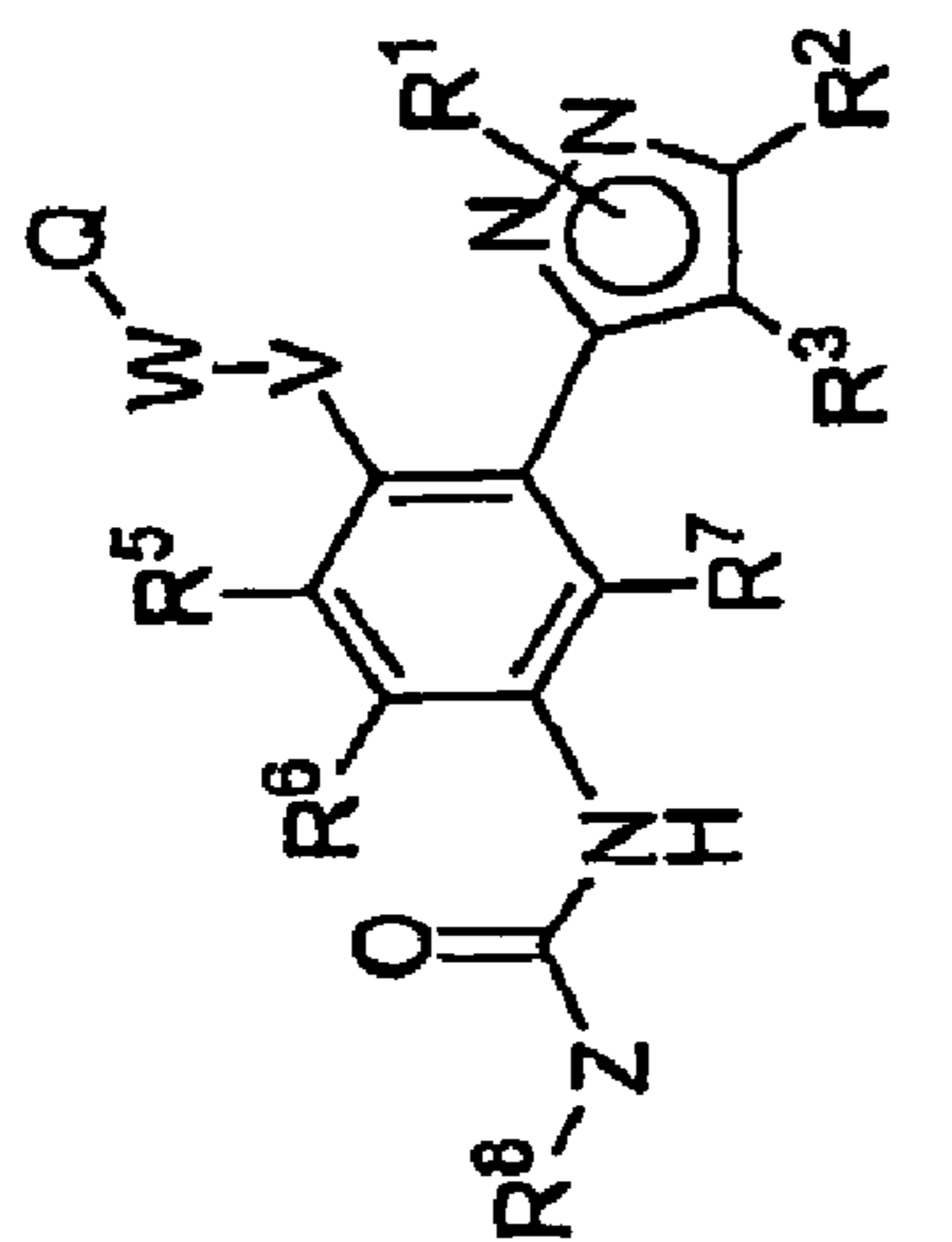


Figure 4





Coupling agents can be used, for example, HATU, EDC in the presence or absence of NHS, or like reagents

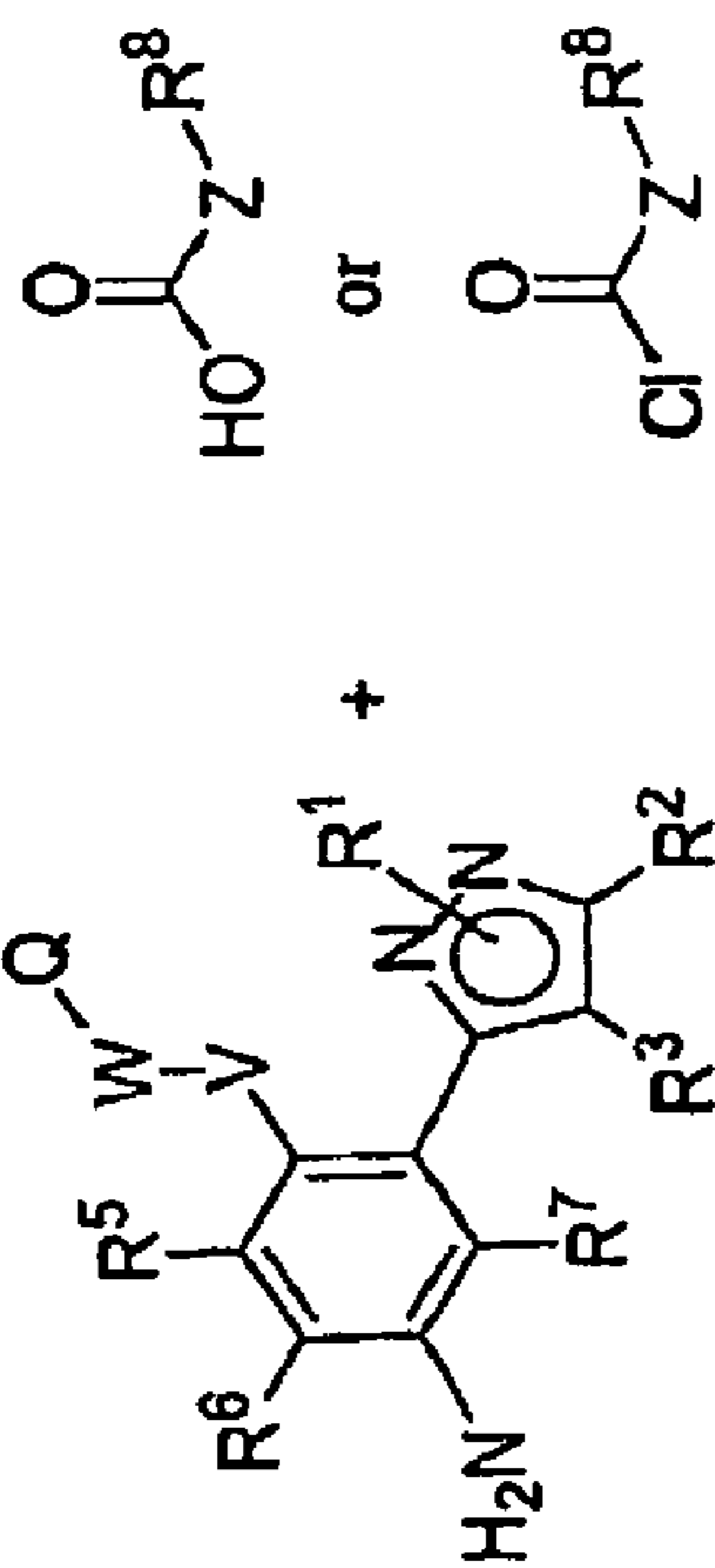


Figure 5

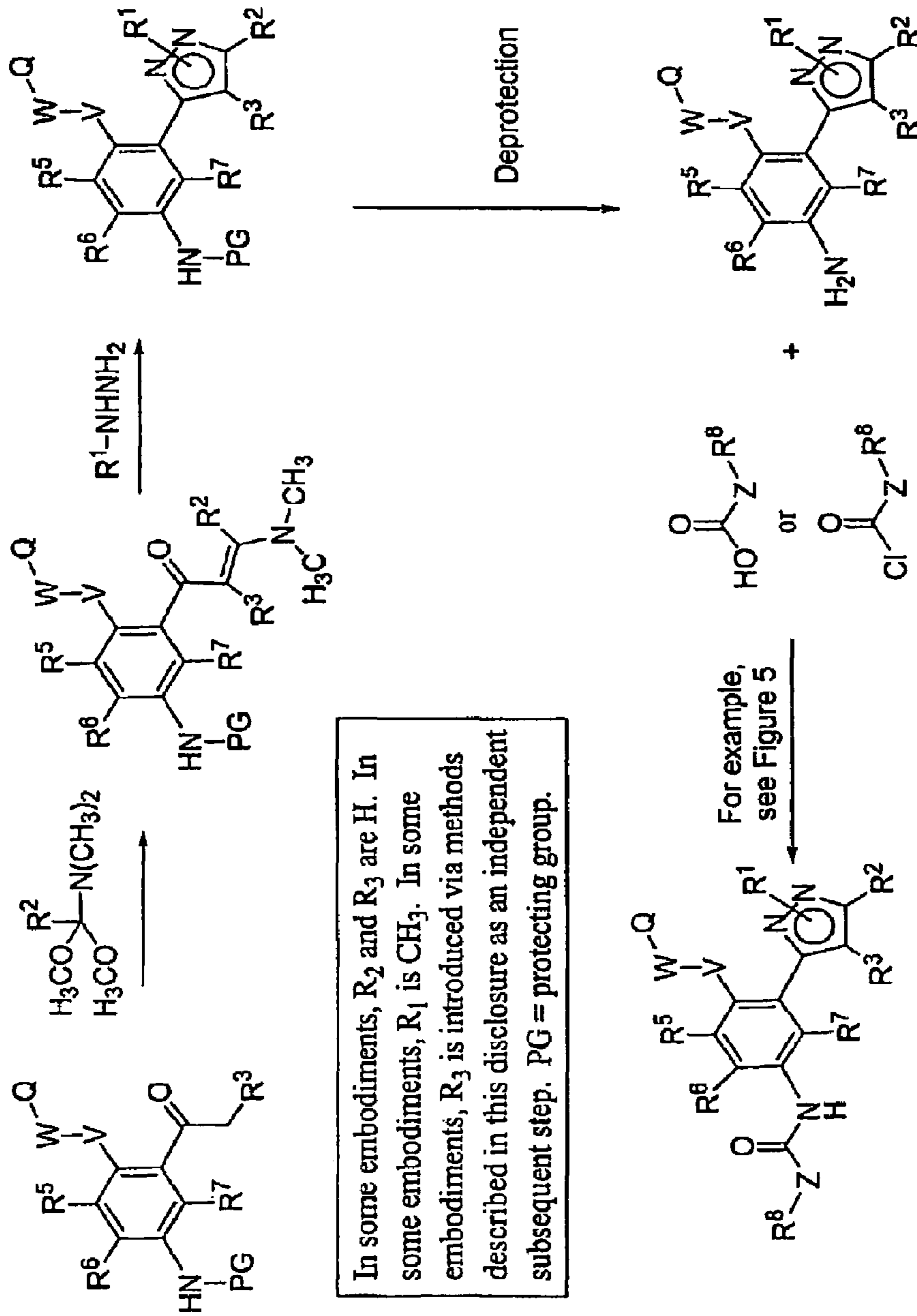


Figure 6



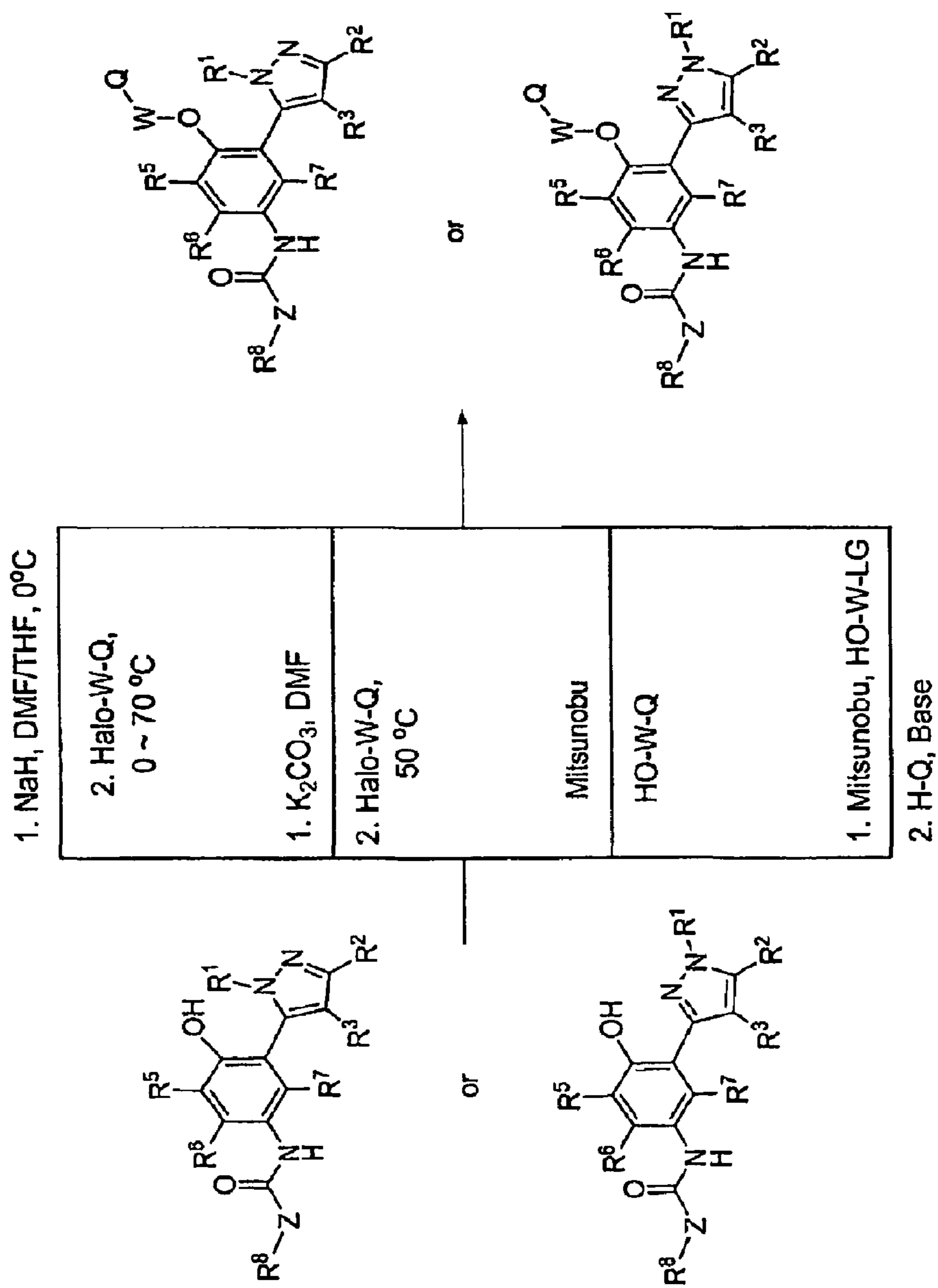


Figure 7

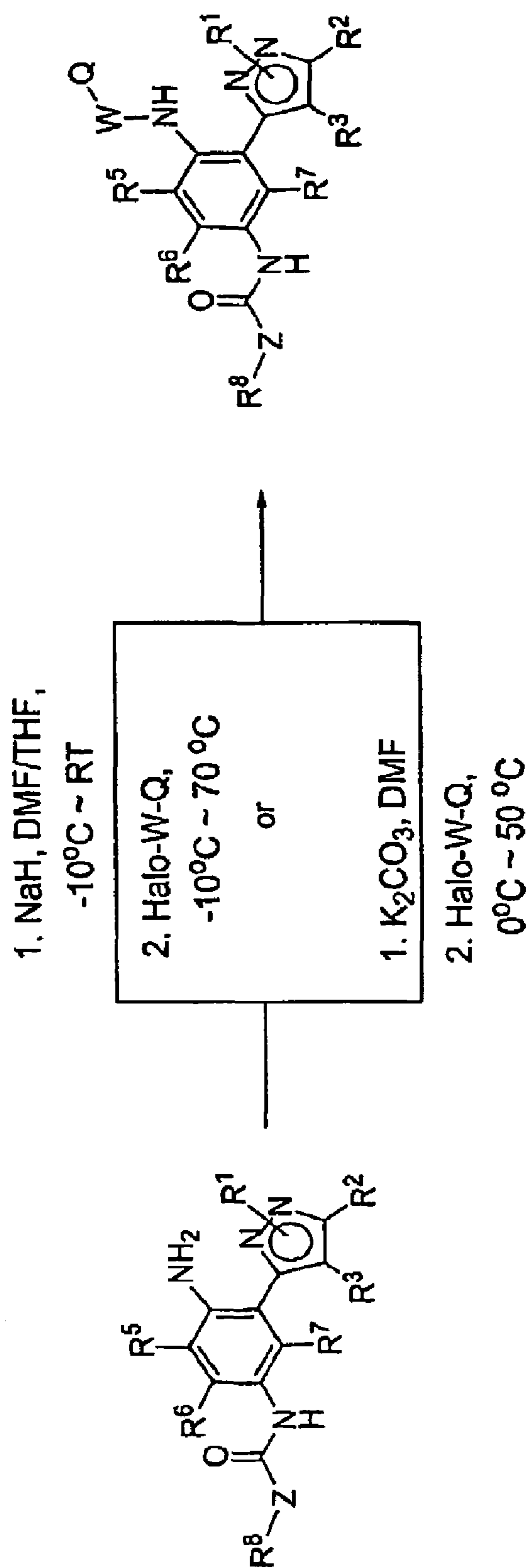


Figure 8



**ETHERS, SECONDARY AMINES AND  
DERIVATIVES THEREOF AS MODULATORS  
OF THE 5-HT<sub>2A</sub> SEROTONIN RECEPTOR  
USEFUL FOR THE TREATMENT OF  
DISORDERS RELATED THERETO**

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.**

CROSS REFERENCE TO RELATED  
APPLICATIONS

This application is a 35 USC 371 National Stage application of International App. No. PCT/US2007/011789, filed May 17, 2007, which claims the benefit of U.S. Ser. No. 60/801,699, filed May 18, 2006, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention pertains to certain compounds of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT<sub>2A</sub> serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, blood clot formation, asthma or symptoms thereof, agitation or a symptom thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, sleep disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy and the like.

The present invention also relates to the methods for the treatment of 5-HT<sub>2A</sub> serotonin receptor associated disorders in combination with other pharmaceutical agents administered separately or together.

BACKGROUND OF THE INVENTION

G Protein Coupled Receptors

G Protein coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified.

Under physiological conditions, G protein coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link

to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

5 A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

15 Serotonin Receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, e.g., lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D<sub>2</sub> receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT<sub>1</sub> through 5-HT<sub>7</sub>, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT<sub>2</sub> subfamily is divided into three receptor subtypes: 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub>. The human 5-HT<sub>2C</sub> receptor was first isolated and cloned in 1987, and the human 5-HT<sub>2A</sub> receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

U.S. Pat. No. 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT<sub>1C</sub> receptor (now known as the 5-HT<sub>2C</sub> receptor). U.S. Pat. Nos. 5,661,024 and 6,541,209 describe the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT<sub>2A</sub> receptor.

55 Mutations of the endogenous forms of the rat 5-HT<sub>2A</sub> and rat 5-HT<sub>2C</sub> receptors have been reported to lead to constitutive activation of these receptors (5-HT<sub>2A</sub>: Casey, C. et al. (1996) Society for Neuroscience Abstracts, 22:699.10, hereinafter "Casey"; 5-HT<sub>2C</sub>: Herrick-Davis, K., and Teitler, M. (1996) Society for Neuroscience Abstracts, 22:699.18, hereinafter "Herrick-Davis 1"; and Herrick-Davis, K. et al. (1997) J. Neurochemistry 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT<sub>2A</sub> receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position

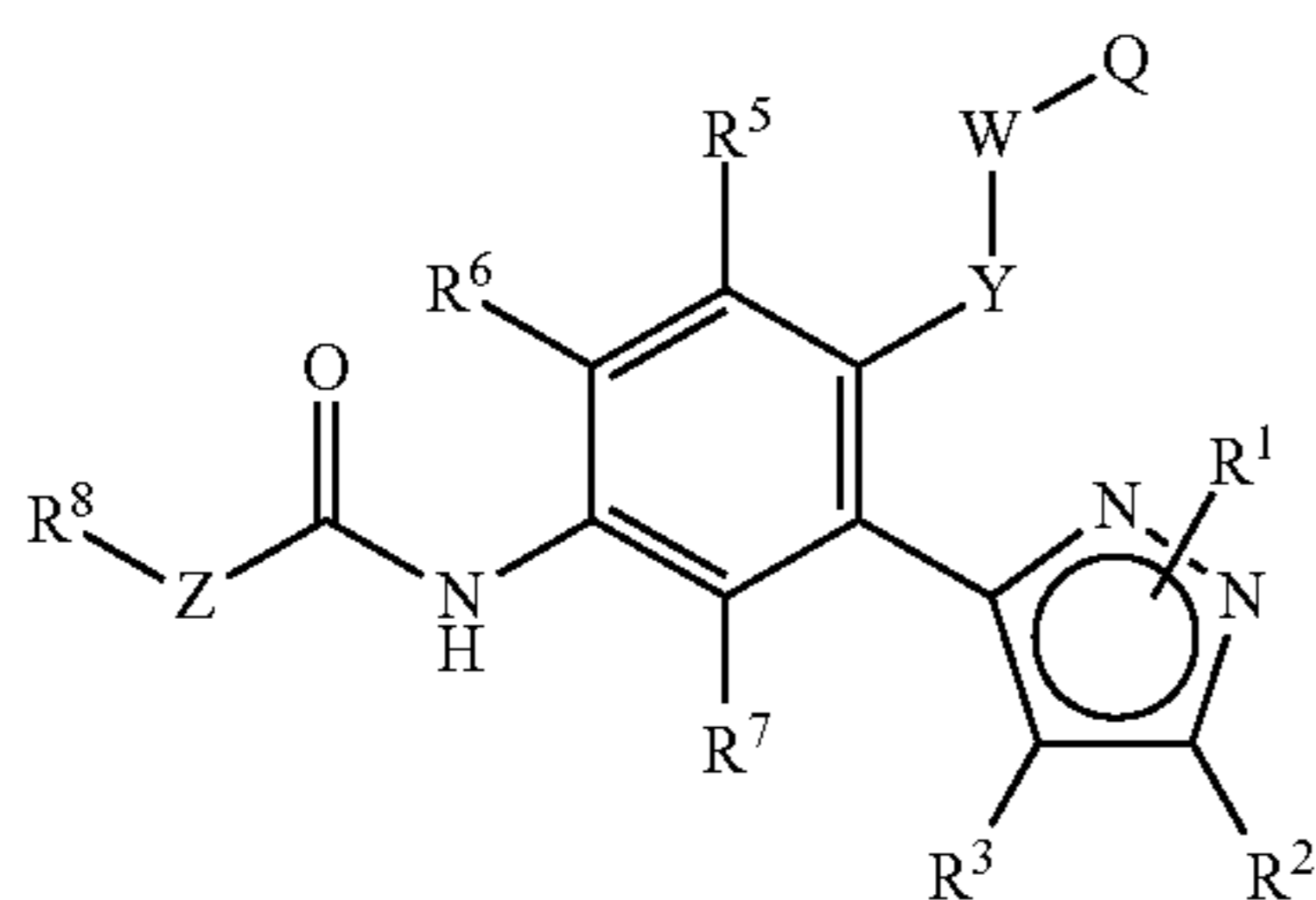


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312 of the rat 5-HT<sub>2C</sub> receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

## SUMMARY OF THE INVENTION

One aspect of the present invention pertains to certain compounds as shown in Formula (Ia):



or a pharmaceutically acceptable salt, hydrate or solvate thereof;

wherein:

V is O or NH;

W is C<sub>1-4</sub> alkylene optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 substituents selected independently from the group consisting of C<sub>1-3</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>1-3</sub> haloalkyl, halogen, and oxo;

Q is NR<sup>4a</sup>R<sup>4b</sup> or —OR<sup>4c</sup>, wherein:

R<sup>4a</sup> is H or a metabolically-labile group;

R<sup>4b</sup> is C<sub>1-6</sub> alkyl, aryl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, heterocyclyl, or heteroaryl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-5</sub> acyl, C<sub>1-5</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylsulfonamide, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylureyl, amino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub> cycloalkyl, C<sub>2-6</sub> dialkylcarboxamide, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkylsulfinyl, C<sub>1-4</sub> haloalkylsulfonyl, C<sub>1-4</sub> haloalkylthio, hydroxyl, imino, nitro, sulfonamide and phenyl; and

R<sup>4c</sup> is H, or R<sup>4c</sup> is C<sub>1-6</sub> alkyl, C<sub>1-12</sub> acyl, aryl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, heterocyclyl, or heteroaryl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-5</sub> acyl, C<sub>1-5</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub>-alkyl sulfonamide, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub>-cycloalkyl, C<sub>2-6</sub> dialkylcarboxamide, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkylsulfinyl, C<sub>1-4</sub> haloalkylsulfonyl, C<sub>1-4</sub> haloalkylthio, heterocyclyl, hydroxyl, imino, nitro, sulfonamide and phenyl;

Z is C<sub>1-4</sub> alkylene optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 substituents selected independently from the group consisting of C<sub>1-3</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, cyano, C<sub>1-3</sub> haloalkyl, halogen and oxo; or Z is absent;

R<sup>1</sup> is selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C<sub>3-7</sub> cycloalkyl;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub>

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alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

R<sup>3</sup> is selected from the group consisting of H, C<sub>2-4</sub> alkenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, halogen, heteroaryl and phenyl; and wherein each of the C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>3-7</sub> cycloalkyl, heteroaryl and phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-5</sub> acyl, C<sub>1-5</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkyl, C<sub>1-4</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylsulfonamide, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylureyl, amino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub> cycloalkyl, C<sub>2-6</sub> dialkylcarboxamide, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkylsulfinyl, C<sub>1-4</sub> haloalkylsulfonyl, C<sub>1-4</sub> haloalkylthio, hydroxyl, nitro and sulfonamide;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each selected independently from the group consisting of H, C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-6</sub> alkylimino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, heterocyclyl, hydroxyl, thiol, and nitro; and

R<sup>8</sup> is C<sub>1-8</sub>-alkyl, aryl, C<sub>3-10</sub> cycloalkyl, heteroaryl, or heterocyclyl each optionally substituted with substituents selected independently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-6</sub> alkylimino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyloxy, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, heteroaryl, heterocyclyl, hydroxyl, thiol, nitro, phenoxy and phenyl, wherein the C<sub>2-4</sub> alkenyl, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> alkylamino, C<sub>1-6</sub> alkylimino, C<sub>2-8</sub> dialkylamino, heteroaryl, heterocyclyl, phenyl, and phenoxy, and each the substituent is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-8</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, heterocyclyl, hydroxyl, thiol and nitro.

One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for modulating the activity of a 5-T<sub>2A</sub> serotonin receptor by con-



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tacting the receptor with a compound according to any of the embodiments described herein or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating a 5-HT<sub>2A</sub> associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating a 5-HT<sub>2A</sub> serotonin receptor associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein wherein R<sup>4a</sup> is metabolically-labile group.

One aspect of the present invention pertains to methods for treating a 5-HT<sub>2A</sub> serotonin receptor associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a prodrug whereby the prodrug undergoes a conversion into a compound according to any of the embodiments described herein wherein R<sup>4a</sup> is H and the conversion takes place within the body of the individual.

One aspect of the present invention pertains to processes for preparing a composition comprising admixing a compound according to any of the embodiments described herein and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to the use of a compound of the present invention for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder.

One aspect of the present invention pertains to compounds according to any of the embodiments described herein for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds according to any of the embodiments described herein for use in a method for the treatment of a 5-HT<sub>2A</sub> associated disorder, as described herein, in the human or animal body by therapy.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the general synthetic scheme for the preparation of intermediate compounds of the present invention. FIG. 1 shows a general coupling method between a pyrazole boronic acid and an aryl triflate, it is understood that similar coupling methods known in the art can also be used, and a halide, such as, I, Br or Cl, can be used in place of the triflate.

FIG. 2 shows the general synthetic scheme for the preparation of intermediate compounds of the present invention wherein "V" is oxygen. FIG. 2 shows a general coupling method between a pyrazole boronic acid and a phenyl halide using coupling methods known in the art, such as a Suzuki coupling, and the like. FIG. 2 further shows the use of orthogonal protecting groups for the oxygen (V=O) and the nitrogen. After the coupling reaction the phenol protecting group is removed and a variety of —W-Q groups can be introduced. Subsequently, the alkyl amide protecting group can be hydrolyzed to provide the amine intermediate of the present invention.

FIG. 3 shows the general synthetic scheme for the preparation of intermediate compounds of the present invention. FIG. 3 illustrates general methods for introducing a variety of halogens to compounds of the invention. It is understood that

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these halogenation reactions can also be conducted later in the synthesis, for example as the last step.

FIG. 4 shows the general synthetic scheme for the preparation of intermediate compounds of the present invention. FIG. 4 shows the general reactions, such as, alkylation and Mitsunobu-like reactions, for introducing the —W-Q group.

FIG. 5 shows the general synthetic scheme for the preparation of compounds of the present invention. FIG. 5 shows the general coupling reactions of the amino-intermediate with carboxylic acids, acyl halides, and the like.

FIG. 6 shows the general synthetic scheme for the preparation of intermediates and compounds of the present invention. FIG. 6 illustrates the general methods for preparing pyrazoles of the present invention using substituted and unsubstituted hydrazines.

FIG. 7 shows the general synthetic scheme for the preparation of compounds of the invention wherein the —W-Q group is introduced in the last step(s). FIG. 7 shows the general reactions, such as, alkylation and Mitsunobu-like reactions, for introducing the —W-Q group.

FIG. 8 shows the general synthetic scheme for the preparation of compounds of the invention wherein V is NH in Formula (Ia) and the —W-Q group is introduced in the last step(s). FIG. 8 shows the general reactions, such as, alkylation reactions, for introducing the —W-Q group wherein V is NH.

## DEFINITIONS

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document.

The term "agonists" shall mean moieties that interact and activate the receptor, such as the 5-HT<sub>2A</sub> receptor, and initiates a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term "antagonist" is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term "contact or contacting" is intended to mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" a H3 receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a H3 receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a H3 receptor.

The term "in need of treatment" is intended to mean a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the



compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term "individual" is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The term "inverse agonist" is intended to mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

The term "isolated" refers to material that is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a metabolite that is formed from a parent compound present in a natural system (e.g. individual) is not isolated, but the same metabolite, separated from some or all of the coexisting materials in the natural system is considered isolated. In addition, the metabolite that is prepared by synthetic means is also considered isolated.

The term "modulate or modulating" is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term "metabolically-labile group" as used herein refers to any group that, following administration of a compound containing the group to an individual, is converted in vivo to a compound of Formula (Ia) wherein  $R^{4a}$  is H. The conversion of the "metabolically-labile group" can be by metabolic and/or chemical processes and can occur in one step or through a series of two or more steps. Representative examples of a "metabolically-labile group" include, but are not limited to,  $-C(=O)O-R^{4d}$  (thus, together with the nitrogen forms a carbamate),  $-C(=O)-R^{4d}$  (together with the nitrogen forms an amide), and the like, wherein  $R^{4d}$  is  $C_{1-18}$  alkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl each optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-6}$  acyl,  $C_{1-6}$  acyloxy,  $C_{2-6}$  alkenyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkylcarboxamide,  $C_{2-6}$  alkynyl,  $C_{1-6}$  alkylsulfonamide,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylureyl, amino,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino, carbo- $C_{1-6}$ -alkoxy, carboxamide, carboxy, cyano,  $C_{3-7}$  cycloalkyl,  $C_{2-8}$  dialkylcarboxamide,  $C_{2-8}$  dialkylsulfonamide, halogen,  $C_{1-6}$  haloalkoxy,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  haloalkylsulfinyl,  $C_{1-6}$  haloalkylsulfonyl,  $C_{1-6}$  haloalkylthio, hydroxyl, thiol, nitro, oxo, phenyl, and sulfonamide. In some embodiments, the "metabolically-labile group" is  $C_{1-12}$  acyl, carbo- $C_{1-12}$ -alkoxy, or  $C(=O)O$ -aryl, wherein the  $C_{1-12}$  acyl, carbo- $C_{1-12}$ -alkoxy, and  $-C(=O)O$ -aryl is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-5}$  acyloxy,  $C_{1-6}$  alkylcarboxamide, amino,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino,  $C_{1-6}$  alkylimino,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  alkylthio, halogen, nitro, and phenyl. The "metabolically-labile groups" illustrated are exemplary and are not exhaustive, and one skilled in the art could prepare other known varieties of groups. In some cases, a "metabolically-labile group" (i.e.,  $R^{4a}$ ) can serve to improve efficacy or safety through improved oral bioavailability, or pharmacodynamic half-life, etc.

The term "pharmaceutical composition" is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates and hydrates of compounds of Formula (Ia); whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term "prodrug" as used herein refers to any compound that when administered to a biological system (e.g., in vivo in an individual, and the like) generates a compound of Formula (Ia), wherein  $R^{4a}$  is H, as a result of chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s). In some embodiments, compounds of the present invention can be converted to "pro-drugs." In some embodiments, "pro-drugs" refer to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

The term "therapeutically effective amount" is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Chemical Group, Moiety or Radical:

The term directly preceding the chemical group beginning with "C" followed directly by a subscript number or a subscript range of numbers refers to the number of carbons associated with the chemical group. For example, the term " $C_{1-6}$ " in the chemical group " $C_{1-6}$  alkyl" refers to an alkyl group containing one, two, three, four, five, or six carbons, and all possible isomers.

The term " $C_{1-12}$  acyl" denotes a  $C_{1-12}$  alkyl radical attached to a carbonyl wherein alkyl has the same definition as described herein, some embodiments are when acyl is  $C_{1-6}$  acyl, some embodiments are when acyl is  $C_{1-5}$  acyl; some



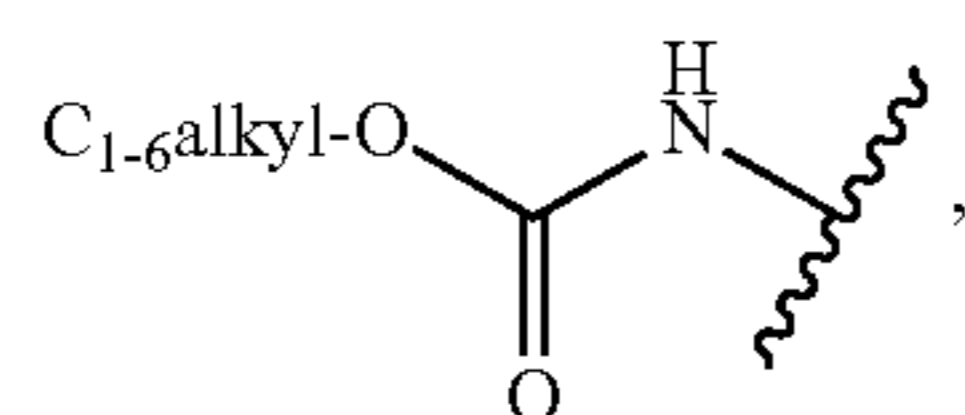
examples include, but are not limited to, acetyl, propionyl, n-butanoyl, iso-butanoyl, sec-butanoyl, t-butanoyl (i.e., pivaloyl), pentanoyl and the like.

The term “C<sub>1-12</sub> acyloxy” denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition as described herein; some embodiments are when acyloxy is C<sub>1-11</sub> acyloxy, some embodiments are when acyloxy is C<sub>1-10</sub> acyloxy, some embodiments are when acyloxy is C<sub>8-10</sub> acyloxy, some embodiments are when acyloxy is C<sub>1-6</sub> acyloxy, some embodiments are when acyloxy is C<sub>1-5</sub> acyloxy, some embodiments are when acyloxy is C<sub>1-4</sub> acyloxy, some embodiments are when acyloxy is C<sub>10-12</sub> acyloxy, some embodiments are when acyloxy is C<sub>8-10</sub> acyloxy. Some examples include, but are not limited to, acetyloxy, propionyloxy, butanoyloxy, iso-butanoyloxy, sec-butanoyloxy, t-butanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, undecanoyloxy, dodecanoyloxy, and the like.

The term “C<sub>2-4</sub> alkenyl” denotes a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both E and Z isomers are embraced by the term “alkenyl.” Furthermore, the term “alkenyl” includes di- and tri-alkenyls. Accordingly, if more than one double bond is present then the bonds may be all E or Z or a mixture of E and Z. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl and the like.

The term “C<sub>1-6</sub> alkoxy” as used herein denotes an alkyl radical, as defined herein, attached directly to an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, iso-butoxy, sec-butoxy and the like.

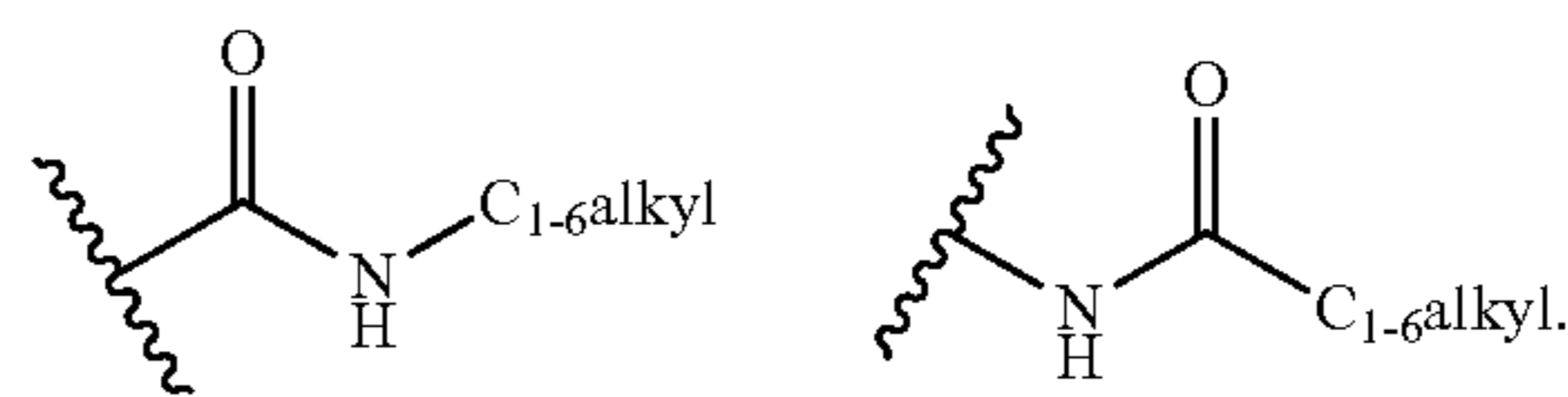
The term “C<sub>1-4</sub> alkoxy-carbonylamino” denotes the group represented by the formula:



wherein C<sub>1-6</sub> alkyl has the same definition as found herein. Examples of C<sub>1-6</sub> alkoxy-carbonylamino include methoxycarbonylamino, ethoxycarbonylamino, isopropoxycarbonylamino, propoxycarbonylamino, tert-butoxycarbonylamino, butoxycarbonylamino, and the like.

The term “C<sub>1-8</sub> alkyl” denotes a straight or branched carbon radical containing 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 4 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl, iso-pentyl, t-pentyl, neo-pentyl, 1-methylbutyl [i.e., —CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>], 2-methylbutyl [i.e., —CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>], n-hexyl and the like.

The term “C<sub>1-6</sub> alkylcarboxamido” or “C<sub>1-6</sub> alkylcarboxamide” denotes a single C<sub>1-6</sub> alkyl group attached to the nitrogen of an amide group, wherein alkyl has the same definition as found herein. The C<sub>1-6</sub> alkylcarboxamido may be represented by the following:

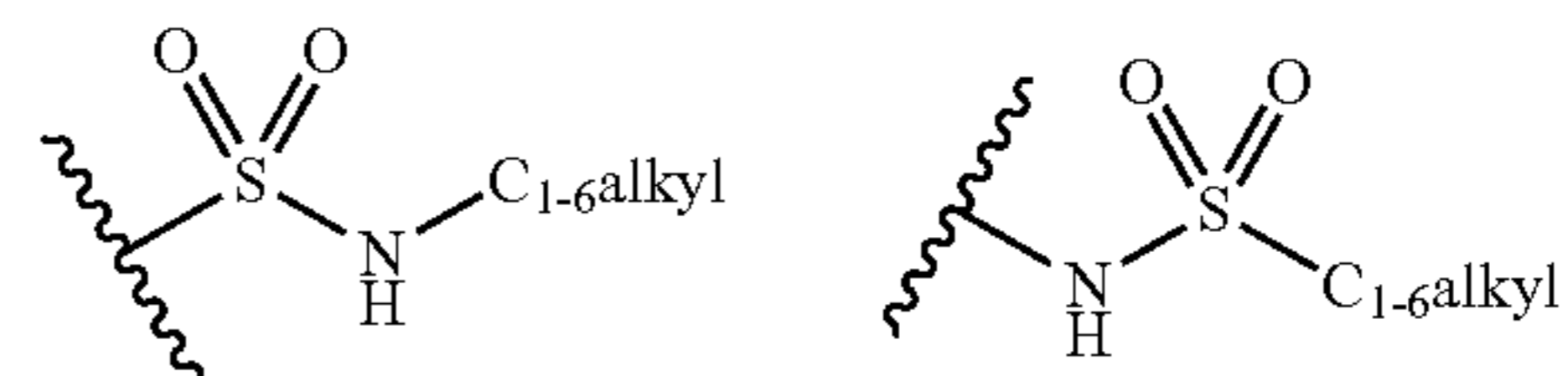


Examples include, but are not limited to, N-methylcarboxamide, N-ethylcarboxamide, N-n-propylcarboxamide, N-iso-propylcarboxamide, N-n-butylcarboxamide, N-sec-butylcarboxamide, N-iso-butylcarboxamide, N-t-butylcarboxamide and the like.

The term “C<sub>1-4</sub> alkylene” refers to a C<sub>1-4</sub> divalent straight carbon group containing 1 to 4 carbons, some embodiments are 1 to 3 carbons, some embodiments are 1 to 2 carbons. In some embodiments alkylene refers to, for example, —CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, and the like.

The term “C<sub>1-6</sub> alkylsulfinyl” denotes a C<sub>1-6</sub> alkyl radical attached to a sulfoxide radical of the formula: —S(O)— wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl, n-butylsulfinyl, sec-butylsulfinyl, iso-butylsulfinyl, t-butylsulfinyl, and the like.

The term “C<sub>1-6</sub> alkylsulfonamide” refers to the groups shown below:

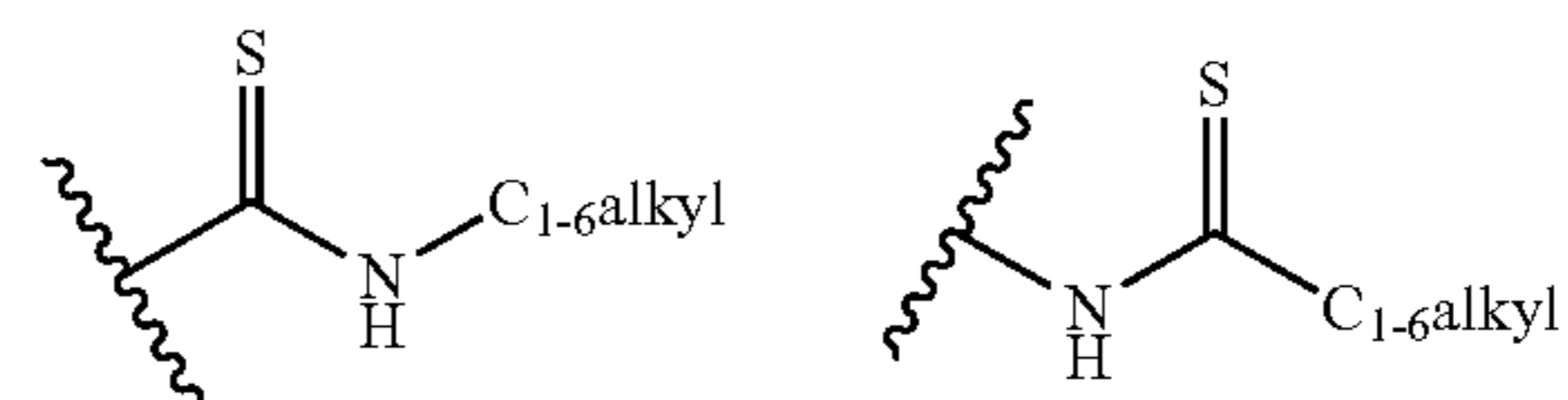


wherein C<sub>1-6</sub> alkyl has the same definition as described herein.

The term “C<sub>1-6</sub> alkylsulfonyl” denotes a C<sub>1-6</sub> alkyl radical attached to a sulfone radical of the formula: —S(O)<sub>2</sub>— wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, iso-butylsulfonyl, t-butylsulfonyl, and the like.

The term “C<sub>1-6</sub> alkylthio” denotes a C<sub>1-6</sub> alkyl radical attached to a sulfide of the formula: —S— wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfanyl (i.e., CH<sub>3</sub>S—), ethylsulfanyl, n-propylsulfanyl, iso-propylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, iso-butylsulfanyl, i-butylsulfanyl, and the like.

The term “C<sub>1-6</sub> alkylthiocarboxamide” denotes a thioamide of the following formulae:



wherein C<sub>1-4</sub> alkyl has the same definition as described herein.

The term “C<sub>1-6</sub> alkylureyl” denotes the group of the formula: —NC(O)N— wherein one or both of the nitrogens are substituted with the same or different C<sub>1-6</sub> alkyl group wherein alkyl has the same definition as described herein.



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Examples of an alkylureyl include, but are not limited to,  $\text{CH}_3\text{NHC(O)NH—}$ ,  $\text{NH}_2\text{C(O)NCH}_3\text{—}$ ,  $(\text{CH}_3)_2\text{NC(O)NH—}$ ,  $(\text{CH}_3)_2\text{NC(O)NCH}_3\text{—}$ ,  $\text{CH}_3\text{CH}_2\text{NHC(O)NH—}$ ,  $\text{CH}_3\text{CH}_2\text{NHC(O)NCH}_3\text{—}$ , and the like.

The term “ $\text{C}_{2-6}$  alkynyl” denotes a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term “alkynyl” includes di- and tri-yne.

The term “amino” denotes the group  $\text{—NH}_2$ .

The term “ $\text{C}_{1-4}$  alkylamino” denotes one alkyl radical attached to an amino radical wherein the alkyl radical has the same meaning as described herein. Some examples include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, sec-butylamino, isobutylamino, t-butylamino, and the like. Some embodiments are “ $\text{C}_{1-2}$  alkylamino.”

The term “aryl” denotes a 6- to 12-membered mono- or bicyclic ring system containing only ring carbons wherein at least one ring is aromatic. Examples include phenyl, 1,2,3,4-tetrahydro-naphthalen-1-yl, 1,2,3,4-tetrahydro-naphthalen-2-yl, 5,6,7,8-tetrahydro-naphthalen-1-yl, 5,6,7,8-tetrahydro-naphthalen-2-yl, indan-4-yl, naphtha-1-yl, naphtha-2-yl, and the like.

The term “arylalkyl” defines a  $\text{C}_1\text{—C}_4$  alkylene, such as  $\text{CH}_2\text{—}$ ,  $\text{CH}_2\text{CH}_2\text{—}$  and the like, which is further substituted with an aryl group. Examples of an “arylalkyl” include benzyl, phenethylene and the like.

The term “arylcarboxamido” denotes a single aryl group attached to the nitrogen of an amide group, wherein aryl has the same definition as found herein. The example is N-phenylcarboxamide.

The term “arylureyl” denotes the group  $\text{—NC(O)N—}$  where one of the nitrogens are substituted with an aryl.

The term “benzyl” denotes the group  $\text{—CH}_2\text{C}_6\text{H}_5$ .

The term “bicyclic” refers to two  $\text{C}_{4-7}$  cyclalkyl groups that share two ring carbons thus forming either a fused or bridged ring. Bicyclic examples include, but are not limited to, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, and the like.

The term “carbo- $\text{C}_{1-6}$ -alkoxy” refers to a  $\text{C}_{1-6}$  alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. Examples include, but are not limited to, carbomethoxy, carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-sec-butoxy, carbo-iso-butoxy, carbo-t-butoxy, carbo-n-pentoxy, carbo-iso-pentoxy, carbo-t-pentoxy, carbo-neo-pentoxy, carbo-n-hexyloxy, and the like.

The term “carboxamide” refers to the group  $\text{CONH}_2$ .

The term “carboxy” or “carboxyl” denotes the group  $\text{—CO}_2\text{H}$ ; also referred to as a carboxylic acid group.

The term “cyano” denotes the group  $\text{—CN}$ .

The term “ $\text{C}_{4-7}$  cycloalkenyl” denotes a non-aromatic ring radical containing 4 to 7 ring carbons and at least one double bond; some embodiments contain 4 to 6 carbons; some embodiments contain 4 to 5 carbons; some embodiments contain 4 carbons. Examples include cyclobutenyl, cyclopentenyl, cyclopentenyl, cyclohexenyl, and the like.

The term “ $\text{C}_{3-10}$  cycloalkyl” denotes a saturated monocyclic, bicyclic, or tricyclic ring radical containing 3 to 8 carbons; some embodiments contain 3 to 7 carbons; some embodiments contain 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 5 to 7 carbons; some embodiments contain 3 to 4 carbons.

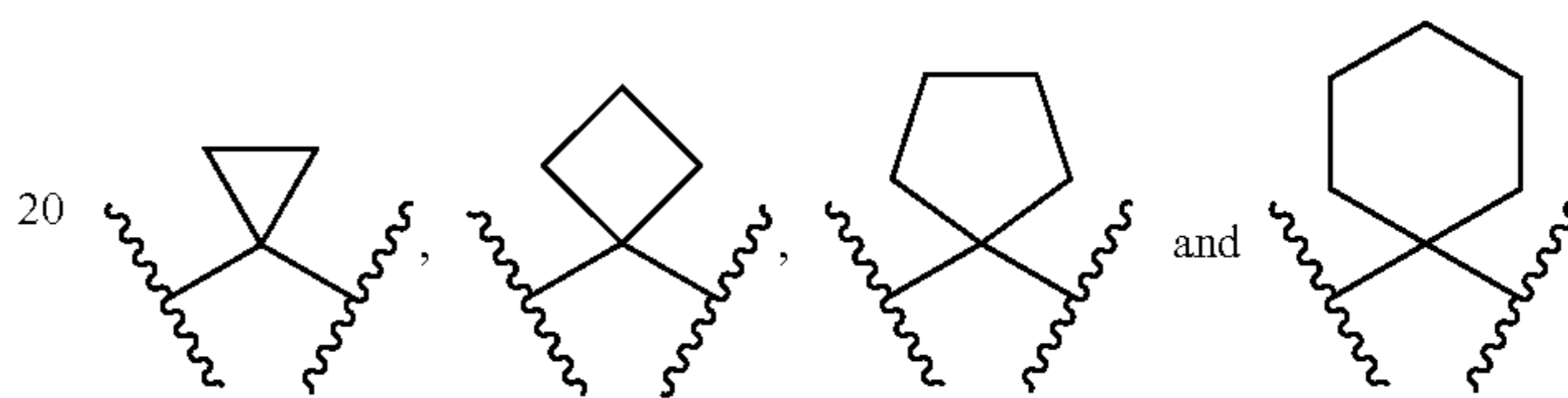
## 12

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, bicyclo[2.2.1]heptyl, and the like.

The term “ $\text{C}_{3-7}$  cycloalkylcarbonyl” denotes a  $\text{C}_{3-7}$  cycloalkyl group, as described herein, bonded to the carbon of a carbonyl group (i.e.,  $\text{—C(=O)—}$ ). Examples of the  $\text{C}_{3-7}$  cycloalkylcarbonyl group include, but are not limited to, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, and the like.

The term “ $\text{C}_{3-6}$  cycloalkylene” refers to a divalent cycloalkyl radical, where cycloalkyl is as defined herein, containing 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. In some embodiments, the  $\text{C}_{3-6}$  cycloalkylene group has the two bonding groups on the same ring carbon, for example:

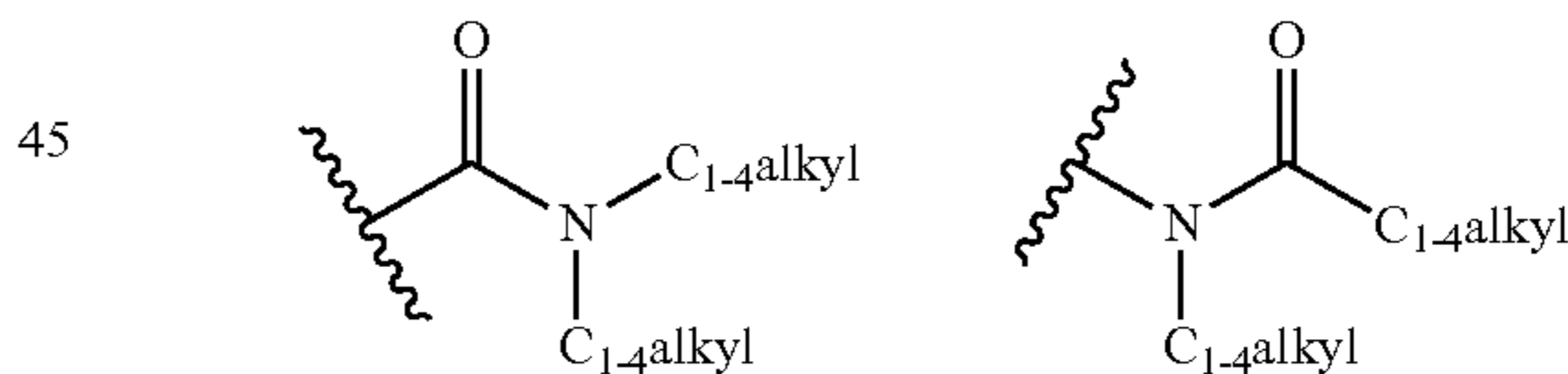
1,1-cyclopropyl



In some embodiments, the  $\text{C}_{3-6}$  cycloalkylene group has the two bonding groups on different ring carbons. It is understood that when the two groups of the  $\text{C}_{3-6}$  cycloalkylene group are on different ring carbons they may be cis or trans or mixtures thereof with respect to each other.

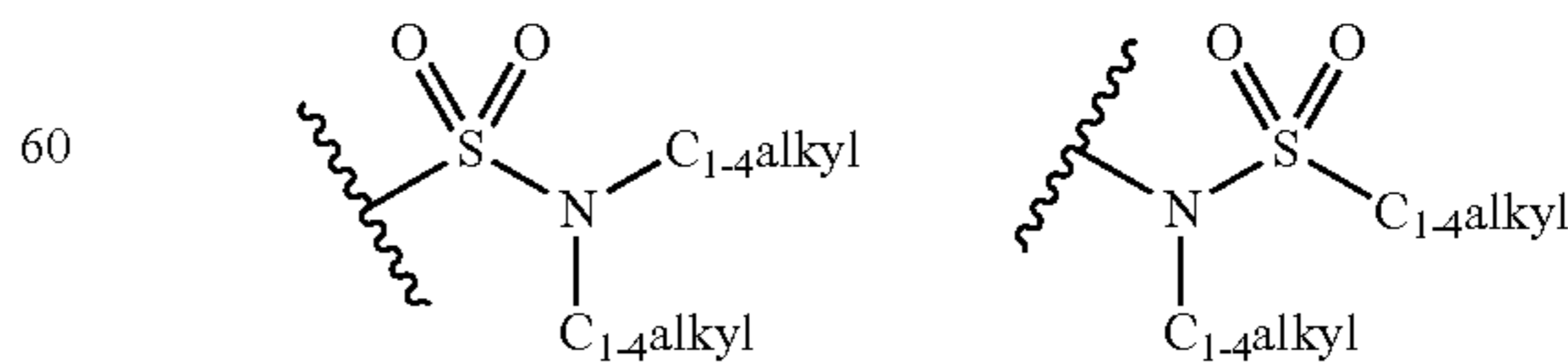
The term “ $\text{C}_{2-8}$  dialkylamino” denotes an amino substituted with two of the same or different  $\text{C}_{1-4}$  alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but are not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like. Some embodiments are “ $\text{C}_{2-4}$  dialkylamino.”

The term “ $\text{C}_{2-8}$  dialkylcarboxamido” or “ $\text{C}_{2-8}$  dialkylcarboxamide” denotes two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A  $\text{C}_{2-8}$  dialkylcarboxamido may be represented by the following groups:



wherein  $\text{C}_{1-4}$  has the same definition as described herein. Examples of a dialkylcarboxamide include, but are not limited to, N,N-dimethylcarboxamide, N-methyl-N-ethylcarboxamide, N,N-diethylcarboxamide, N-methyl-N-isopropylcarboxamide, and the like.

The term “ $\text{C}_{2-8}$  dialkylsulfonamide” refers to one of the following groups shown below:



wherein  $\text{C}_{1-4}$  has the same definition as described herein, for example but are not limited to, methyl, ethyl, n-propyl, isopropyl, and the like.







## 15

One aspect of the present invention pertains to certain compounds as shown in Formula (Ia) wherein:

$R^{4a}$  is H,  $C_{1-12}$  acyl, carbo- $C_{1-12}$ -alkoxy, or  $C(=O)O$ -aryl, wherein the  $C_{1-12}$  acyl, carbo- $C_{1-12}$ -alkoxy, and  $-C(=O)O$ -aryl is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-5}$  acyloxy,  $C_{1-6}$  alkylcarboxamide, amino,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino,  $C_{1-6}$  alkylimino,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  alkylthio, halogen, nitro, and phenyl.

In some embodiments, the present invention pertains to compounds of Formula (Ia), as described herein, that are isolated.

In some embodiments, the present invention pertains to compounds of Formula (Ia), as described herein, that are isolated outside the body of an individual.

In some embodiments, the present invention pertains to compounds of Formula (Ia), as described herein, that are isolated outside the body of an individual. In some embodiments, isolated compounds of Formula (Ia) have a purity of greater than about 0.1%, about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 98%, or about 99%.

In some embodiments, the present invention pertains to compounds of Formula (Ia), as described herein, or a pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g.,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ , V, W, Q, Z, etc.) contained within the generic chemical formulae described herein [e.g. (Ia), (Ic), (Ie), etc.] are specifically embraced by the present invention just as if they were explicitly disclosed, to the extent that such combinations embrace compounds that result in stable compounds (ie., compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each of such subcombination of chemical groups and subcombination of uses and medical indications were explicitly disclosed herein.

As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

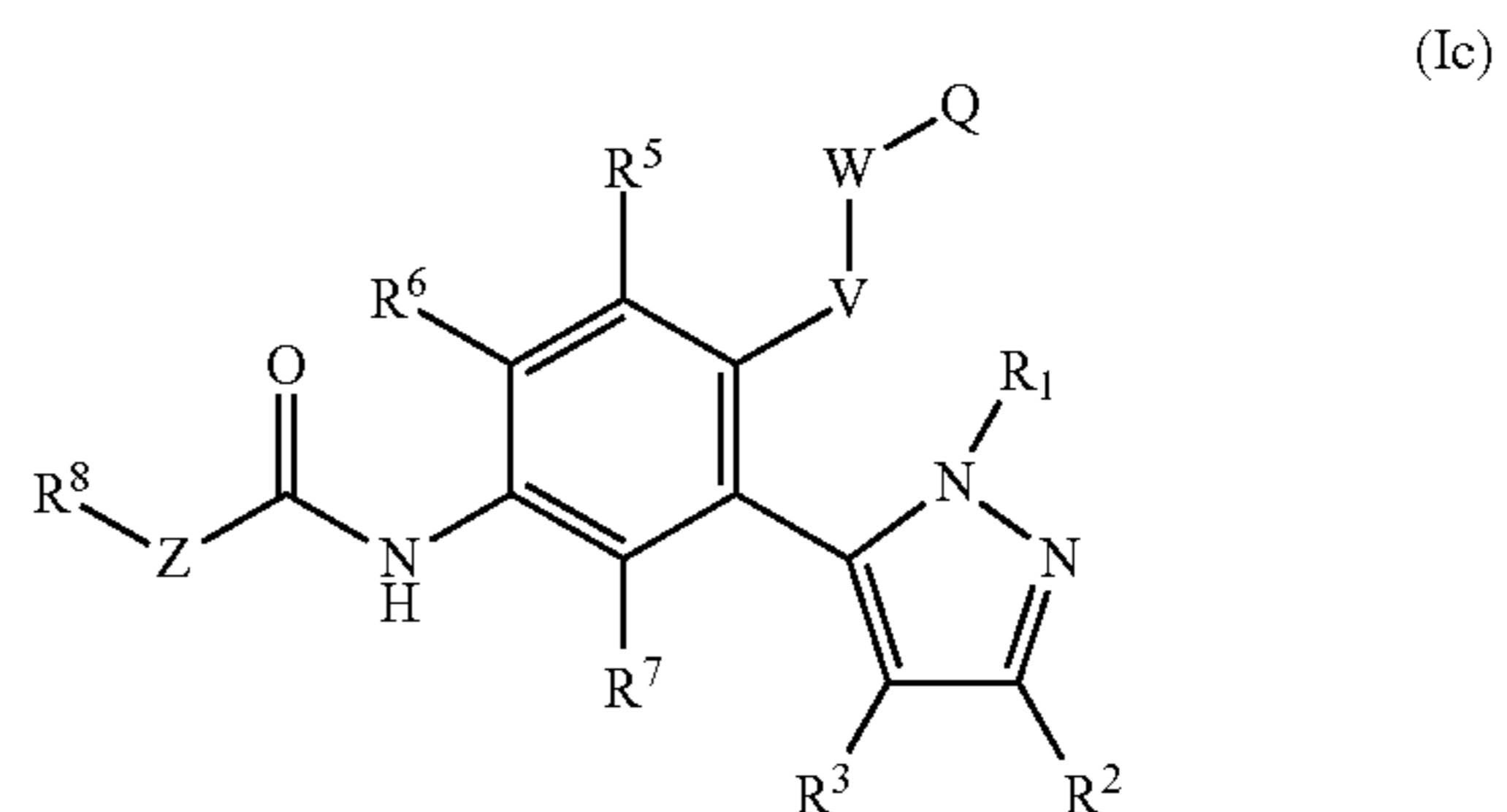
## 16

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers, and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

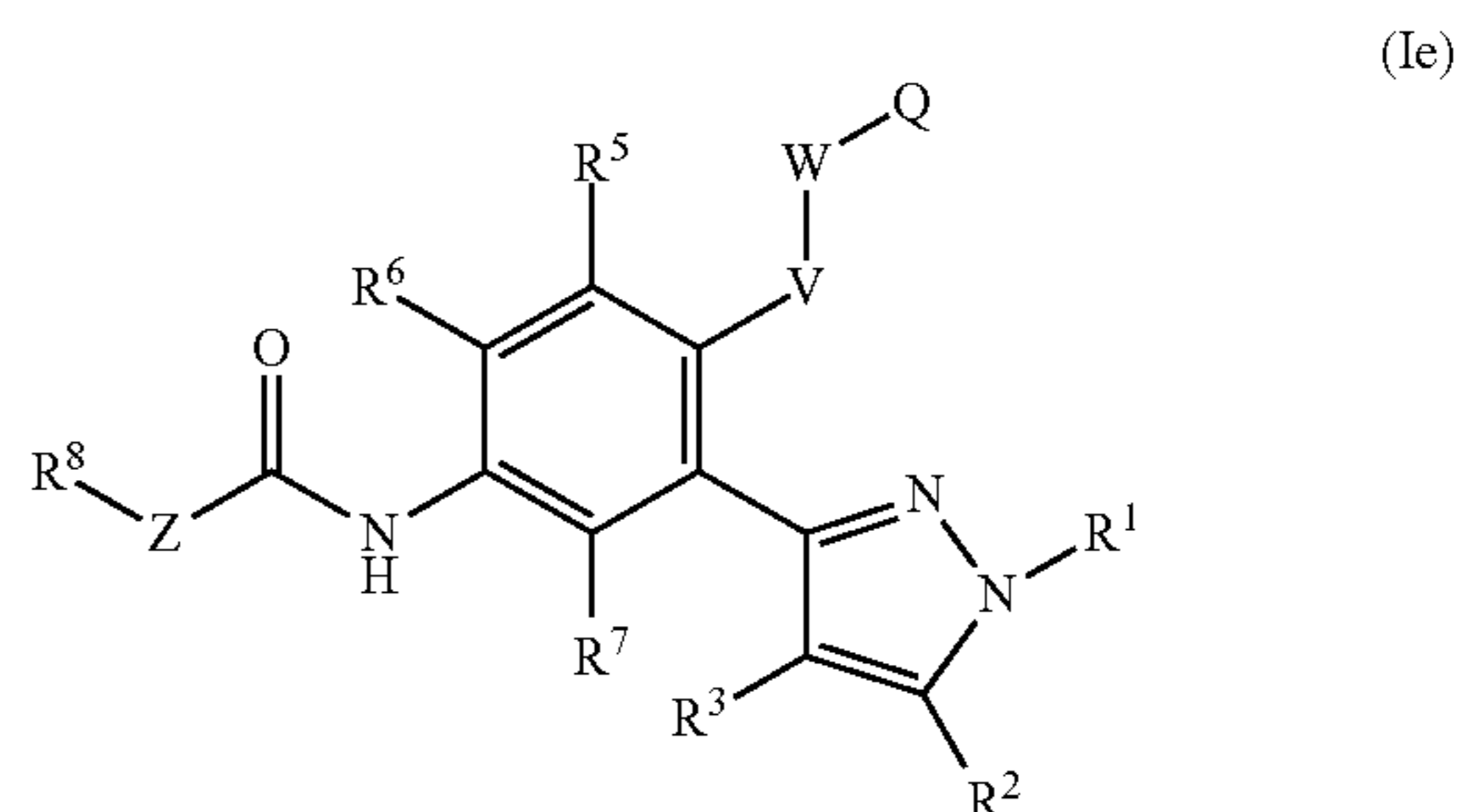
It is understood and appreciated that compounds of the present invention may have one or more chiral centers, and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including but not limited, to racemates. Accordingly, some embodiments of the present invention pertain to compounds of the present invention that are R enantiomers. Further, some embodiments of the present invention pertain to compounds of the present invention that are S enantiomers. In examples where more than one chiral center is present, then, some embodiments of the present invention include compounds that are RS or SR enantiomers. In further embodiments, compounds of the present invention are RR or SS enantiomers. It is understood that compounds of the present invention are intended to represent all possible individual enantiomers and mixtures thereof just as if each had been individually named with the structure provided, unless stated or shown otherwise.

Some embodiments of the present invention pertain to certain compounds as shown in the following Formula (Ic):



wherein each variable in Formula (Ic) has the same meaning as described herein, supra and infra.

Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ie):



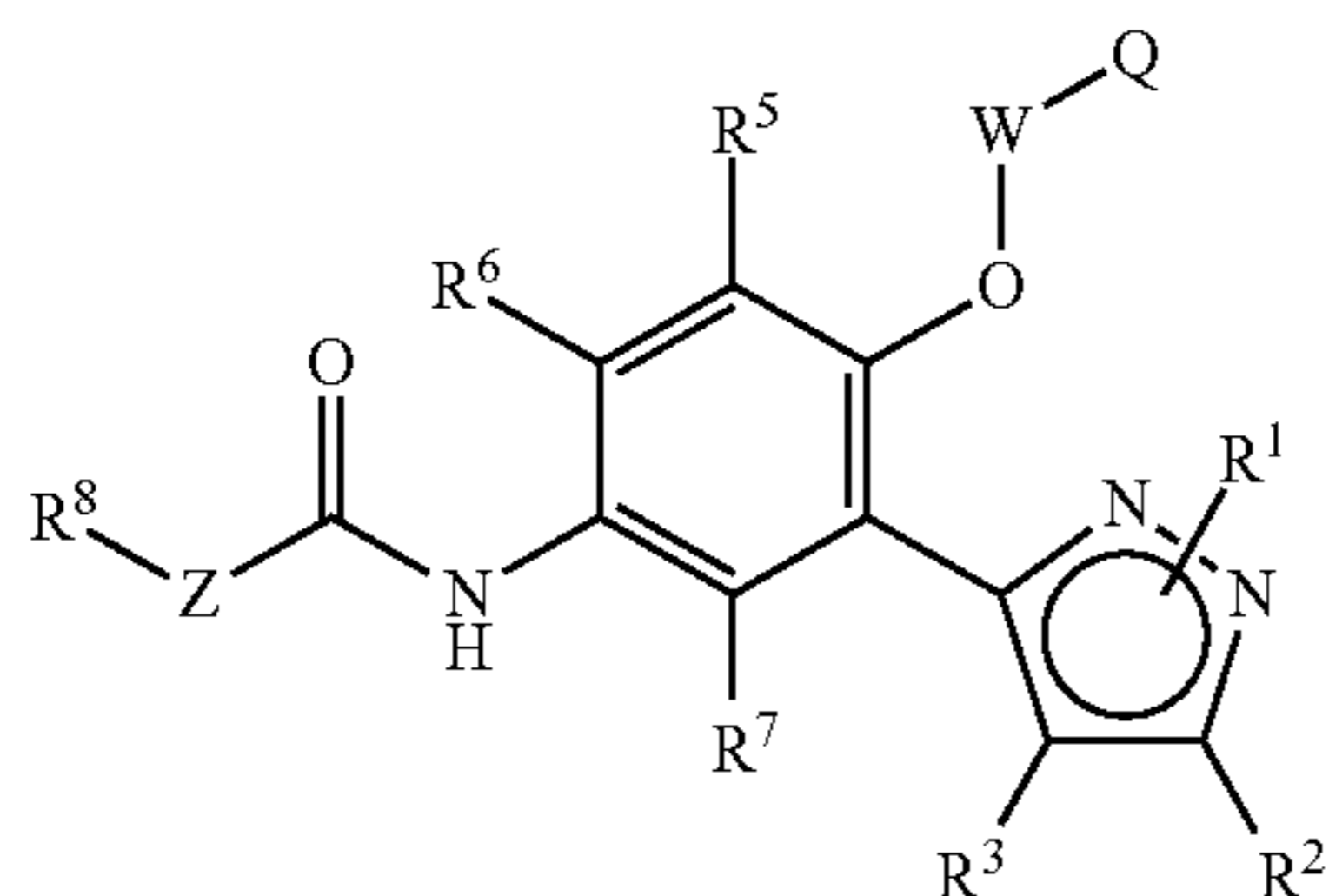
wherein each variable in Formula (Ie) has the same meaning as described herein, supra and infra.

In some embodiments, V is O.



17

Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ig):



wherein each variable in Formula (Ig) has the same meaning as described herein, supra and infra

(Ig)

5

wherein each variable in Formula (Ik) has the same meaning as described herein, supra and infra.

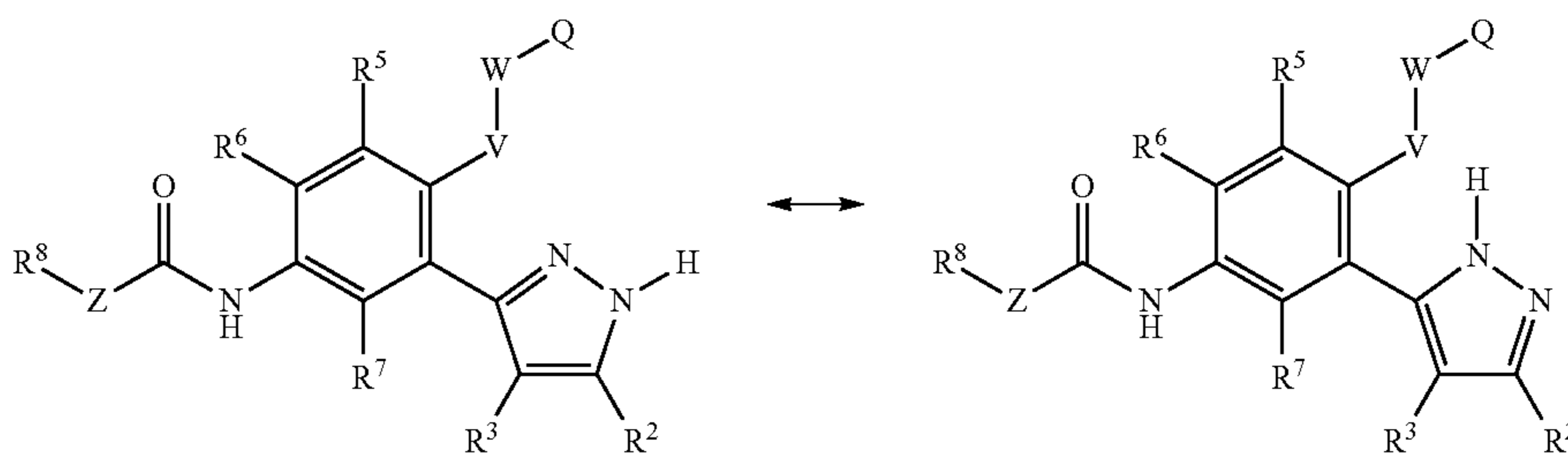
In some embodiments, Z is  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ .

In some embodiments,  $\text{R}^1$  is  $\text{C}_{1-4}$  alkyl.

In some embodiments,  $\text{R}^1$  is  $-\text{CH}_3$ .

In some embodiments,  $\text{R}_1$  is H.

It is understood when  $\text{R}_1$  is H that tautomers are possible. It is well understood and appreciated in the art that pyrazoles can exist in various tautomeric forms. Two possible tautomeric forms are illustrated below:



(Im)

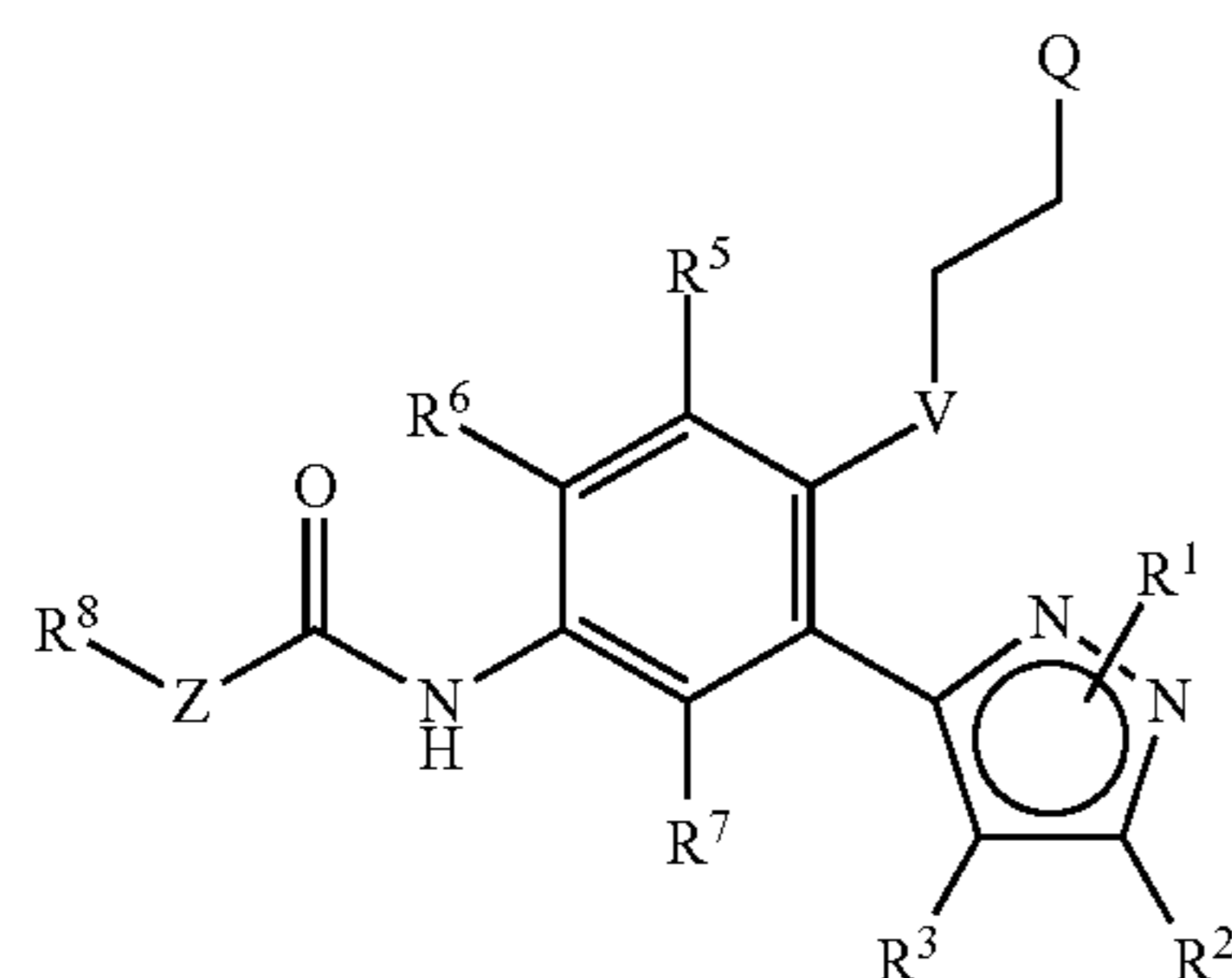
(In)

In some embodiments, W is  $-\text{CH}_2\text{CH}_2-$  optionally substituted with 1 to 2 substituents selected independently from the group consisting of  $\text{C}_{1-3}$  alkyl and oxo.

In some embodiments, W is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2-$ , or  $-\text{CH}_2\text{C}(=\text{O})-$ .

In some embodiments; W is  $-\text{CH}_2\text{CH}_2-$ .

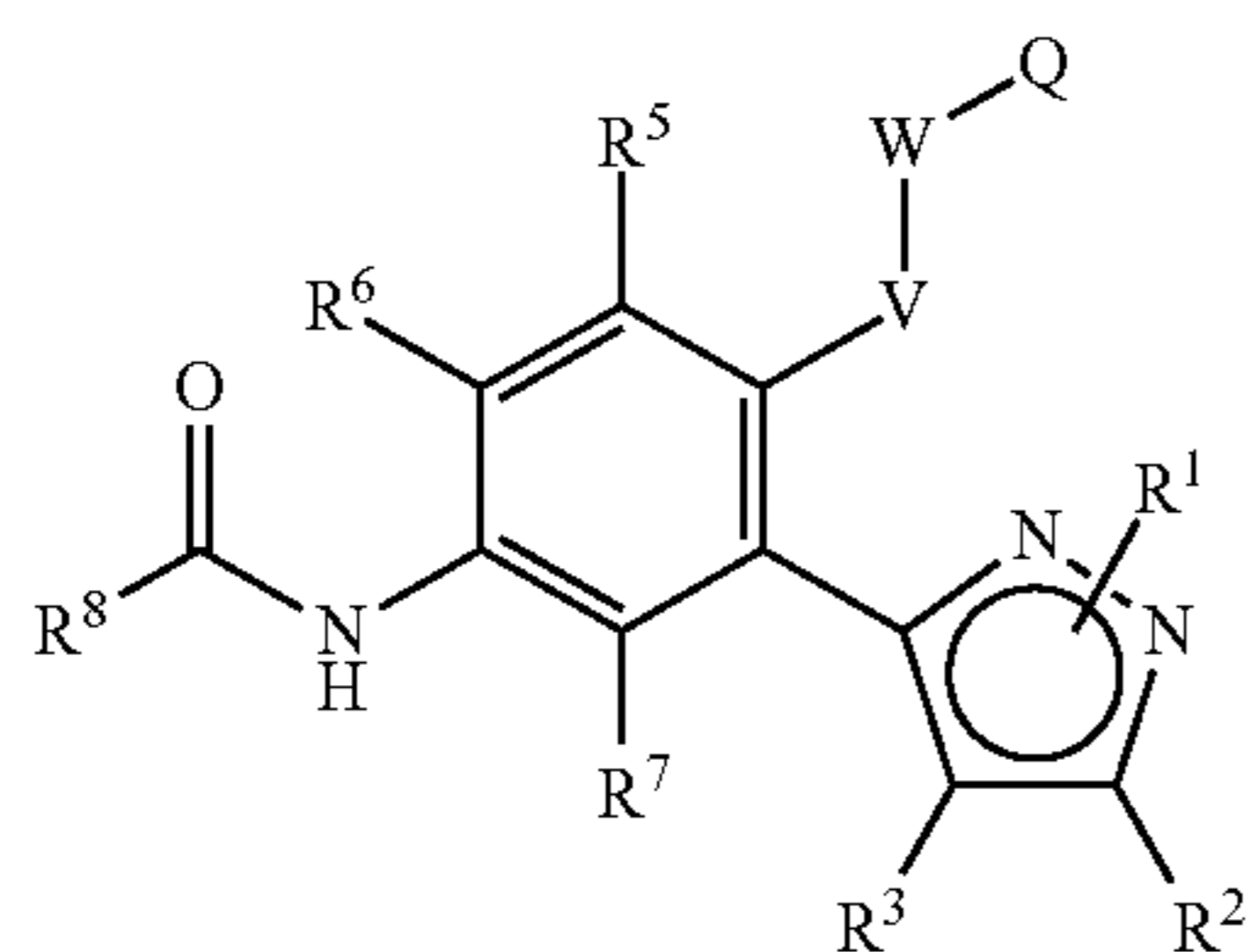
Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ii):



wherein each variable in Formula (Ii) has the same meaning as described herein, supra and infra.

In some embodiments, Z is absent.

Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ik):



(Ik)

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It is further understood that tautomeric forms can also have corresponding nomenclature for each represented tautomer, for example, the pyrazol-3-yl groups in Formula (Im) and Formula (In) can be represented by the general chemical names 1H-pyrazol-3-yl and 2H-pyrazol-3-yl respectively. Therefore, the present invention includes all tautomers and the various nomenclature designations.

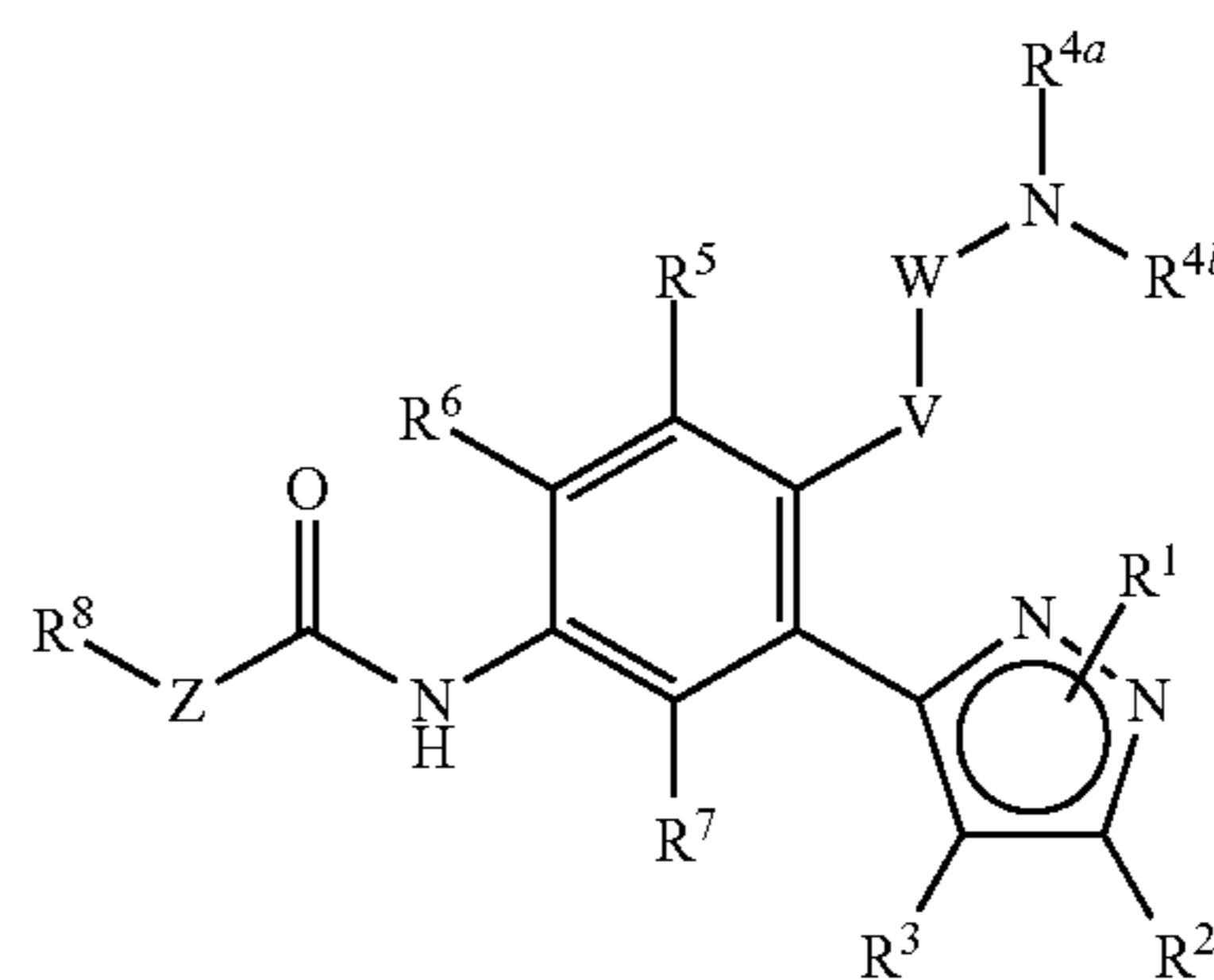
In some embodiments,  $\text{R}^2$  is H.

In some embodiments,  $\text{R}^3$  is H or halogen.

In some embodiments,  $\text{R}^3$  is H, Cl, or Br.

In some embodiments, Q is  $-\text{NR}^4\text{R}^{4b}$ .

Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ip):



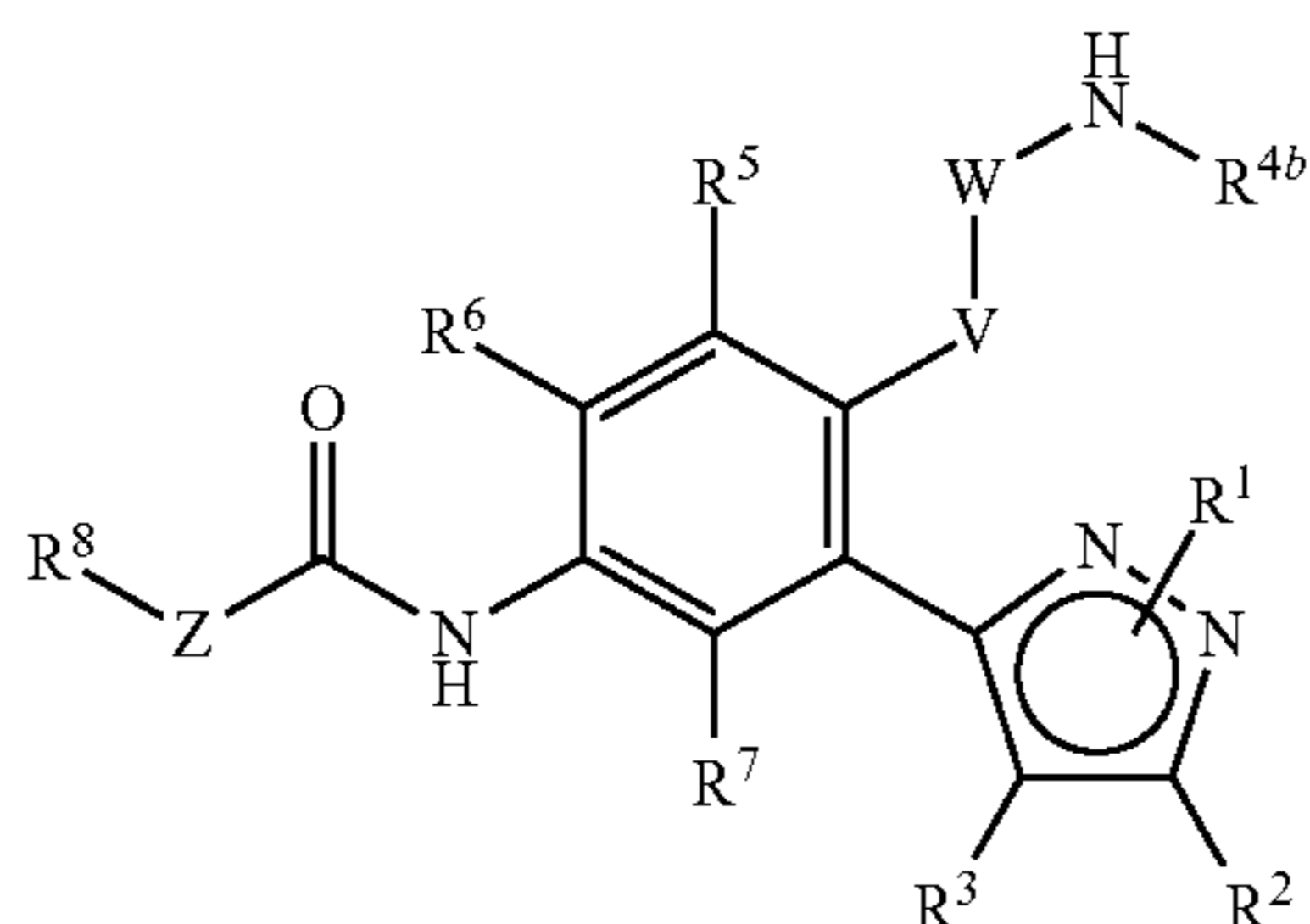
(Ip)

wherein each variable in Formula (Ip) has the same meaning as described herein, supra and infra.

In some embodiments,  $\text{R}^{4a}$  is H,

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Some embodiments of the present invention pertain to certain compounds as shown in Formula (Ir):



(Ir) 5

wherein each variable in Formula (Ir) has the same meaning as described herein, supra and infra.

In some embodiments,  $R^{4a}$  is  $C_{1-12}$  acyl, or carbo- $C_{1-12}$ -alkoxy each optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-5}$  acyloxy,  $C_{1-6}$  alkylcarboxamide, amino,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino,  $C_{1-4}$  alkylimino,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  alkylthio, halogen, nitro, and phenyl.

In some embodiments,  $R^{4b}$  is  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{1-6}$  haloalkyl, heterocyclyl, or heteroaryl, and each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-4}$  alkoxy,  $C_{1-8}$  alkyl,  $C_{1-4}$  alkylsulfonyl, amino, carbo- $C_{1-6}$ -alkoxy, carboxamide, cyano, hydroxyl, imino, and phenyl.

In some embodiments,

$R^{4a}$  is H; and

$R^{4b}$  is  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{1-6}$  haloalkyl, heterocyclyl, or heteroaryl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-4}$  alkoxy,  $C_{1-8}$  alkyl,  $C_{1-4}$  alkylsulfonyl, amino, carbo- $C_{1-6}$ -alkoxy, carboxamide, cyano, hydroxyl, imino, and phenyl.

In some embodiments,

$R^{4a}$  is H; and

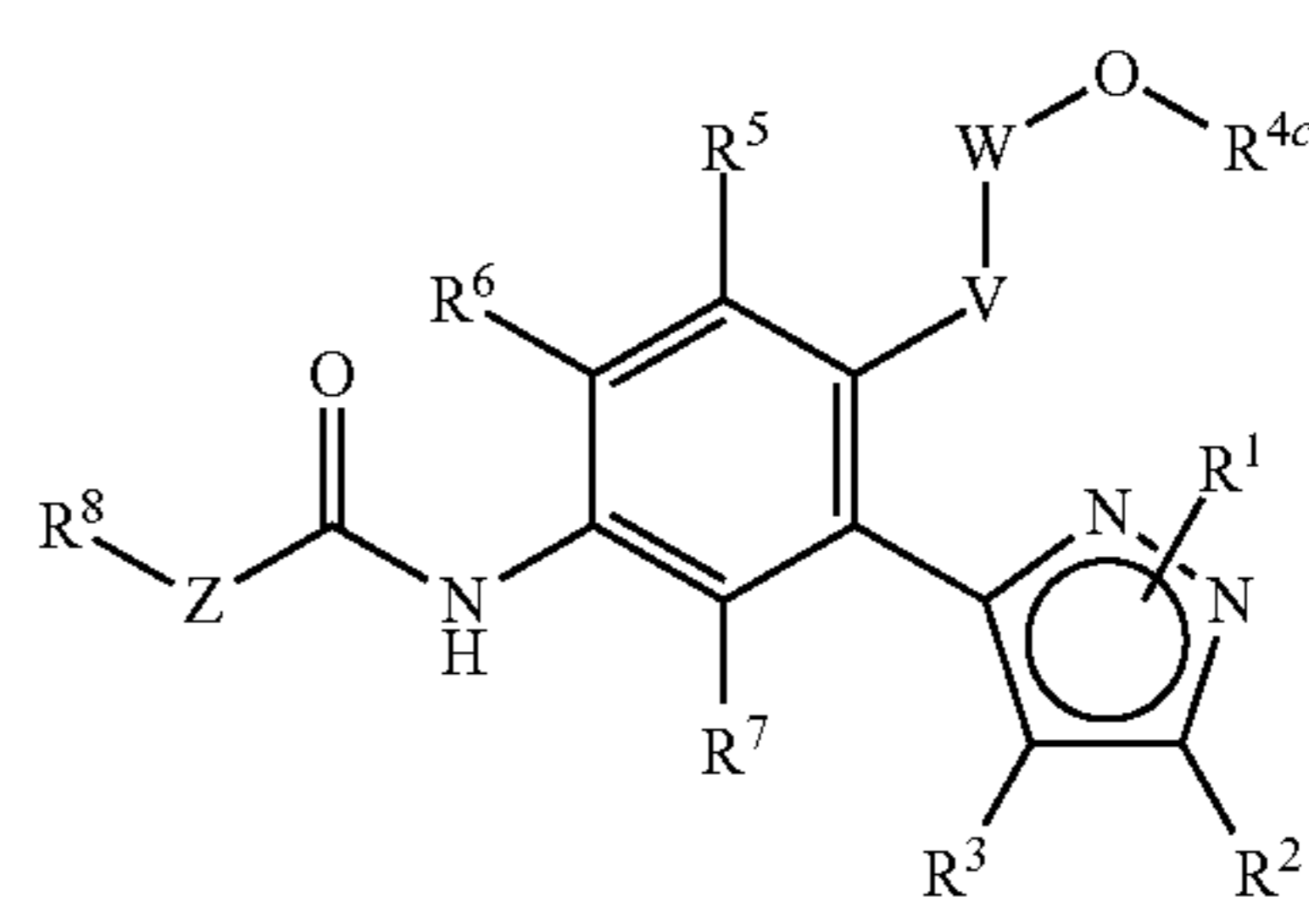
$R^{4b}$  is  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{1-6}$  haloalkyl, heterocyclyl, or heteroaryl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $-OCH_3$ ,  $-OCH_2CH_3$ ,  $-CH_3$ ,  $-S(=O)_2CH_3$ , amino,  $-C(=O)OC(CH_3)_3$ ,  $-C(=O)OCH_2CH_3$ ,  $-C(=O)NH_2$ , cyano, hydroxyl, imino, and phenyl.

In some embodiments, Q is selected from the group consisting of  $-NHCH_2CH_2CF_3$ ,  $-NHCH_2CH_2OH$ ,  $-NHCH_2CH_2S(=O)_2CH_3$ ,  $-NHCH_2CH_3$ ,  $-NHCH_2CF_2CH_3$ ,  $-NHCH_2CH_2OCH_3$ ,  $-NHCH_2CH_2CN$ ,  $-NHC(CH_3)CH_2CH_3$ ,  $-NH$ -tetrahydro-pyran-4-yl, tetrahydro-pyran-4-ylamino,  $-NHC(=NH)CH_3$ , piperidin-4-ylamino, 1-tert-butoxycarbonyl-piperidin-4-ylamino,  $-NHCH_2CH_2CH_2CH_3$ , 1-methylpiperidin-4-ylamino,  $-NHCH_2C(=O)NH_2$ ,  $-NHCH(CH_3)_2$ ,  $-NHCH_2CN$ ,  $-NH$ -benzyl,  $-NHCH_2CH_2F$ , 1-ethoxycarbonyl-piperidin-4-ylamino, 1H-[1,2,4]triazol-3-ylamino,  $-NHC(=NH)NH_2$ ,  $-NH$ -cyclopropyl, thiazol-2-ylamino, 6-oxo-piperidin-3-ylamino, 1H-tetrazol-5-ylamino,  $-NHCH_2CH_2OCH_2CH_3$ ,  $-NHCH_2CH_2OCH(CH_3)_2$ ,  $-NHC(CH_3)_3$ ,  $-NHCH_2CH_2CH_3$ ,  $-NHCH(CH_3)_2$ , and  $-NHCH_2CH_2CH_2CN$ .

In some embodiments, Q is  $-OR^{4c}$ .

## 20

Some embodiments of the present invention pertain to certain compounds as shown in Formula (It):



(It)

wherein each variable in Formula (It) has the same meaning as described herein, supra and infra.

In some embodiments;  $R^{4c}$  is H.

In some embodiments,  $R^{4c}$  is  $C_{1-6}$  alkyl,  $C_{1-12}$  acyl, aryl,  $C_{3-7}$  cycloalkyl,  $C_{2-6}$  haloalkyl, heterocyclyl, or heteroaryl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of  $C_{1-5}$  acyl,  $C_{1-5}$  acyloxy,  $C_{2-6}$  alkenyl,  $C_{1-4}$  alkoxy,  $C_{1-8}$  alkyl,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino,  $C_{1-4}$  alkylcarboxamide,  $C_{2-6}$  alkynyl,  $C_{1-4}$  alkylsulfonamide,  $C_{1-4}$  alkylsulfinyl,  $C_{1-4}$  alkylsulfonyl,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkylureyl, amino,  $C_{1-6}$  alkylamino,  $C_{2-8}$  dialkylamino, carbo- $C_{1-6}$ -alkoxy, carboxamide, carboxy, cyano,  $C_{3-6}$  cycloalkyl,  $C_{2-6}$  dialkylcarboxamide, halogen,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  haloalkylsulfinyl,  $C_{1-4}$  haloalkylsulfonyl,  $C_{1-4}$  haloalkylthio, heterocyclyl, hydroxyl, imino, nitro, sulfonamide and phenyl.

In some embodiments,  $R^{4c}$  is  $C_{1-6}$  alkyl,  $C_{1-12}$  acyl, heterocyclyl, or heteroaryl each optionally substituted with 1 to 2 substituents selected independently from the group consisting of  $C_{1-8}$  alkyl,  $C_{2-8}$  dialkylamino, and heterocyclyl.

In some embodiments, Q is  $-OH$ ,  $OCH_3$ ,  $-OC(=O)CH_2$ -morpholin-4-yl,  $-OC(=O)CH_2N(CH_3)_2$ ,  $OC(=O)CH_2$ -pyrrolidin-1-yl, or 1-methyl-piperidin-4-yloxy.

In some embodiments,  $R^5$  is H.

In some embodiments,  $R^6$  is H.

In some embodiments,  $R^7$  is H.

In some embodiments,  $R^5$ ,  $R^6$  and  $R^7$  are each H.

In some embodiments,  $R^8$  is aryl,  $C_{3-10}$  cycloalkyl, or heteroaryl each optionally substituted with substituents selected independently from the group consisting of  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl, cyano, halogen,  $C_{1-6}$  haloalkoxy, and  $C_{1-6}$  haloalkyl.

In some embodiments,  $R^8$  is phenyl, cyclopropyl, or heteroaryl each optionally substituted with substituents selected independently from the group consisting of  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl, cyano, halogen,  $C_{1-6}$  haloalkoxy, and  $C_{1-6}$  haloalkyl.

In some embodiments,  $R^8$  is phenyl, cyclopropyl, or isoxazolyl each optionally substituted with substituents selected independently from the group consisting of  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl, cyano, halogen,  $C_{1-6}$  haloalkoxy, and  $C_{1-6}$  haloalkyl.

In some embodiments,  $R^8$  is phenyl, cyclopropyl, or isoxazolyl and each optionally substituted with substituents selected independently from the group consisting of  $CH_3$ , Br,  $CF_3$ ,  $-OCH_3$ , Cl, F,  $-OCF_3$ , and cyano.

In some embodiments,  $R^8$  is selected from the group consisting of 5-methyl-isoxazol-4-yl, 3-bromo-phenyl, 3-trifluoromethyl-phenyl, 3-methoxy-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, phenyl, 2-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 2-trifluo-



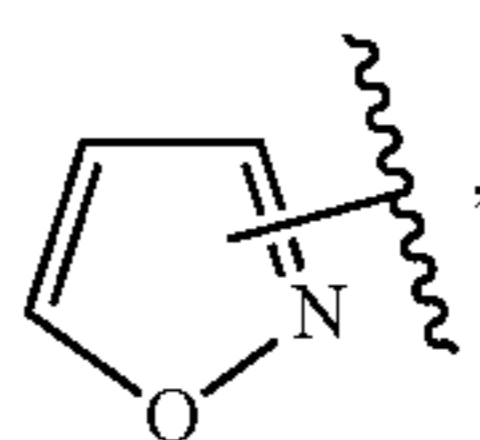
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romethyl-phenyl, 4-trifluoromethyl-phenyl, 4-bromo-phenyl, 3-cyano-phenyl, and cyclopropyl.

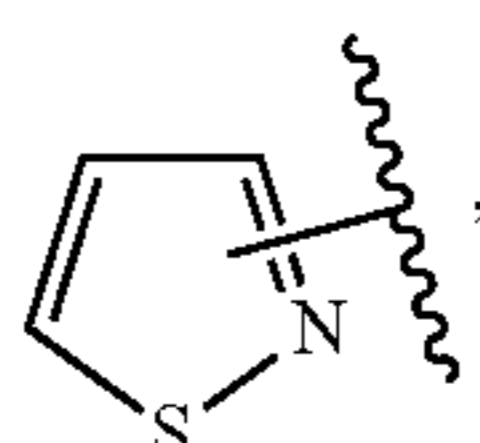
In some embodiments, R<sup>8</sup> is heteroaryl.

In some embodiments, heteroaryl is a 5-membered heteroaryl, for example, a 5-membered heteroaryl as shown in TABLE 1:

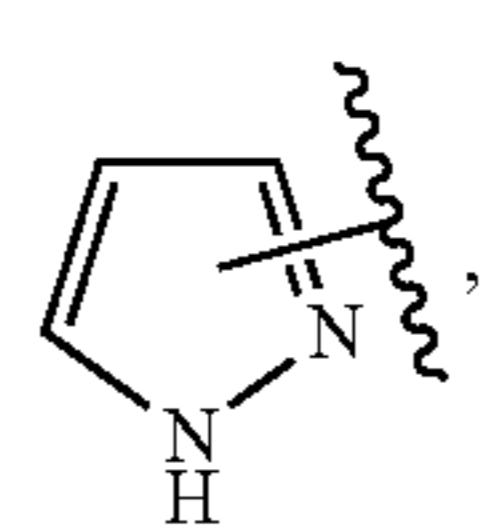
TABLE 1



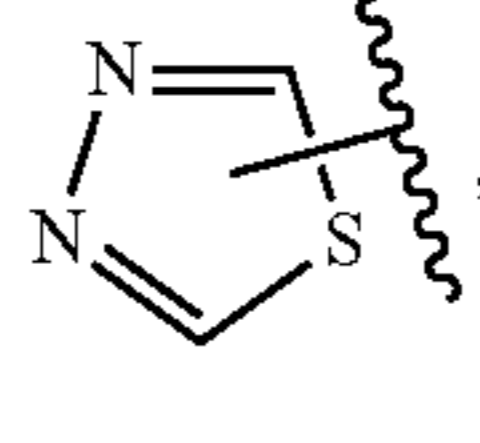
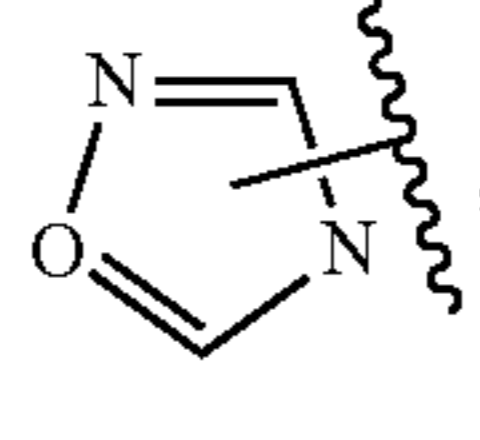
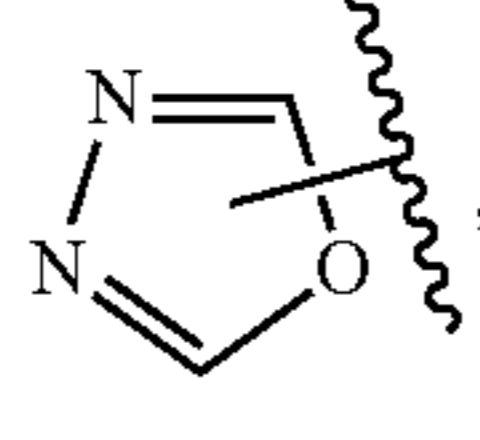
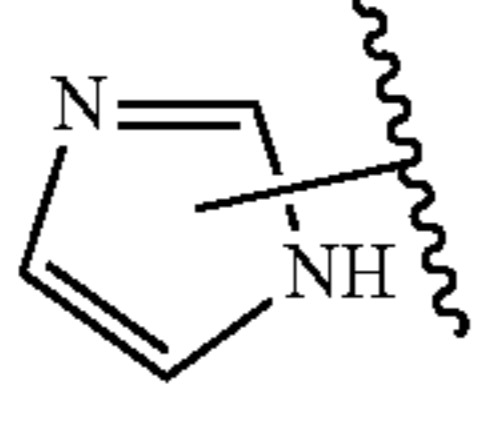
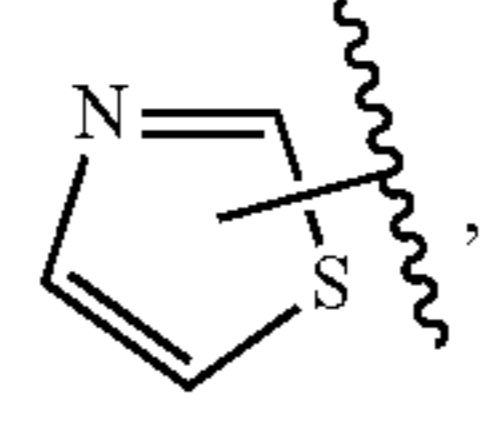
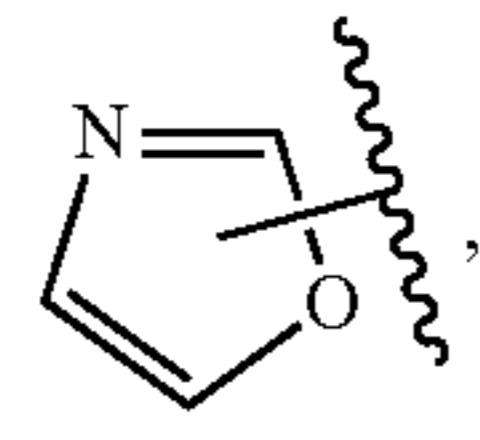
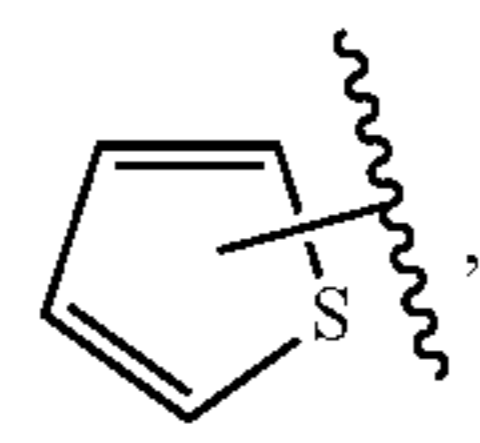
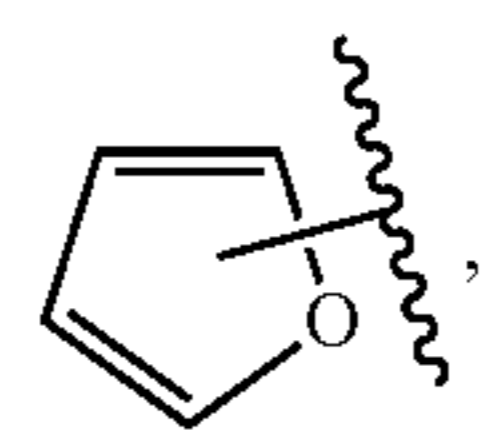
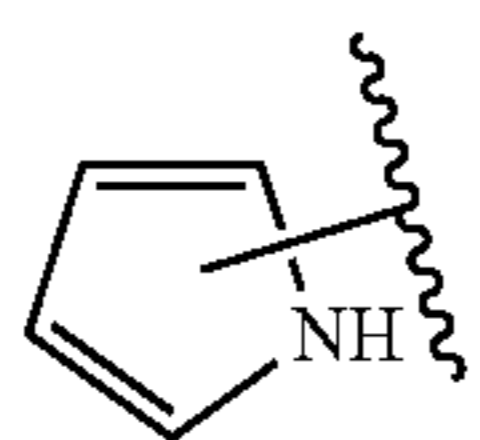
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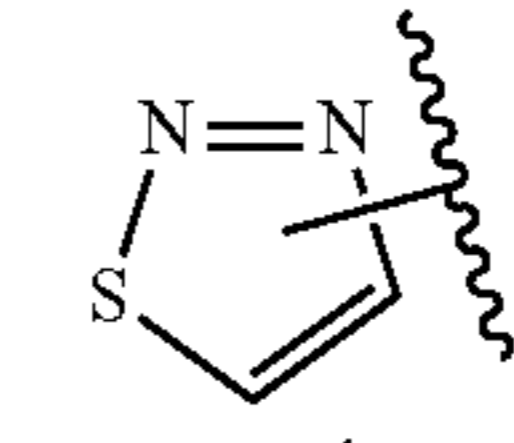
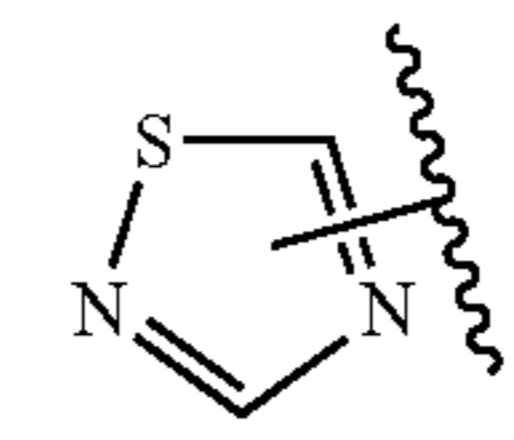
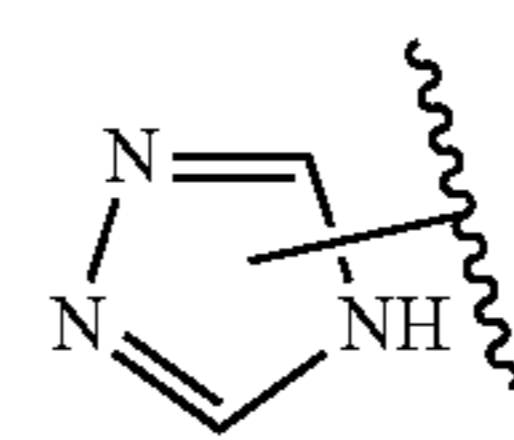
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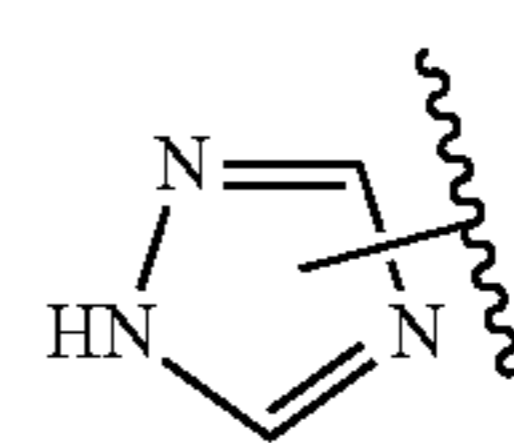
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TABLE 1-continued



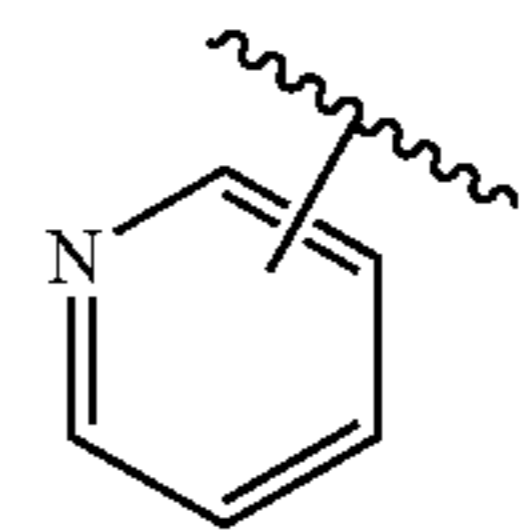
and



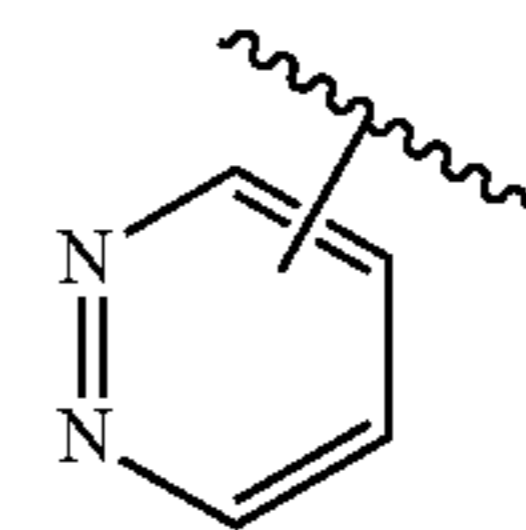
wherein the 5-membered heteroaryl is bonded at any available position of the ring, for example, a imidazolyl ring can be bonded at one of the ring nitrogens (i.e., imidazol-1-yl group) or at one of the ring carbons (i.e., imidazol-2-yl, imidazol-4-yl or imiadazol-5-yl group).

In some embodiments, heteroaryl is a 6-membered heteroaryl, for example, a 6-membered heteroaryl as shown in TABLE 2:

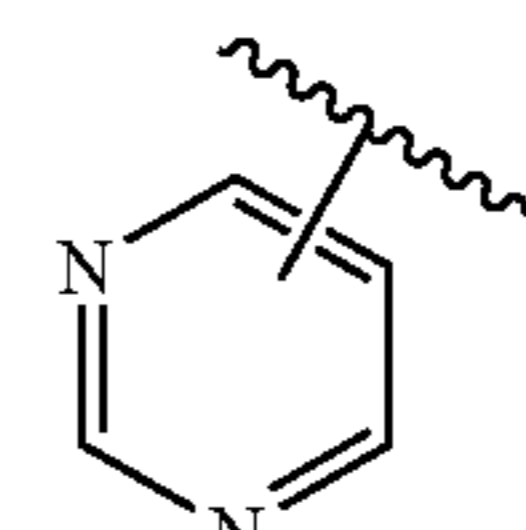
TABLE 2



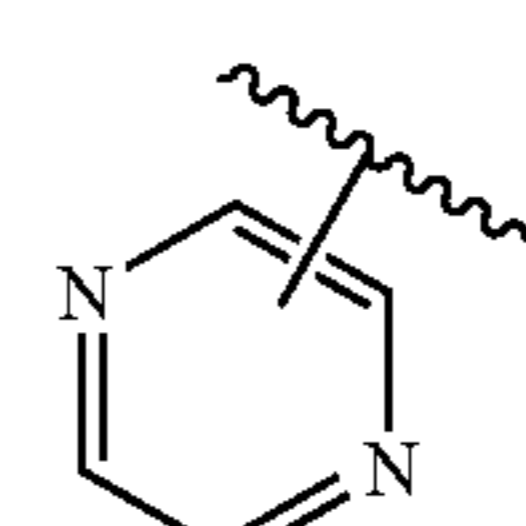
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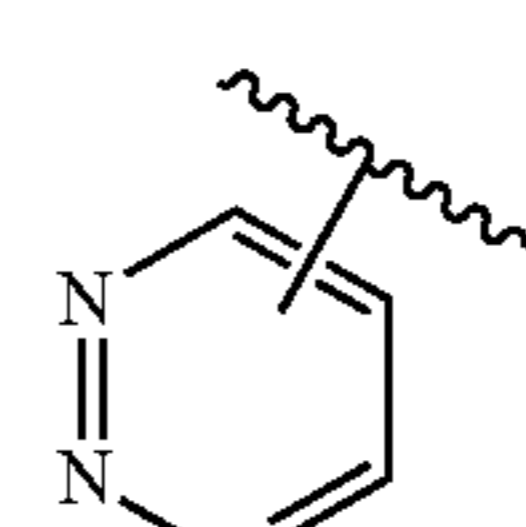
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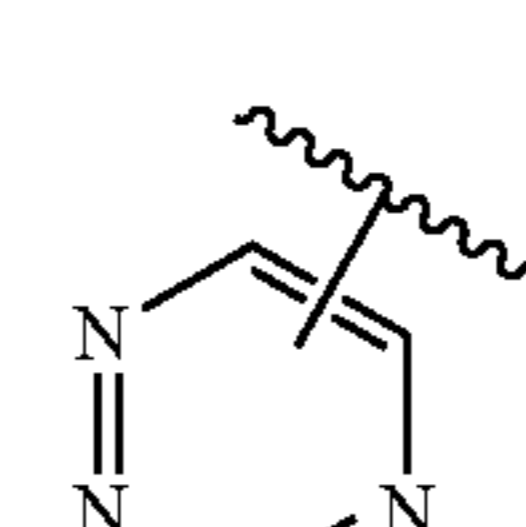
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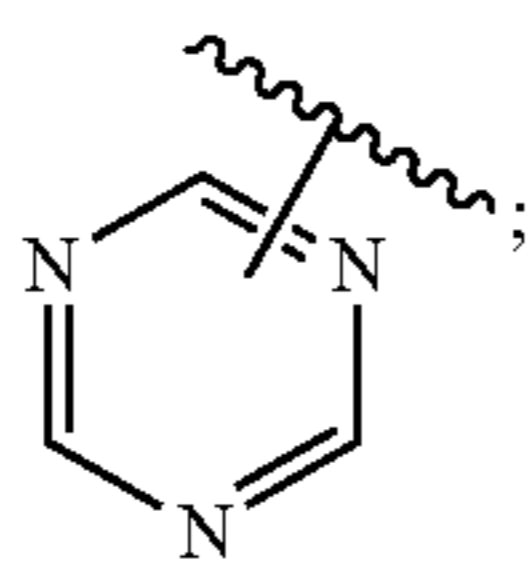


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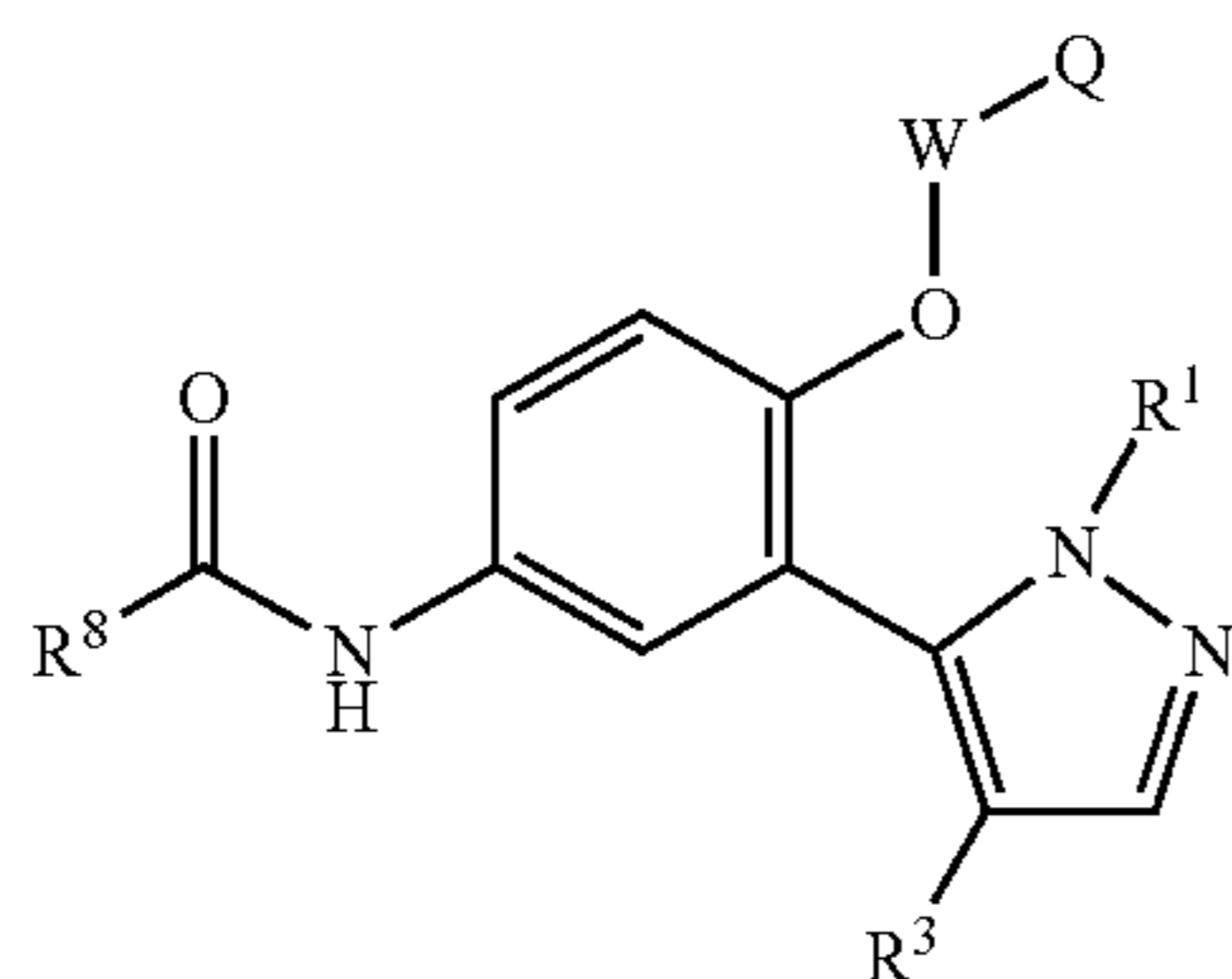
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TABLE 2-continued

and



wherein the heteroaryl group is bonded at any ring carbon.  
Some embodiments of the present invention pertain to certain compounds of Formula (IIa):



wherein:

W is  $-\text{CH}_2\text{CH}_2-$  optionally substituted with 1 to 2 substituents selected independently from the group consisting of  $\text{C}_{1-3}$  alkyl and oxo;

Q is selected from the group consisting of  $-\text{NHCH}_2\text{CH}_2\text{CF}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,  $-\text{NHCH}_2\text{CH}_2\text{S}(\text{=O})_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CF}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{CN}$ ,  $-\text{NHC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ ,  $-\text{NH-tetrahydro-pyran-4-yl}$ , tetrahydro-pyran-4-ylamino,  $-\text{NHC}(\text{=NH})\text{CH}_3$ , piperidin-4-ylamino, 1-tert-butoxycarbonyl-piperidin-4-ylamino,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ , 1-methyl-piperidin-4-ylamino,  $-\text{NHCH}_2\text{C}(\text{=O})\text{NH}_2$ ,  $-\text{NHCH}(\text{CH}_3)_2$ ,  $-\text{NHCH}_2\text{CN}$ ,  $-\text{NH-benzyl}$ ,  $-\text{NHCH}_2\text{CH}_2\text{F}$ , 1-ethoxycarbonyl-piperidin-4-ylamino, 1H-[1,2,4]triazol-3-ylamino,  $-\text{NHC}(\text{=NH})\text{NH}_2$ ,  $-\text{NH-cyclopropyl}$ , thiazol-2-ylamino, 6-oxo-piperidin-3-ylamino, 1H-tetrazol-5-ylamino,  $-\text{NHCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$ ,  $-\text{NHC}(\text{CH}_3)_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{NHCH}(\text{CH}_3)_2$ , and  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CN}$ ;

$\text{R}^1$  is  $\text{C}_{1-6}$  alkyl;

$\text{R}^3$  is H or halogen; and

$\text{R}^8$  is selected from the group consisting of 5-methyl-isoxazol-4-yl, 3-bromo-phenyl, 3-trifluoromethyl-phenyl, 3-methoxy-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, phenyl, 2-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-bromo-phenyl, 3-cyano-phenyl, and cyclopropyl.

Some embodiments of the present invention pertain to certain compounds of Formula (IIa) wherein:

wherein:

W is  $-\text{CH}_2\text{CH}_2-$ ;

Q is selected from the group consisting of  $-\text{NHCH}_2\text{CH}_2\text{CF}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,  $-\text{NHCH}_2\text{CH}_2\text{S}(\text{=O})_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CF}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{CN}$ ,  $-\text{NHC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ ,  $-\text{NH-tetrahydro-pyran-4-yl}$ , tetrahydro-pyran-4-

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ylamino,  $-\text{NHC}(\text{NH})\text{CH}_3$ , piperidin-4-ylamino, 1-tert-butoxycarbonyl-piperidin-4-ylamino,

$-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ , 1-methyl-piperidin-4-ylamino,  $-\text{NHCH}_2\text{C}(\text{=O})\text{NH}_2$ ,  $-\text{NHCH}(\text{CH}_3)_2$ ,  $-\text{NHCH}_2\text{CN}$ ,  $-\text{NH-benzyl}$ ,  $-\text{NHCH}_2\text{CH}_2\text{F}$ , 1-ethoxycarbonyl-piperidin-4-ylamino, 1H-[1,2,4]triazol-3-ylamino,  $-\text{NHC}(\text{=NH})\text{NH}_2$ ,  $-\text{NH-cyclopropyl}$ , thiazol-2-ylamino, 6-oxo-piperidin-3-ylamino, 1H-tetrazol-5-ylamino,  $-\text{NHCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$ ,  $-\text{NHC}(\text{CH}_3)_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{NHCH}(\text{CH}_3)_2$ , and  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CN}$ ;

$\text{R}^1$  is  $-\text{CH}_3$ ;

$-\text{R}^3$  is H, or Cl; and

$\text{R}^8$  is selected from the group consisting of 5-methyl-isoxazol-4-yl, 3-bromo-phenyl, 3-trifluoromethyl-phenyl, 3-methoxy-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, phenyl, 2-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-bromo-phenyl, 3-cyano-phenyl, and cyclopropyl.

Some embodiments of the present invention pertain to certain compounds of Formula (IIa) wherein:

wherein:

W is  $-\text{CH}_2\text{CH}_2-$  optionally substituted with 1 to 2 substituents selected independently from the group consisting of  $\text{C}_{1-3}$  alkyl and oxo;

Q is  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{-morpholin-4-yl}$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{-pyrrolidin-1-yl}$ , or 1-methyl-piperidin-4-yloxy;

$\text{R}^1$  is  $\text{C}_{1-6}$  alkyl;

$\text{R}^3$  is H or halogen; and

$\text{R}^8$  is selected from the group consisting of 5-methyl-isoxazol-4-yl, 3-bromo-phenyl, 3-trifluoromethyl-phenyl, 3-methoxy-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, phenyl, 2-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-bromo-phenyl, 3-cyano-phenyl, and cyclopropyl.

Some embodiments of the present invention pertain to certain compounds of Formula (IIa) wherein:

wherein:

W is  $-\text{CH}_2\text{CH}_2-$ ;

Q is  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{-morpholin-4-yl}$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{OC}(\text{=O})\text{CH}_2\text{-pyrrolidin-1-yl}$ , or 1-methyl-piperidin-4-yloxy;

$\text{R}^1$  is  $-\text{CH}_3$ ;

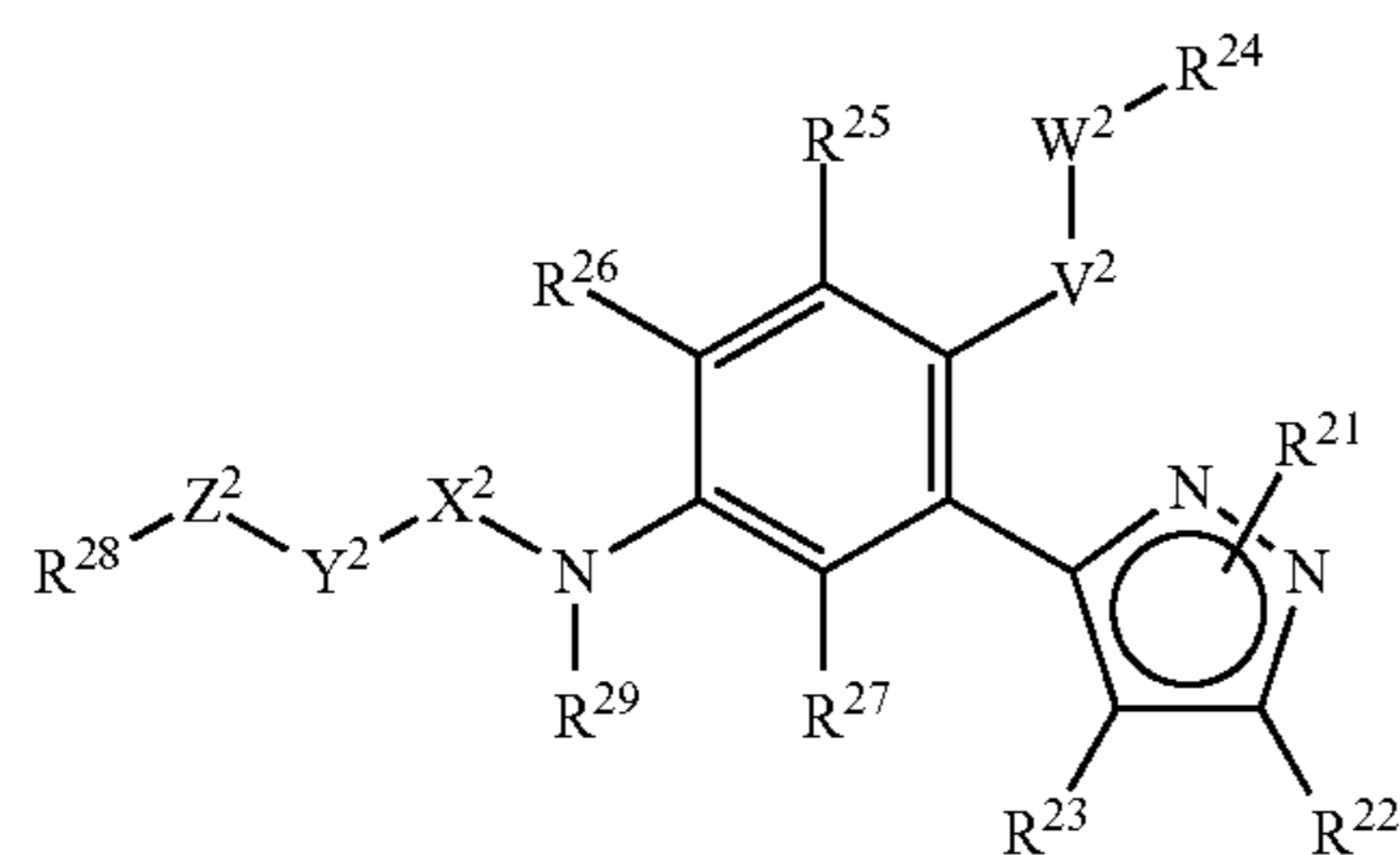
$\text{R}^3$  is H, or Cl; and

$\text{R}^8$  is selected from the group consisting of 5-methyl-isoxazol-4-yl, 3-bromo-phenyl, 3-trifluoromethyl-phenyl, 3-methoxy-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3-fluoro-phenyl, 2-fluoro-phenyl, phenyl, 2-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 2-fluoro-4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-bromo-phenyl, 3-cyano-phenyl, and cyclopropyl.



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In some embodiments, a compound of the present invention is other than a compound of Formula (III):



or a pharmaceutically acceptable salt, hydrate or solvate thereof;

wherein:

V<sup>2</sup> is O, S, S(=O), S(=O)<sub>2</sub> or NR<sup>30</sup>;

W<sup>2</sup> is C<sub>1-4</sub> alkylene optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 substituents selected independently from the group consisting of C<sub>1-3</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, cyano, C<sub>1-3</sub> haloalkyl, halogen and oxo; or W is absent;

X<sup>2</sup> is C(=O), C(=S) or absent;

Y<sup>2</sup> is O, NR<sup>31</sup> or absent;

Z<sup>2</sup> is C<sub>1-4</sub> alkylene, or C<sub>3-4</sub> cycloalkylene, each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 substituents selected independently from the group consisting of C<sub>1-3</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, cyano, haloalkyl, halogen, hydroxyl, and oxo; or Z is absent;

R<sup>21</sup> is selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C<sub>3-7</sub> cycloalkyl;

R<sup>22</sup> is selected from the group consisting of H, C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

R<sup>23</sup> is selected from the group consisting of H, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, halogen, heteroaryl and phenyl; and wherein each of the C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>3-7</sub> cycloalkyl, heteroaryl and phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-5</sub> acyl, C<sub>1-5</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylsulfonamide, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylureyl, amino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub> cycloalkyl, C<sub>2-6</sub> dialkylcarboxamide, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkylsulfinyl, C<sub>1-4</sub> haloalkylsulfonyl, C<sub>1-4</sub> haloalkylthio, hydroxyl, nitro and sulfonamide;

R<sup>24</sup> is heterobicyclic, heterocyclic, or heteroaryl each optionally substituted with substituents selected indepen-

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5 dently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-12</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylsulfonamide, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylureyl, amino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylcarbonyl, C<sub>2-6</sub> dialkylcarboxamide, formyl, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkylsulfinyl, C<sub>1-4</sub> haloalkylsulfonyl, C<sub>1-4</sub> haloalkylthio, heteroaryl, hydroxyl, nitro, phenyl and sulfonamide; wherein the C<sub>1-5</sub> acyl, C<sub>1-5</sub> acyloxy, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-4</sub> alkylcarboxamide, amino, carbo-C<sub>1-6</sub>-alkoxy, and heteroaryl are each optionally substituted with substituents selected independently from the group consisting of C<sub>1-6</sub> alkyl, C<sub>1-5</sub> acyl, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-4</sub> alkylcarboxamide, C<sub>1-4</sub> alkylsulfonyl, amino, carbo-C<sub>1-9</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-6</sub> cycloalkyl, halogen, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> haloalkyl, hydroxyl, and phenyl;

10 R<sup>25</sup>, R<sup>26</sup>, and R<sup>27</sup> are each selected independently from the group consisting of H, C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-6</sub> alkylimino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, heterocyclic, hydroxyl, thiol, nitro, phenoxy and phenyl;

15 R<sup>28</sup> is C<sub>1-8</sub> alkyl, C<sub>2-6</sub> alkenyl, aryl, C<sub>3-7</sub> cycloalkyl, or heteroaryl each optionally substituted with substituents selected independently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, C<sub>1-6</sub> alkylimino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, C<sub>2-8</sub> dialkylsulfonamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, heterocyclic, hydroxyl, thiol, nitro, phenoxy and phenyl, or two adjacent substituents together with the aryl or the heteroaryl form a C<sub>5-7</sub> cycloalkyl optionally comprising 1 to 2 oxygen atoms and optionally substituted with F, Cl or Br; and wherein the C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylamino, C<sub>1-4</sub> alkylimino, C<sub>2-8</sub> dialkylamino, heterocyclic, and phenyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-6</sub> acyloxy, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarboxamide, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylsulfonamide, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylureyl, amino, C<sub>1-6</sub> alkylamino, C<sub>2-8</sub> dialkylamino, carbo-C<sub>1-6</sub>-alkoxy, carboxamide, carboxy, cyano, C<sub>3-7</sub> cycloalkyl, C<sub>2-8</sub> dialkylcarboxamide, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkylsulfinyl, C<sub>1-6</sub> haloalkylsulfonyl, C<sub>1-6</sub> haloalkylthio, hydroxyl, thiol and nitro; and

20 R<sup>29</sup>, R<sup>30</sup>, and R<sup>31</sup> are each independently H or C<sub>1-8</sub> alkyl.

25 Some embodiments of the present invention include every combination of one or more compounds selected from the following table:

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 1        |                    | 5-Methyl-isoxazole-3-carboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-amide |
| 2        |                    | 3-Bromo-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 3        |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide                     |
| 4        |                    | N-[4-[2-(2-Methanesulfonyl-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide                              |
| 5        |                    | 4-Chloro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 6        |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-ethylamino-2-methyl-propoxy)-phenyl]-3-trifluoromethyl-benzamide                       |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 7        |                    | 3-Chloro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide   |
| 8        |                    | 5-Methyl-isoxazole-3-carboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-methanesulfonyl-ethylamino)-ethoxy]-phenyl}-amide |
| 9        |                    | 2-Chloro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide   |
| 10       |                    | N-[4-[2-(2,2-Difluoro-propylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide                                    |
| 11       |                    | 4-Fluoro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide   |
| 12       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-ethylamino-ethoxy)-phenyl]-3-trifluoromethylbenzamide                                   |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 13       |                    | 2,4-Difluoro-N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                   |
| 14       |                    | 3-Fluoro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                                      |
| 15       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-methoxy-ethylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide     |
| 16       |                    | N-[4-[2-(2-Cyano-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-fluoro-benzamide                         |
| 17       |                    | 2-Fluoro-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                                      |
| 18       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1,1-dimethyl-propylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide |



-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 19       |                    | 2,4-Difluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-benzamide   |
| 20       |                    | N-[4-(2-Methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 21       |                    | N-[4-(2-Acetimidoylaminoethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide  |
| 22       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-fluorobenzamide  |
| 23       |                    | 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-trifluoromethylbenzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic acid tert-butyl ester |

-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 24       |                    | 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-methoxybenzoylamino)-phenoxy]ethylamino}-piperidine-1-carboxylic acid tert-butyl ester |
| 25       |                    | 4-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 26       |                    | N-[4-(2-Butylamino-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide   |
| 27       |                    | 2,4-Difluoro-N-[4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                              |
| 28       |                    | 3-Fluoro-N-[4-[2-(2-methanesulfonyl-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                                  |



-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 29       |                    | N-[4-[2-(Carbamoylmethylamino)-ethoxy]-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide |
| 30       |                    | 3-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                                 |
| 31       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-isobutylamino-ethoxy)-phenyl]-3-trifluoromethyl-benzamide          |
| 32       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide          |
| 33       |                    | N-[4-[2-(Cyanomethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide                      |
| 34       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-fluoro-benzamide  |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 35       |                    | 2-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide   |
| 36       |                    | N-[4-(2-Benzylamino-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide  |
| 37       |                    | N-[4-[2-(2-Fluoroethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide  |
| 38       |                    | 3-Methoxy-N-[4-[2-(2-methoxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 39       |                    | 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-trifluoromethyl-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic acid ethyl ester |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 40       |                    | N-[4-(2-Methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethoxybenzamide                         |
| 41       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-methoxybenzamide |
| 42       |                    | 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(1H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-benzamide           |
| 43       |                    | N-[4-[2-(2-Hydroxyethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide                   |
| 44       |                    | N-[4-(2-Guanidinoethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide                                |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 45       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide |
| 46       |                    | N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethoxy-benzamide                                |
| 47       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-cyclopropylamino-ethoxy)-phenyl]-3-trifluoromethyl-benzamide               |
| 48       |                    | 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(4-methyl-thiazol-2-ylamino)-ethoxy]-phenyl}-benzamide                     |
| 49       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[(R)-6-oxo-piperidin-3-ylamino]-ethoxy]-phenyl}-3-methoxy-benzamide           |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 50       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[(2-methoxy-ethylcarbamoyl)-methoxy]-phenyl}-3-trifluoromethyl-benzamide |
| 51       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-3-fluoro-benzamide       |
| 52       |                    | N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide                            |
| 53       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide      |
| 54       |                    | 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(1H-tetrazol-5-ylamino)-ethoxy]-phenyl}-benzamide                     |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 55       |                    | N-[4-[2-(2-Ethoxyethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide                           |
| 56       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoropropylamino)ethoxy]-phenyl}-2-fluoro-4-methoxy-benzamide |
| 57       |                    | N-[4-(2-Methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-2-(trifluoromethyl)-benzamide                              |
| 58       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-fluoroethylamino)ethoxy]-phenyl}-3-(trifluoromethyl)-benzamide        |
| 59       |                    | N-[4-[2-(2-Hydroxyethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-4-(trifluoromethyl)-benzamide                |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 60       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide                         |
| 61       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide                  |
| 62       |                    | 4-Bromo-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide  |
| 63       |                    | N-[4-[2-(2-Isopropoxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide                                      |
| 64       |                    | 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-fluorobenzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic acid tert-butyl ester |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 65       |                    | Cyclopropanecarboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-hydroxyethylamino)ethoxy]-phenyl}-amide |
| 66       |                    | N-[4-(2-tert-Butylaminoethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide                            |
| 67       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-methyl-2-propylamino-propoxy)-phenyl]-3-trifluoromethyl-benzamide    |
| 68       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-hydroxyethoxy)-phenyl]-3-methoxy-benzamide                           |
| 69       |                    | 3-Fluoro-N-[4-[2-(2-hydroxyethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide                       |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 70       |                    | N-[4[2-(2-Cyanoethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide                   |
| 71       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methylpiperidin-4-yloxy)ethoxy]-phenyl}-3-methoxybenzamide |
| 72       |                    | 3-Methoxy-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoropropylamino)ethoxy]-phenyl}-benzamide        |
| 73       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methylpiperidin-4-yloxy)ethoxy]-phenyl}-3-fluorobenzamide  |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 74       |                    | N-[4-(2-Isopropylaminoethoxy)-3-(2-methyl-2H-pyrazol-3-yl) phenyl]-3-methoxy-benzamide                                 |
| 75       |                    | N-[4-(2-Butylamino-2-methyl-propoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl) phenyl]-3-trifluoromethyl-benzamide         |
| 76       |                    | N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-hydroxy-ethoxy)-phenyl]-3-fluoro-benzamide                               |
| 77       |                    | 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-propylamino)-ethoxy]-phenyl}-benzamide                                   |
| 78       |                    | N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-yloxy)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide |



-continued

| Cmpd No. | Chemical Structure | Chemical Name   |
|----------|--------------------|---|
| 79       |                    | 3-Methoxy-N-[3-(2-methyl-2H-pyrazol-3-yl)-4-(2-propylaminoethoxy)phenyl]benzamide                                   |
| 80       |                    | N-[4-[2-(3-cyano-propylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide                       |
| 81       |                    | 3-cyano-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]benzamide                                       |
| 82       |                    | Morpholin-4-yl-acetic acid 2-[2-(4-chloro-2-methyl-2H-pyrazo]-3-yl)-4-(3-methoxy-benzoylamino)-phenoxy]-ethyl ester |
| 83       |                    | Dimethylamino-acetic acid 2-[2-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-methoxy-benzoylamino)-phenoxy]-ethyl ester  |

-continued

| Cmpd No. | Chemical Structure | Chemical Name  |
|----------|--------------------|--|
| 84       |                    | Pyrrolidin-1-yl-acetic acid 2-[2-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-methoxy-benzoylamino)-phenoxy]-ethyl ester |

Additionally, individual compounds and chemical genera of the present invention, such as Formula (Ia) and related Formulae therefrom, encompass all pharmaceutically acceptable salts, solvates, and particularly hydrates, thereof.

It is understood that the present invention embraces each diastereomer, each enantiomer and mixtures thereof of each compound and generic Formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral atom, for example carbon. Separation of the individual isomers (such as, chiral HPLC, recrystallization of diastereomeric mixture, and the like) or selective synthesis (such as, enantiomeric selective synthesis, and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

The compounds of the Formula (Ia) of the present invention can be prepared according to the general synthetic schemes in FIGS. 1 through 8 as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup> Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

#### Indications and Methods of Treatment

In addition to the foregoing beneficial uses for the modulators of 5-HT<sub>2A</sub> receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

#### 1. Antiplatelet Therapies (Conditions Related to Platelet Aggregation):

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

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A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5-HT<sub>2A</sub> receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT<sub>2A</sub> inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see Satimura, K, et al., *Clin Cardiol* 2002 Jan. 25 (1):28-32; and Wilson, H. C et al., *Thromb Haemost* 1991 Sep. 2; 66(3):355-60).

5-HT<sub>2A</sub> inverse agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications (see *Br. Med. J.* 298: 424-430, 1989),



Arterial thrombosis (see, Pawlak, D. et al. *Thrombosis Research* 90: 259-270, 1998), atherosclerosis (see, Hayashi, T. et al. *Atherosclerosis* 168: 23-31, 2003), vasoconstriction, caused by serotonin (see, Fujiwara, T. and Chiba, S. *Journal of Cardiovascular Pharmacology* 26: 503-510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. et al. *Am Heart J.* 145:e16 2003). It can also be used alone or in combination with thrombolytic therapy, for example, tPA (see, Yamashita, T. et al. *Haemostasis* 30:321-332, 2000), to provide cardioprotection following MI or post-ischemic myocardial dysfunction (see, Muto, T. et al. *Mol. Cell. Biochem.* 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see, Horibe, E. *Circulation Research* 68: 68-72, 2004), and the like, including complications resulting therefrom.

5-HT<sub>2A</sub> inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and atherosclerosis (see Nomura, Shosaku, et al. *Blood Coagulation and Fibrinolysis* 2005, 16, 423-428).

The 5-HT<sub>2A</sub> inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein at a time where such risk exists.

One aspect of the present invention provides a therapeutic agent for treating indications associated with the pathophysiology of platelet aggregation used in combination with compounds of the present invention as disclosed herein. Accordingly, compounds of the present invention can be used alone or in combination with other therapeutic agent(s), such as, thromboxane A<sub>2</sub> blocker (aspirin and the like), and ADP-mediated platelet aggregation inhibitor (ticlopidine, clopidogrel, and the like) either administered together or separately.

## 2. Asthma

5-HT (5-hydroxytryptamine) has been linked to the pathophysiology of acute asthma (see Cazzola, M. and Matera, M. G., *TIPS*, 2000, 21, 13; and De Bie, J. J. et al., *British J. Pharm.*, 1998, 124, 857-864). The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

## 3. Agitation

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), *Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc* 34(10): 711-721).

Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), *Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord* 11 (suppl 2):S45-S50).

An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia; of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia.

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging-evidence that agents acting at the 5-HT<sub>2A</sub> receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I. R., et al., *J Clin Psychiatry* 1999 February, 60(2):107-115; and Street, J. S., et al., *Arch Gen Psychiatry* 2000 October, 57(10):968-976).

The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimer's disease, Lewy body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including, without limitation, stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

## 4. Add-On Therapy to Haloperidol in the Treatment of Schizophrenia and Other Disorders:

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (mul-



tiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of inter-human relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (See, American Statistical and Diagnostic Handbook).

Haloperidol (Haldol) is a potent dopamine D<sub>2</sub> receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5-HT<sub>2A</sub> inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5-HT<sub>2A</sub> inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient a dopamine D<sub>2</sub> receptor antagonist and a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient haloperidol and a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine D<sub>2</sub> receptor antagonist and a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for treating schizophrenia in a patient in need of the treatment comprising administering to the patient a dopamine D<sub>2</sub> receptor antagonist and a 5-HT<sub>2A</sub> inverse agonist disclosed herein. Preferably, the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

The administration of the dopamine D<sub>2</sub> receptor antagonist can be concomitant with administration of the 5-HT<sub>2A</sub> inverse agonist, or they can be administered at different times. Those

of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the 5-HT<sub>2A</sub> inverse agonist are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from schizophrenia, comprising administering to the patient a 5-HT<sub>2A</sub> inverse agonist as disclosed herein.

#### 5. Sleep Disorders

It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, more than one-half of the adults surveyed (58%) report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, about three in ten (35%) say they have experienced insomnia-like symptoms every night or almost every night.

The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of Sleep Disorders, there are over 80 recognized sleep disorders. Of these, compounds of the present invention are effective, for example, in any one or more of the following sleep disorders (ICSD—International Classification of Sleep Disorders: Diagnostic and Coding Manual. Diagnostic Classification Steering Committee, American Sleep Disorders Association, 1990):

#### A. Dyssomnias

##### a. Intrinsic Sleep Disorders:

Psychophysiological insomnia, Sleep state misperception, Idiopathic insomnia, Obstructive sleep apnea syndrome, Central sleep apnea syndrome, Central alveolar hypoventilation syndrome, Periodic limb movement disorder, Restless leg syndrome and Intrinsic sleep disorder NOS.

##### b. Extrinsic Sleep Disorders:

Inadequate sleep hygiene, Environmental sleep disorder, Altitude insomnia, Adjustment sleep disorder, Insufficient sleep syndrome, Limit-setting sleep disorder, SleepOnset association disorder, Nocturnal eating (drinking) syndrome, Hypnotic dependent sleep disorder, Stimulant-dependent sleep disorder, Alcohol-dependent sleep disorder, Toxin-induced sleep disorder and Extrinsic sleep disorder NOS.

##### c. Circadian Rhythm Sleep Disorders:

Time zone change (jet lag) syndrome, Shift work sleep disorder, Irregular sleep-wake pattern, Delayed sleep phase syndrome, Advanced sleep phase syndrome, Non-24 hour sleep-wake disorder and Circadian rhythm sleep disorder NOS.

#### B. Parasomnias

##### a. Arousal Disorders:

Confusional arousals, Sleepwalking and Sleep terrors.

##### b. Sleep-Wake Transition Disorders:

Rhythmic movement disorder, Sleep starts, Sleep talking and Nocturnal leg cramps.

#### C. Sleep Disorders Associated with Medical/Psychiatric Disorders

##### a. Associated with Mental Disorders:

Psychoses, Mood disorders, Anxiety disorders, Panic disorders and Alcoholism.

##### b. Associated with Neurological Disorders:

Cerebral degenerative disorders, Dementia, Parkinsonism, Fatal familial insomnia, Sleep-related epilepsy, Electrical status epilepticus of sleep and Sleep-related headaches.



## c. Associated with Other Medical Disorders:

Sleeping sickness, Nocturnal cardiac ischemia, Chronic obstructive pulmonary disease, Sleep-related asthma, Sleep-related gastroesophageal reflux, Peptic ulcer disease, Fibrositis syndrome, Osteoarthritis, Rheumatoid arthritis, Fibromyalgia and Post-surgical.

The effects of sleep deprivation are more than excessive daytime sleepiness. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung, and Blood Institute, Insomnia Facts Sheet, October 1995). Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction, compromised glucose tolerance, increased obesity and metabolic syndrome. Compounds of the present invention are useful to prevent or alleviate these complications by improving sleep quality.

The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used. In addition, benzodiazepines are used to induce sleep, but have little to no effect on the maintenance of sleep, sleep consolidation or slow wave sleep. Therefore, sleep maintenance disorders are not currently well treated.

Clinical studies with agents of a similar mechanism of action as are compounds of the present invention have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpley A L, et al. Slow Wave Sleep in Humans: Role of 5-HT<sub>2A</sub> and 5HT<sub>2C</sub> Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4): 467-71; Winokur A, et al. Acute Effects of Mirtoazpine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc of Biol Psych*, 2000, Vol. 48:75-78; and Landolt H P, et al. Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology*, 1999, Vol. 21(3):455-66].

Some sleep disorders are sometimes found in conjunction with other conditions and accordingly those conditions are treatable by compounds of Formula (Ia). For example, but not limited to, patients suffering from mood disorders typically suffer from a sleep disorder that can be treatable by compounds of Formula (Ia). Having one pharmacological agent which treats two or more existing or potential conditions, as does the present invention, is more cost effective, leads to better compliance and has fewer side effects than taking two or more agents.

It is an object of the present invention to provide a therapeutic agent for the use in treating Sleep Disorders. It is another object of the present invention to provide one pharmaceutical agent, which may be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. Compounds of the present invention described herein may be used alone or in combination with a mild sleep inducer, such as, a sedating antihistamine (diphenhydramine,

chloropheniramine, bromopheniramine and the like), GABA-A receptor modulators (Ambien, Sonata, Indiplon, Gaboxadol, and the like), melatonin agonists (ML1 receptor agonist, such as Ramelteon and the like), sedating antidepressants (such as a tricyclic antidepressant, doxepine and the like), and benzodiazepines (diazepam and the like) and either administered together or separately.

## Sleep Architecture:

Sleep comprises two physiological states: Non rapid eye movement (NREM and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. So called delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning the patient spends a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. As used herein, the term "fragmented sleep architecture" means an individual, such as a sleep disorder patient, spends the majority of their sleep time in NREM sleep stages 1 and 2, lighter periods of sleep from which the individual can be easily aroused to a Waking state by limited external stimuli. As a result, the individual cycles through frequent bouts of light sleep interrupted by frequent awakenings throughout the sleep period. Many sleep disorders are characterized by a fragmented sleep architecture. For example, many elderly patients with sleep complaints have difficulty achieving long bouts of deep refreshing sleep (NREM stages 3 and 4) and instead spend the majority of their sleep time in NREM sleep stages 1 and 2.

In contrast to fragmented sleep architecture, as used herein the term "sleep consolidation" means a state in which the number of NRAM sleep bouts, particularly Stages 3 and 4, and the length of those sleep bouts are increased, while the number and length of waling bouts are decreased. In essence, the architecture of the sleep disorder patient is consolidated to a sleeping state with increased periods of sleep and fewer awakenings during the night and more time is spent in slow wave sleep (Stages 3 and 4) with fewer oscillation Stage 1 and 2 sleep. Compounds of the present invention can be effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall, and muscles relax. In normal sleep architecture, NREM sleep makes up about 75% of total sleep time; stage 1 accounting for 5-10% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 12%, and stage 4 13-15%. About 90 minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night. REM makes up approximately 25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration, and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as "paradoxical sleep." Sleep onset occurs during NREM sleep and takes 10-20 minutes in healthy young adults. The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable; a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods



may last up to 40 minutes. With aging, the time between retiring and sleep onset increases and the total amount of night-time sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

As used herein, the term "delta power" means a measure of the duration of EEG activity in the 0.5 to 3.5 Hz range during NREM sleep and is thought to be a measure of deeper, more refreshing sleep. Delta power is hypothesized to be a measure of a theoretical process called Process S and is thought to be inversely related to the amount of sleep an individual experiences during a given sleep period. Sleep is controlled by homeostatic mechanisms; therefore, the less one sleeps the greater the drive to sleep. It is believed that Process S builds throughout the wake period and is discharged most efficiently during delta power sleep. Delta power is a measure of the magnitude of Process S prior to the sleep period. The longer one stays awake, the greater Process S or drive to sleep and thus the greater the delta power during NREM sleep. However, individuals with sleep disorders have difficulty achieving and maintaining delta wave sleep, and thus have a large build-up of Process S with limited ability to discharge this buildup during sleep. 5-HT<sub>2A</sub> agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT<sub>2A</sub> inverse agonist or antagonist will be able to achieve deeper more refreshing sleep. These same effects have not been observed with currently marketed pharmacotherapies. In addition, currently marketed pharmacotherapies for sleep have side effects such as hangover effects or addiction that are associated with the GABA receptor. 5-HT<sub>2A</sub> inverse agonists do not target the GABA receptor and so these side effects are not a concern.

#### Subjective and Objective Determinations of Sleep Disorders:

There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times does the patient wake up during the night, how restless is the patient during sleep, etc. Another method is to objectively measure the stages of sleep using polysomnography.

Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electroculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and

occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 8-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

In addition, the compounds of the invention can be useful for the treatment of the sleep disorders characterized by excessive daytime sleepiness such as narcolepsy. Inverse agonists at the serotonin 5-HT<sub>2A</sub> receptor improve the quality of sleep at nighttime which can decrease excessive daytime sleepiness.

Accordingly, another aspect of the present invention relates to the therapeutic use of compounds of the present invention for the treatment of Sleep Disorders. Compounds of the present invention are potent inverse agonists at the serotonin 5-HT<sub>2A</sub> receptor and can be effective in the treatment of Sleep Disorders by promoting one or more of the following: reducing the sleep onset latency period (measure of sleep induction), reducing the number of nighttime awakenings, and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement and sleep consolidation) without effecting REM sleep. In addition, compounds of the present invention can be effective either as a monotherapy or in combination with sleep inducing agents, for example but not limited to, antihistamines.

#### 6. Diabetic-Related Pathologies:

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), increased plasma serotonin concentration in diabetic patients has also been implicated to play a role in disease progression (Pietraszek, M. H., et al. *Thrombosis Res.* 1992, 66(6), 765-74; and Andrzejewska-Buczko J, et al., *Klin Oczna.* 1996; 98(2), 101-4). Serotonin is believed to play a role in vasospasm and increased platelet aggregability. Improving microvascular blood flow is able to benefit diabetic complications.

A recent study by Cameron and Cotter in *Naunyn Schmiedebergs Arch Pharmacol.* 2003 June; 367(6):607-14, used a 5-HT<sub>2A</sub> antagonist experimental drug AT-1015, and other non-specific 5-HT<sub>2A</sub> antagonists including ritanserin and sarpogrelate. These studies found that all three drugs were able to produce a marked correction (82.6-99.7%) of a 19.8% sciatic motor conduction deficit in diabetic rats. Similarly, 44.7% and 14.9% reductions in sciatic endoneurial blood flow and saphenous sensory conduction velocity were completely reversed.

In a separate patient study, sarpogrelate was evaluated for the prevention of the development or progression of diabetic nephropathy (Takahashi, T., et al., *Diabetes Res Clin Pract.* 2002 November; 58(2):123-9). In the trial of 24 months of treatment, sarpogrelate significantly reduced urinary albumin excretion level.

#### 7. Glaucoma

Topical ocular administration of 5-HT<sub>2</sub> receptor antagonists result in a decrease in intra ocular pressure (IOP) in



monkeys (Chang et al., *J. Ocul Pharmacol* 1:137-147 (1985)) and humans (Mastropasqua et al., *Acta Ophthalmol Scand Suppl* 224:24-25 (1997)) indicating utility for similar compounds such as 5-HT<sub>2A</sub> inverse agonists in the treatment of ocular hypertension associated with glaucoma. The 5-HT<sub>2</sub> receptor antagonist ketanserin (Mastropasqua supra) and sarpogrelate (Takenaka et al., *Investig Ophthalmol Vis Sci* 36:S734 (1995)) have been shown to significantly lower IOP in glaucoma patients.

#### 8. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a lethal demyelinating disease caused by an opportunistic viral infection of oligodendrocytes in immunocompromised patients. The causative agent is JC virus, a ubiquitous papovavirus that infects the majority of the population before adulthood and establishes a latent infection in the kidney. In immunocompromised hosts, the virus can reactivate and productively infect oligodendrocytes. This previously rare condition, until 1984 reported primarily in persons with underlying lymphoproliferative disorders, is now more common because it occurs in 4% of patients with AIDS. Patients usually present with relentlessly progressive focal neurologic defects, such as hemiparesis or visual field deficits, or with alterations in mental status. On brain MRI, one or more white matter lesions are present; they are hyperintense on T2-weighted images and hypointense on T1-weighted images. There is no mass effect, and contrast enhancement is rare. Diagnosis can be confirmed by brain biopsy, with demonstration of virus by in situ hybridization or immunocytochemistry. Polymerase chain reaction amplification of JC virus sequences from the CSF can confirm diagnosis without the need for biopsy [see, e.g., Antinori et al., *Neurology* (1997) 48:687-694; Berger and Major, *Seminars in Neurology* (1999) 19:193-200; and Portegies, et al., *Eur. J. Neurol.* (2004) 11:297-304]. Currently, there is no effective therapy. Survival after diagnosis is about 3 to 5 months in AIDS patients.

JC virus enters cells by receptor-mediated clathrin-dependent endocytosis. Binding of JC virus to human glial cells (e.g., oligodendrocytes) induces an intracellular signal that is critical for entry and infection by a ligand-inducible clathrin-dependent mechanism [Querbes et al., *J Virology* (2004) 78:250-256]. Recently, 5-HT<sub>2A</sub> was shown to be the receptor on human glial cells mediating infectious entry of JC virus by clathrin-dependent endocytosis [Elphick et al., *Science* (2004) 306:1380-1383]. 5-HT<sub>2A</sub> antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT<sub>2A</sub>.

5-HT<sub>2A</sub> antagonists including inverse agonists have been contemplated to be useful in the treatment of PML [Elphick et al., *Science* (2004) 306:1380-1383]. Prophylactic treatment of HIV-infected patients with 5-HT<sub>2A</sub> antagonists is envisioned to prevent the spread of JC virus to the central nervous system and the development of PML. Aggressive therapeutic treatment of patients with PML is envisioned to reduce viral spread within the central nervous system and prevent additional episodes of demyelination.

In some embodiments, methods are provided for treating progressive multifocal leukoencephalopathy in a patient in need of such treatment, comprising administering to the patient a composition comprising a 5-HT<sub>2A</sub> inverse agonist disclosed herein.

#### 9. Hypertension

Serotonin has been observed to play an important role in the regulation of vascular tone, vasoconstriction, and pulmonary hypertension (see, Deuchar, G. et al. *Pulm. Pharmacol.*

*Ther.* 18(1):23-31. 2005; and Marcos, E. et al. *Circ. Res.* 94(9):1263-70 2004). Ketanserin, a 5-HT<sub>2A</sub> inverse agonist, have been demonstrated to protect against circulatory shocks, intracranial hypertension, and cerebral ischemia during heat-stroke (see, Chang, C. et al. *Shock* 24(4): 336-340 2005); and to stabilize blood pressure in spontaneously hypertensive rats (see, Miao, C. *Clin. Exp. Pharmacol. Physiol.* 30(3): 189-193). Mianserin, a 5-HT<sub>2A</sub> inverse agonist, has been shown to prevent DOCA-salt induced hypertension in rats (see, Silva, A. *Eur. J. Pharmacol.* 518(2-3): 152-7 2005).

#### 10. Pain

5-HT<sub>2A</sub> inverse agonists are also effective for the treatment of pain. Sarpogrelate has been observed to provide a significant analgesic effect both on thermal induced pain in rats after intraperitoneal administration and on inflammatory pain in rats after either intrathecal or intraperitoneal administration (see, Nishiyama, T. *Eur. J. Pharmacol.* 516:18-22 2005). This same 5-HT<sub>2A</sub> inverse agonist in humans has been shown to be an effective treatment for lower back pain, leg pain and numbness associated with sciatica brought on by lumbar disc herniation (see, Kanayama, M. et al. *J. Neurosurg: Spine* 2:441-446 2005).

#### Representative Methods of the Invention:

One aspect of the present invention pertains to methods for modulating the activity of a 5-HT<sub>2A</sub> serotonin receptor by contacting the receptor with a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for the treatment of platelet aggregation in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for the treatment of an indication selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for the treatment of asthma in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

One aspect of the present invention pertains to methods for the treatment of a symptom of asthma in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.



One aspect of the present invention pertains to methods for the treatment of agitation or a symptom thereof in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the individual is a cognitively intact elderly individual.

One aspect of the present invention pertains to methods for the treatment of agitation or a symptom thereof in an individual suffering from dementia comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dementia is due to a degenerative disease of the nervous system. In some embodiments, the dementia is Alzheimers disease, Lewy body, Parkinson's disease or Huntington's disease. In some embodiments, the dementia is due to diseases that affect blood vessels. In some embodiments, the dementia is due to stroke or multi-infarct dementia.

One aspect of the present invention pertains to methods for the treatment of an individual suffering from at least one of the indications selected from the group consisting of behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D<sub>2</sub> receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One aspect of the present invention pertains to methods for the treatment of an individual with infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D<sub>2</sub> receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One aspect of the present invention pertains to methods for the treatment of schizophrenia in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D<sub>2</sub> receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One aspect of the present invention pertains to methods for the treatment of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to an individual suffering from the schizophrenia, comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms. In some embodiments, the haloperidol and the compound or pharmaceutical composition are administered in a single dosage form.

One aspect of the present invention pertains to methods for the treatment of a sleep disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

In some embodiments, the sleep disorder is a dyssomnia. In some embodiments, the dyssomnia is selected from the group consisting of psychophysiological insomnia, sleep state misperception, idiopathic insomnia, obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome, periodic limb movement disorder, restless leg syndrome, inadequate sleep hygiene, environmental sleep disorder, altitude insomnia, adjustment sleep disorder, insufficient sleep syndrome, limit-setting sleep disorder, sleep-onset association disorder, nocturnal eating or drinking syndrome, hypnotic dependent sleep disorder, stimulant-dependent sleep disorder, alcohol-dependent sleep disorder, toxin-induced sleep disorder, time zone change (jet lag) syndrome, shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, and non-24-hour sleep-wake disorder.

In some embodiments, the sleep disorder is a parasomnia. In some embodiments, the parasomnia is selected from the group consisting of confusional arousals, sleepwalking and sleep terrors, rhythmic movement disorder, sleep starts, sleep talking and nocturnal leg cramps. In some embodiments, the sleep disorder is characterized by excessive daytime sleepiness such as narcolepsy.

In some embodiments, the sleep disorder is associated with a medical or psychiatric disorder. In some embodiments, the medical or psychiatric disorder is selected from the group consisting of psychoses, mood disorders, anxiety disorders, panic disorders, alcoholism, cerebral degenerative disorders, dementia, parkinsonism, fatal familial insomnia, sleep-related epilepsy, electrical status epilepticus of sleep, sleep-related headaches, sleeping sickness, nocturnal cardiac ischemia, chronic obstructive pulmonary disease, sleep-related asthma, sleep-related gastroesophageal reflux, peptic ulcer disease, fibrositis syndrome, osteoarthritis, rheumatoid arthritis, fibromyalgia and post-surgical sleep disorder.

One aspect of the present invention pertains to methods for the treatment of a diabetic-related disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

In some embodiments, the diabetic-related disorder is diabetic peripheral neuropathy.

In some embodiments, the diabetic-related disorder is diabetic nephropathy.

In some embodiments, the diabetic-related disorder is diabetic retinopathy.

One aspect of the present invention pertains to methods for the treatment of glaucoma or other diseases of the eye with abnormal intraocular pressure.

One aspect of the present invention pertains to methods for the treatment of progressive multifocal leukoencephalopathy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

In some embodiments, the individual in need thereof has a lymphoproliferative disorder. In some embodiments, the lymphoproliferative disorder is leukemia or lymphoma. In some embodiments, the leukemia or lymphoma is chronic lymphocytic leukemia, Hodgkin's disease, or the like.

In some embodiments, the individual in need thereof has a myeloproliferative disorder.

In some embodiments, the individual in need thereof has carcinomatosis.



In some embodiments, the individual in need thereof has a granulomatous or inflammatory disease. In some embodiments, the granulomatous or inflammatory disease is tuberculosis or sarcoidosis.

In some embodiments, the individual in need thereof is immunocompromised. In some embodiments, the immunocompromised individual has impaired cellular immunity. In some embodiments, the impaired cellular immunity comprises impaired T-cell immunity.

In some embodiments, the individual in need thereof is infected with HIV. In some embodiments, the HIV-infected individual has a CD4+ cell count of  $\leq 200/\text{mm}^3$ . In some embodiments, the HIV-infected individual has AIDS. In some embodiments, the HIV-infected individual has AIDS-related complex (ARC). In certain embodiments, ARC is defined as the presence of two successive CD4+ cell counts below  $200/\text{mm}^3$  and at least two of the following signs or symptoms: oral hairy leukoplakia, recurrent oral candidiasis, weight loss of at least 2.5 kg or 10% of body weight within last six months, multidermatomal herpes zoster, temperature above  $38.5^\circ\text{C}$ . for more than 14 consecutive days or more than 15 days in a 30-day period, or diarrhea with more than three liquid stools per day for at least 30 days [see, e.g., Yamada et al., Clin. Diagn. Virol. (1993) 1:245-256].

In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent [see, e.g., Mueller, Ann Thorac Surg (2004) 77:354-362; and Krieger and Emre, Pediatr Transplantation (2004) 8:594-599]. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent selected from the group consisting of: corticosteroids (for example, prednisone and the like), calcineurin inhibitors (for example, cyclosporine, tacrolimus, and the like), antiproliferative agents (for example, azathioprine, mycophenolate mofetil, sirolimus, everolimus, and the like), T-cell depleting agents (for example, OKT®3 monoclonal antibody (mAb), anti-CD3 immunotoxin FN18-CRM9, Campath-1H (antiCD52) mAb, anti-CD4 mAb, anti-T cell receptor mAb, and the like), anti-IL-2 receptor (CD25) mAb (for example, basiliximab, daclizumab, and the like), inhibitors of co-stimulation (for example, CTLA4-Ig, anti-CD154 (CD40 ligand) mAb, and the like), deoxyspergualin and analogs thereof (for example, 15-DSG, LF-08-0299, LF14-0195, and the like), leflunomide and analogs thereof (for example, leflunomide, FK778, FK779, and the like), FTY720, anti-alpha-4-integrin monoclonal antibody, and anti-CD45 RB monoclonal antibody. In some embodiments, the immunosuppressive agent and the compound or pharmaceutical composition are administered in separate dosage forms. In some embodiments, the immunosuppressive agent and the compound or pharmaceutical composition are administered in a single dosage form.

In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy after organ transplantation. In some embodiments, the organ is liver, kidney, lung, heart, or the like [see, e.g., Singh et al., Transplantation (2000) 69:467-472].

In some embodiments, the individual in need thereof is undergoing treatment for a rheumatic disease. In some embodiments, the rheumatic disease is systemic lupus erythematosus or the like.

In some embodiments, the compound or the pharmaceutical composition inhibits JC virus infection of human glial cells.

One aspect of the present invention encompasses processes for preparing a composition comprising admixing a com-

pound according any embodiments described herein and a pharmaceutically acceptable carrier.

One aspect of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is platelet aggregation.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is a blood clot formation in an angioplasty or coronary bypass surgery individual.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is a blood clot formation in an individual suffering from atrial fibrillation.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is asthma.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is a symptom of asthma.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is agitation or a symptom thereof in an individual. In some embodiments the individual is a cognitively intact elderly individual.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is agitation or a symptom thereof in an individual suffering from dementia. In some embodiments the dementia is due to a degenerative disease of the nervous system. In some embodiment the dementia is Alzheimers disease, Lewy body, Parkinson's disease, or Huntington's disease. In some embodiments the dementia is due to diseases that affect blood vessels. In some embodiments the dementia is due to stroke or multi-infract dementia.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder further comprising a dopamine D<sub>2</sub> receptor antagonist wherein the disorder is selected from the group consisting of a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia. In some embodiments the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder further comprising a dopamine D<sub>2</sub> receptor antagonist wherein the disorder is infantile autism, Huntington's chorea, or nausea and vomit-



ing from chemotherapy or chemotherapeutic antibodies. In some embodiments the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder further comprising a dopamine D<sub>2</sub> receptor antagonist wherein the disorder is schizophrenia. In some embodiments the dopamine D<sub>2</sub> receptor antagonist is haloperidol.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is a negative symptom or symptoms of schizophrenia induced by the administration of haloperidol.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the haloperidol and the compound or pharmaceutical composition are administered in a single dosage form.

One embodiment of the present invention is the use of a compound for the production of a medicament for use in the treatment of a 5-HT<sub>2A</sub> associated disorder wherein the disorder is progressive multifocal leukoencephalopathy.

One aspect of the present invention are compounds according to any of the embodiments described herein for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention are compounds according to any of the embodiments described herein for use in a method for the treatment of a 5-HT<sub>2A</sub> associated disorder, as described herein, in the human or animal body by therapy.

One aspect of the present invention are compounds according to any of the embodiments described herein for use in a method for the treatment of a sleep disorder, as described herein, in the human or animal body by therapy.

One aspect of the present invention are compounds according to any of the embodiments described herein for use in a method for the treatment of platelet aggregation in the human or animal body by therapy.

One aspect of the present invention are compounds according to any of the embodiments described herein for use in a method for the treatment of progressive multifocal leukoencephalopathy in the human or animal body by therapy.

#### Pharmaceutical Compositions

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral adminis-

tration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro, A. R., et al.).

While it is possible that, for use in the treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably



made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 5-HT<sub>2A</sub> receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits, as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, 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 ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, or whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether farther active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in

accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimens outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

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 sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid prepara-



tions can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension.

In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Science*, 66, 2 (1977); incorporated herein by reference in its entirety.



The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when the 5-HT<sub>2A</sub> receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as 5-HT<sub>2A</sub> receptor modulators, for the treatment of a 5-HT<sub>2A</sub> mediated disease or disorder in domestic animals (e.g., cats and dogs) and in other domestic animals (e.g., such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

#### Combination Therapy:

While the compounds of the present invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), they can also be used in combination with other pharmaceutical agents (i.e., combination-therapy) for the treatment of the diseases/conditions/disorders described herein. Accordingly, another aspect of the present invention includes methods of treatment of 5-HT<sub>2A</sub> serotonin receptor associated disorders comprising administering to an individual in need of such treatment a therapeutically-effective amount of a compound of the present invention in combination with one or more additional pharmaceutical agent as described herein.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include other antiplatelet, antithrombotic or anticoagulant drugs, anti-arrhythmic agents, Cholesteryl ester transfer protein (CETP) inhibitors, Niacin or niacin analogs, Adenosine or adenosine analogs, Nitroglycerin or nitrates, prothrombolytic agents, and the like. Other pharmaceutical agents, including the agents set forth infra, are well known or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

The compounds of the present invention can also be used in combination with other antiplatelet, antithrombotic or anticoagulant drugs such as thrombin inhibitors, platelet aggregation inhibitors such as aspirin, clopidogrel (Plavix®), ticlopidine or CS-747 [i.e., acetic acid 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl ester and its active metabolite R-99224, (Z)-2-[1-[2-cyclopropyl-1(S)-(2-fluorophenyl)-2-oxoethyl]-4(R)-sulfanylpiperidin-3-ylidene]acetic acid}, abciximab ReoPro®, eptifibatide (Integrilin®), tirofiban (Aggrastat®), warfarin, low molecular weight heparins (such as LOVENOX), GPIIb/GPIIIa blockers, PAI-1 inhibitors such as XR-330 [i.e., (3Z,6Z)-3-Benzylidene-6-(4-methoxybenzylidene)-1-methylpiperazine-2,5-dione] and T-686 [i.e., 3(E)-Benzylidene-4(E)-(3,4,5-trimethoxybenzylidene)pyrrolidine-2,5-dione], inhibitors of  $\alpha$ -2-antiplasmin such as anti- $\alpha$ -2-antiplasmin antibody and thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, phosphodiesterase (PDE) inhibitors, such as dipyridamole (Per-

santine®) or cilostazol, PDE inhibitors in combination with thromboxane receptor antagonists/thromboxane A synthetase inhibitors (such as picotamide), serotonin-2-receptor antagonists (such as ketanserin), fibrinogen receptor antagonists, hypolipidemic agents, such as HMG-CoA reductase inhibitors, e.g., pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, AZ4522, and itavastatin (Nissan/Kowa); microsomal triglyceride transport protein inhibitors (such as disclosed in U.S. Pat. Nos. 5,739,135, 5,712,279 and 5,760,246), antihypertensive agents such as angiotensin-converting enzyme inhibitors (e.g., captopril, lisinopril or fosinopril); angiotensin-II receptor antagonists (e.g., irbesartan, losartan or valsartan); and/or ACE/NEP inhibitors (e.g., omapatrilat and gemopatrilat);  $\beta$ -blockers (such as propranolol, nadolol and carvedilol), PDE inhibitors in combination with aspirin, ifetroban, picotamide, ketanserin, or clopidogrel (Plavix®) and the like.

The compound of the present invention can also be used in combination with anti-arrhythmic agents such as for atrial fibrillation, for example, aniodarone or dofetilide.

The compound of the present invention can also be used in combination with Cholesteryl ester transfer protein (CETP) inhibitors for dislipidemia and atherosclerosis, Niacin or niacin analogs for dislipidemia and atherosclerosis, Adenosine or adenosine analogs for vasodilation, Nitroglycerin or nitrates for vasodilation.

The compounds of the present invention can be used in combination with prothrombolytic agents, such as tissue plasminogen activator (natural or recombinant), streptolysin, reteplase, activase, lanoteplase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, and the like. The compounds of the present invention may also be used in combination with  $\beta$ -adrenergic agonists such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, or fenoterol; anticholinergics such as ipratropium bromide; anti-inflammatory corticosteroids such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide or dexarnethasone; and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, montelukast and pranleukast.

Suitable pharmaceutical agents that can be used in combination with compounds of the present invention include anti-retrovirals [see, e.g., Turpin, Expert Rev Anti Infect Ther (2003) 1:97-128]. Some embodiments of the present invention include methods of treatment of progressive multifocal leukoencephalopathy as described herein comprising administering to an individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: nucleoside reverse transcriptase inhibitors (for example, Retrovir®, Epivir®, Combivir®, Hivid®, Videx®, Trizvir®, Zerit®, Ziagen®, Vired®, Emtricitabin®, DAPD, and the like), non-nucleoside reverse transcriptase inhibitors (for example, Viramune®, Rescriptor®, Sustiva®, GW687, DPC083, TMC 125, Emivirine, Capravirine, BMS 561390, UC-781 and other oxathiin carboxyanilides, SJ-3366, Alkenyldiarylmethane (ADAM), Tivirapine, Calanolide A, HBY097, Loviride, HEPT Family Derivatives, TIBO Derivatives, and the like), protease inhibitors (for example, Fortovase®, Invitase®, Novir®, Crixivan®, Viracep®, Ageberase®, Kaletra®, Atazanavir, Tipranavir, DMP450, and the like), inhibitors of HIV-cell interaction (for example, soluble CD4, toxin-conjugated CD4, monoclonal antibodies to CD4 or gp120, PRO 542, dextran sulfate, Rersobene, FP-23199, Cyanovirin-N, Zintevir (T30177, AR177), L-chicoric acid and deriva-



tives, and the like), coreceptor inhibitors ligands (for example, R5, X4, modified ligands (R5), modified ligands (X4), and the like), coreceptor inhibitors X4 (for example, T22, T134, ALX40-4C, AMD3100, bicyclam derivatives, and the like), coreceptor inhibitors R5 (for example, TAK-779, SCH-C (SCH-351125), SCH-D (SCH-350634), NSC 651016, ONO Pharmaceutical, Merck, and the like), fusion inhibitors (for example, Fuzeono® (T-20, DP 178, enfuvritide) trimeris, T-1249, TMC125, and the like), integrase inhibitors (for example, 5CITEP, L731,988, L708,906, L-870,812, S-1360, and the like), NCp7 nucleocapsid Zn finger inhibitors (for example, NOBA, DIBA, dithianes, PD-161374, pyridinioalkanoyl thioesters (PATES), azodicarbonamide (ADA), cyclic 2,2 dithio bisbenzamide, and the like), RNase H inhibitors (for example, BBHN, CPHM PD-26388, and the like), Tat inhibitors (for example, dominant negative mutants, Ro24-7429, Ro5-3335, and the like), Rev inhibitors (for example, dominant negative mutants, Lepotomycin B, PKF050-638, and the like), transcriptional inhibitors (for example, Temacrazine, K-12 and K-37, EM2487, and the like), inhibitors of HIV assembly/maturation (for example, CAP-1 and CAP-2, and the like), and pharmaceutical agents directed to cellular anti-HIV targets (for example, LB6-B275 and HRM1275, Cdk9 inhibitors, and the like).

In a certain embodiment, a compound of the invention can be used in conjunction with highly active antiretroviral therapy (HAART). When antiretroviral drugs are used in combinations of three or four drugs, this treatment is called HAART [see, e.g., Portegies, et al., *Eur. J. Neurol.* (2004) 11:297-304].

In accordance with the present invention, the combination of a compound of the present invention and pharmaceutical agent can be prepared by mixing the respective active components either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, diluent, etc. as described herein, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition(s). When a compound or a mixture of compounds of Formula (Ia) are administered as a combination therapy with another active compound each can be formulated as separate pharmaceutical compositions given at the same time or at different times. Alternatively, in some embodiments, pharmaceutical compositions of the present invention comprise a compound or a mixture of compounds of Formula (Ia) and the pharmaceutical agent(s) as a single pharmaceutical composition.

#### Other Utilities

Another object of the present invention relates to radiolabeled compounds of the present invention that would be useful not only in radio-imaging but also in assays, both in vitro and in vivo, for localizing and quantitating the 5-HT<sub>2A</sub> receptor in tissue samples, including human, and for identifying 5-HT<sub>2A</sub> receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel 5-HT<sub>2A</sub> receptor assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. An "isotopically" or "radio-labeled" compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include, but are not limited to, <sup>2</sup>H (also written as D for deuterium), <sup>3</sup>H (also written as T for tritium), <sup>11</sup>C, <sup>13</sup>C, <sup>14</sup>C, <sup>13</sup>N, <sup>15</sup>N, <sup>15</sup>O, <sup>17</sup>O, <sup>18</sup>O, <sup>18</sup>F, <sup>35</sup>S, <sup>36</sup>Cl,

<sup>82</sup>Br, <sup>75</sup>Br, <sup>76</sup>Br, <sup>77</sup>Br, <sup>123</sup>I, <sup>124</sup>I, <sup>251</sup>I and <sup>131</sup>I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for in vitro 5-HT<sub>2A</sub> receptor labeling and competition assays, compounds that incorporate <sup>3</sup>H, <sup>14</sup>C, <sup>82</sup>Br, <sup>125</sup>I, <sup>131</sup>I, <sup>35</sup>S or will generally be most useful. For radio-imaging applications <sup>11</sup>C, <sup>18</sup>F, <sup>125</sup>I, <sup>123</sup>I, <sup>124</sup>I, <sup>131</sup>I, <sup>75</sup>Br, <sup>76</sup>Br or <sup>77</sup>Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound of Formula (Ia) that has incorporated at least one radionuclide; in some embodiments the radionuclide is selected from the group consisting of <sup>3</sup>H, <sup>14</sup>C, <sup>125</sup>I, <sup>35</sup>S and <sup>82</sup>Br. Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide <sup>3</sup>H and/or <sup>14</sup>C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., <sup>2</sup>H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes supra and Examples infra, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed infra. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the more scarce radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas—This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [<sup>3</sup>H]—This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

C. Reduction with Lithium Aluminum Hydride [<sup>3</sup>H]—This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

D. Tritium Gas Exposure Labeling—This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. N-Methylation using Methyl Iodide [<sup>3</sup>H]—This procedure is usually employed to prepare O-methyl or N-methyl (3H) products by treating appropriate precursors with high specific activity methyl iodide (3. This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of <sup>125</sup>I into target molecules include:

A. Sandmeyer and like reactions—This procedure transforms an aryl or heteroaryl amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to <sup>125</sup>I labeled compound using Na<sup>125</sup>I. A represented procedure was reported by Zhu, D.-G. and co-workers in *J. Org. Chem.* 2002, 67, 943-948.

B. Ortho <sup>125</sup>Iodination of phenols—This procedure allows for the incorporation of <sup>125</sup>I at the ortho position of a phenol



as reported by Collier, T. L. and co-workers in *J. Labeled Compd Radiopharm.* 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with  $^{125}\text{I}$ —This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e.  $\text{Pd}(\text{Ph}_3\text{P})_4$ ] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g.,  $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$ ]. A represented procedure was reported by Bas, M.-D. and co-workers in *J. Labeled Compd Radiopharm.* 2001, 44, S280-S282.

A radio-labeled 5-HT<sub>2A</sub> receptor compound of Formula (Ia) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the “radio-labeled compound of Formula (Ia)” to the 5-HT<sub>2A</sub> receptor. Accordingly, the ability of a test compound to compete with the “radio-labeled compound of Formula (Ia)” for the binding to the 5-HT<sub>2A</sub> receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the 5-HT<sub>2A</sub> receptor. In one embodiment the labeled compound has an IC<sub>50</sub> less than about 500 μM, in another embodiment the labeled compound has an IC<sub>50</sub> less than about 100 μM, in yet another embodiment the labeled compound has an IC<sub>50</sub> less than about 10 μM, in yet another embodiment the labeled compound has an IC<sub>50</sub> less than about 1 μM, and in still yet another embodiment the labeled inhibitor has an IC<sub>50</sub> less than about 0.1 μM.

Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, inter alia, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

## EXAMPLES

### Example 1

#### Syntheses of Compounds of the Present Invention

Illustrated syntheses for compounds of the present invention are shown in FIGS. 1 through 8 where the symbols have the same definitions as used throughout this disclosure.

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, supra and infra, are named according to CS Chem Draw Ultra Version 7.0.1 or AutoNom 2000. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on a Varian Mercury Vx400 equipped with a 4 nucleus auto switchable probe and z-gradient or a Bruker Avance-400 or 500 MHz equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s=singlet, d=doublet, dd=doublet of doublet, ddd=doublet of doublet of doublet, dt=doublet of triplet,

t=triplet, q=quartet, m=multiplet, br=broad. Microwave irradiations were carried out using the Emrys Synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F<sub>254</sub> (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Buchi rotary evaporator. Celite 545® was used during palladium filtrations.

LCMS specs: 1) PC: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2. 2) Mac: HPLC-pumps: LC-8A VP, Shimadzu Inc; HPLC system controller: SCL-10A VP, Shimadzu Inc. UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex Software: Masschrom 1.5.2.

### Example 1.1

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 45)

To a solution of N-(4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-trifluoromethyl-benzamide (0.050 g, 99.5 μmol) in DMA (3 mL) were added 1-methyl-piperidin-4-ylamine (17.0 mg, 149 μmol) and N,N-diisopropylethylamine (34.7 μL, 199 μmol). The reaction mixture was heated at 150° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube, then purified by preparative HPLC. The corresponding fractions were collected and lyophilized to afford a double TFA salt of the title compound in 40.1% yield as a white solid (hygroscopic). LCMS m/z (%)=536 (M+H,  $^{35}\text{Cl}$ , 100), 538 (M+H,  $^{37}\text{Cl}$ , 43).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 9.11-8.92 (m, 2H), 8.31-8.24 (m, 2H), 8.01-7.95 (m, 2H), 7.80 (t, J=7.8 Hz, 1H), 7.73 (d, J=2.6 Hz, 1H), 7.71 (s, 1H), 7.31 (d, J=9.1 Hz, 1H), 4.37-4.23 (m, 2H), 3.69 (s, 3H), 3.42-3.05 (m, 4H), 2.93-2.80 (m, 2H), 2.78 (s, 3H), 2.18-2.07 (m, 2H), 1.99-1.82 (m, 1H), 1.71-1.58 (m, 2H).

### Example 1.2

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-[2-(tetrahydro-pyran-4-ylamino)ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 61)

A mixture of N-(4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-trifluoromethyl-benzamide (0.050 g, 99.5 μmol), tetrahydropyran-4-ylamine (15.1 mg, 149 μmol) and N,N-diisopropylethylamine (34.7 μL, 199 μmol) in DMA (3 mL) was heated at 150° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube then purified by preparative HPLC. The corresponding fractions were collected and lyophilized to afford a TFA salt of the title compound in 66.7% yield as a white solid (hygroscopic). LCMS m/z (%)=523 (M+H,  $^{35}\text{Cl}$ , 100), 525 (M+H,  $^{37}\text{C}$ , 40).  $^1\text{H}$  NMR (400, DMSO-d<sub>6</sub>) δ 10.55 (s, 1H), 8.79-8.61 (m, 2H), 8.29-8.26 (m, 2H), 7.99-7.96 (m, 2H), 7.80 (t, J=7.8 Hz, 1H),



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7.71 (d, J=2.6 Hz, 1H), 7.69 (s, 1H), 7.31 (d, J=9.1 Hz, 1H), 4.39-4.22 (m, 2H), 3.91-3.82 (m, 2H), 3.6 g (s, 3H), 3.41-3.29 (m, 1H), 3.22-3.05 (m, 4H), 1.85-1.73 (m, 2H), 1.51-1.32 (m, 2H).

## Example 1.3

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-yloxy)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 78)

To a solution of N-(4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-trifluoromethyl-benzamide (0.100 g, 199  $\mu\text{mol}$ ) in DMA (3 mL) were added 1-methylpiperidin-4-ol (34.4 mg, 298  $\mu\text{mol}$ ) and N,N-diisopropylethylamine (69.5  $\mu\text{L}$ , 398  $\mu\text{mol}$ ). The reaction mixture was heated at 150° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube then purified by preparative HPLC. The corresponding fractions were collected and lyophilized to afford a TFA salt of the title compound in 35.5% yield as a white solid. LCMS m/z (%)=537 (N+H,  $^{35}\text{Cl}$ , 100), 539 (M+H,  $^{37}\text{Cl}$ , 40).

## Example 1.4

Preparation of 3-Methoxy-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-benzamide (Compound 72)

A mixture of N-(4-(2-aminoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (14.5 mg, 81.9  $\mu\text{mol}$ ), 3-bromo-1,1,1-trifluoropropane (30 mg, 81.9  $\mu\text{mol}$ ) and triethylamine (34.2  $\mu\text{L}$ , 246  $\mu\text{mol}$ ) in DMF was heated to 150° C. for 1 hour under microwave irradiation in a heavy-walled sealed tube. The crude product was purified by PLC. The proper fractions were collected and lyophilized to afford the title compound as a brown solid in 2.3% yield. LCMS m/z (%)=463 (M+H, 100).  $^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  2.6 (m, 2H) 3.2 (dd, J=15.4, 7.8 Hz, 2H) 3.5 (m, 2H) 3.8 (s, 3H) 3.9 (s, 3H) 4.4 (m, 2H) 6.4 (d, J=2.0 Hz, 1H) 7.2 (dd, J=8.6, 3.5 Hz, 1H) 7.3 (d, J=9.1 Hz, 1H) 7.4 (t, J=8.1 Hz, 1H) 7.5 (m, 2H) 7.6 (d, J=2.0 Hz, 1H) 7.7 (d, J=2.5 Hz, 1H) 7.9 (dd, J=9.1, 2.5 Hz, 1H).

## Example 1.5

Preparation of N-[4-[2-(3-Cyano-propylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 80)

The title compound was prepared in a similar manner as described in Example 1.4 to give a white solid in 15.9% yield. LCMS m/z (%)=434 (M+H, 100).  $^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  1.8 (m, 2H) 2.4 (t, J=7.1 Hz, 2H) 2.9 (m, 2H) 3.4 (m, 2H) 3.7 (s, 3H) 3.8 (s, 3H) 4.1 (m, 1H) 4.2 (m, 2H) 6.3 (d, J=2.0 Hz, 1H) 7.0 (dd, J=8.1, 2.5 Hz, 1H) 7.1 (d, J=9.1 Hz, 1H) 7.3 (t, J=8.1 Hz, 1H) 7.4 (m, 2H) 7.5 (d, J=2.0 Hz, 1H) 7.6 (d, J=2.5 Hz, 1H) 7.7 (dd, J=9.1, 2.5 Hz, 1H).

## Example 1.6

Preparation of N-[4-[2-(Cyanomethyl-amino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 33)

The title compound was prepared in a similar manner as described in Example 1.4 to give a yellow oil in 16.1% yield.

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LCMS m/z=406 (M+H).  $^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  3.5 (m, 2H) 3.8 (s, 3H) 3.9 (s, 3H) 4.0 (s, 2H) 4.3 (m, 2H) 6.4 (d, J=2.0 Hz, 1H) 7.2 (dd, J=7.8, 3.3 Hz, 1H) 7.2 (d, J=9.1 Hz, 1H) 7.4 (t, J=7.8 Hz, 1H) 7.5 (m, 2H) 7.6 (d, J=2.0 Hz, 1H) 7.7 (d, J=2.5 Hz, 1H) 7.9 (dd, J=8.8, 2.8 Hz, 1H).

## Example 1.7

Preparation of N-[4-[2-(2-Cyano-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 70)

The title compound was prepared in a similar manner as described in Example 1.4 to give a yellow oil in 4.72% yield. LCMS m/z (%)=420 (M+H, 100).

## Example 1.8

Preparation of N-[4-[2-(2-Methanesulfonyl-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 4)

A mixture of 2-(methylsulfonyl)ethyl methanesulfonate (16.6 mg, 81.9  $\mu\text{mol}$ ) and N-(4-(2-aminoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (30 mg, 81.9  $\mu\text{mol}$ ) in DMF was heated to 150° C. for 1 hour under microwave irradiation in a heavy-walled sealed tube. The crude product was purified by HPLC. The proper fractions were collected and lyophilized to afford the title compound as a yellow solid in 18.5% yield. LCMS m/z (%)=473 (M+H, 100).

## Example 1.9

Preparation of N-[4-[2-(2,2-Difluoro-propylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 10)

The title compound was prepared in a similar manner as described in Example 1.8 to give a yellow oil in 5.63% yield. LCMS m/z (%)=445 (M+H, 100).

## Example 1.10

Preparation of N-[4-(2-Acetimidoylamino-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 21)

A mixture of N-4-(2-aminoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (30 mg, 81.9  $\mu\text{mol}$ ), ethyl acetimidate hydrochloride (12.1 mg, 98.2  $\mu\text{mol}$ ) and triethylamine (22.8  $\mu\text{L}$ , 164  $\mu\text{mol}$ ) in dichloromethane was stirred at room temperature overnight. The mixture was concentrated and the crude product was purified by HPLC. The proper fractions were collected and lyophilized to afford the title compound as a white solid in 7.01% yield. LCMS m/z (%)=408 M+H, 100).  $^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  2.2 (s, 2H) 2.7 (s, 3H) 3.0 (s, 1H) 3.6 (t, J=5.1 Hz, 2H) 3.7 (p, 3H) 3.9 (s, 3H) 4.2 (t, J=5.1 Hz, 2H) 6.3 (d, J=2.0 Hz, 1H) 7.2 (dd, J=7.3, 2.8 Hz, 1H) 7.2 (d, J=8.6 Hz, 1H) 7.4 (t, J=7.8 Hz, 1H) 7.5 (m, 2H) 7.6 (d, J=2.0 Hz, 1H) 7.7 (d, J=3.0 Hz, 1H) 7.8 (dd, J=9.1, 2.5 Hz, 1H).



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## Example 1.11

Preparation of N-[4-(2-Guanidino-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 44)

A mixture of N-(4-(2-aminoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (30 mg, 81.87  $\mu\text{mol}$ ), 1,3-di-boc-2-trifluoromethylsulfonylguanidine (38.45 mg, 98.25  $\mu\text{mol}$ ) and triethylamine (22.82  $\mu\text{L}$ , 163.7  $\mu\text{mol}$ ) in DCM was stirred at room temperature for 5 hours. Then to the mixture was added TFA (6.308  $\mu\text{L}$ , 81.87  $\mu\text{mol}$ ) and the mixture was stirred overnight. The crude product was purified by column chromatography to afford the title compound as brown oil in 49.43% yield. LCMS  $m/z$  (%)=409 (M+H, 100).  $^1\text{H}$  NMR (400 MHz,  $\text{MeOH-d}_4$ )  $\delta$  3.5 (t, J=5.1 Hz, 2H) 3.7 (s, 3H) 3.9 (s, 3H) 4.1 (t, J=5.1 Hz, 2H) 6.3 (d, J=2.0 Hz, 1H) 7.1 (d, J=5.6 Hz, 1H) 7.2 (d, J=9.1 Hz, 1H) 7.4 (t, J=7.8 Hz, 1H) 7.5 (m, 2H) 7.5 (d, J=2.0 Hz, 1H) 7.6 (d, J=3.0 Hz, 1H) 7.8 (dd, J=8.8, 2.8 Hz, 1H).

## Example 1.12

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-2-fluoro-4-methoxy-benzamide (Compound 56)

Step A: Preparation of N-(4-(2-Aminoethoxy)-3-(4-chloro-1-methyl-1H-pyrazol-5-yl)phenyl)-2-fluoro-methoxybenzamide

A mixture of 2-fluoro-4-methoxybenzoic acid (92.8 mg, 545  $\mu\text{mol}$ ), tert-butyl 2-(4-amino-2-(4-chloro-1-methyl-1H-pyrazol-5-yl)phenoxy)ethylcarbamate (200 mg, 545  $\mu\text{mol}$ ), HATU (207 mg, 545  $\mu\text{mol}$ ) and triethylamine (76.0  $\mu\text{L}$ , 545  $\mu\text{mol}$ ) in dichloromethane was stirred at room temperature overnight. The reaction was diluted with dichloromethane and washed with water. The organic layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. To the crude product was added 2M HCl (5 eq.). The mixture was stirred at room temperature overnight. The mixture was concentrated and the title compound was obtained as a yellow oil. LCMS  $m/z$  (%)=419 (M+H,  $^{35}\text{Cl}$ , 100), 421 (M+H,  $^{37}\text{Cl}$ , 40).

Step B: Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-2-fluoro-4-methoxy-benzamide (Compound 56)

The title compound was prepared in a similar manner as described in Example 1.4 to give a yellow solid in 2.85% yield. LCMS  $m/z$  (%)=515 (M+H,  $^{35}\text{Cl}$ , 100), 517 (M+H,  $^{37}\text{Cl}$ , 31).

## Example 1.13

Preparation of 5-Methyl-isoxazole-3-carboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-amide (Compound 1)

Step A: Preparation of N-(4-(2-Aminoethoxy)-3-(4-chloro-1-methyl-1H-pyrazol-5-yl)phenyl)-5-methyl-isoxazole-3-carboxamide

The title compound was prepared in a similar manner as described in Example 1.12, Step A. LCMS  $m/z$  (%)=376 (M+H,  $^{35}\text{Cl}$ , 100), 378 (M+H,  $^{37}\text{Cl}$ , 28).

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Step B: Preparation of 5-Methyl-isoxazole-3-carboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-amide (Compound 1)

The title compound was prepared in a similar manner as described in Example 1.4 to give a brown oil in 2.79% yield. LCMS  $m/z$ =472 (M+H).

## Example 1.14

Preparation of 5-Methyl-isoxazole-3-carboxylic acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-methanesulfonyl-ethylamino)-ethoxy]-phenyl}-amide (Compound 8)

The title compound was prepared in a similar manner as described in Example 1.8 to give a brown oil in 1.3% yield. LCMS  $m/z$  (%)—482 (M+H, 100).

## Example 1.15

Preparation of 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(3,3,3-trifluoro-propylamino)-ethoxy]-phenyl}-benzamide (Compound 77)

The title compound was prepared in a similar manner as described in Example 1.4 to give a brown oil in 5.2% yield. LCMS  $m/z$  (%)=451 (M+H, 100).  $^1\text{H}$  NMR (400 MHz,  $\text{MeOH-d}_4$ )  $\delta$  2.6 (m, 2H) 3.2 (m, 2H) 3.5 (m, 2H) 3.8 (s, 3H) 4.4 (m, 2H) 6.4 (d, J=2.0 Hz, 1H) 7.3 (d, J=9.1 Hz, 1H) 7.4 (m, 1H) 7.6 (m, 2H) 7.7 (m, 2H) 7.8 (d, J=8.6 Hz, 1H) 7.9 (dd, J=8.8, 2.8 Hz, 1H).

## Example 1.16

Preparation of N-[4-[2-(2-Cyano-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-fluoro-benzamide (Compound 16)

The title compound was prepared in a similar manner as described in Example 1.4 to give a yellow oil in 2.85% yield. LCMS  $m/z$  (%)=408 (M+H, 100).  $^1\text{H}$  NMR (400 MHz,  $\text{MeOH-d}_4$ )  $\delta$  2.8 (t, J=6.8 Hz, 2H) 3.2 (t, J=7.1 Hz, 2H) 3.5 (m, 2H) 3.8 (s, 3H) 4.4 (m, 2H) 6.4 (d, J=2.0 Hz, 1H) 7.3 (d, J=8.6 Hz, 1H) 7.4 (m, 1H) 7.6 (m, 1H) 7.6 (t, J=2.3 Hz, 1H) 7.7 (m, 2H) 7.8 (d, J=8.1 Hz, 1H) 7.9 (dd, J=8.6, 2.5 Hz, 1H).

## Example 1.17

Preparation of 3-Fluoro-N-[4-[2-(2-methanesulfonyl-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 28)

The title compound was prepared in a similar manner as described in Example 1.8 to give a brown oil in 9.4% yield. LCMS  $m/z$  (%)=461 (M+H, 100).

## Example 1.18

Preparation of 2,4-Difluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-benzamide (Compound 19)

To a solution of N-[4-(2-bromo-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-2,4-difluoro-benzamide (0.050 g, 0.12 mmol) in N,N-dimethylacetamide (2.0 mL) was added N,N-diisopropylethylamine (0.040 mL, 0.23 mmol) and 4-aminotetrahydropyran (0.032 mL, 0.32 mmol) in a heavy-walled



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sealed tube. The solution was heated under microwave irradiation at 120° C. for 1 h. The solution was concentrated and purified by RP-HPLC. Lyophilization afforded a TFA salt as a brown solid (0.039 g, 59%). LCMS m/z (%)=457 (M+H, 100). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.45 (s, 1H), 7.81 (dd, J=2.6, 9.0 Hz, 1H), 7.79-7.72 (, 1H), 7.66 (d, J=2.6 Hz, 1H), 7.52 (d, J=1.8 Hz, 1H), 7.48-7.40 (m, 1H), 7.28-7.20 (m, 2H), 6.34 (d, J=1.8 Hz, 1H), 4.28-4.23 (m, 2H), 3.84 (dd, J=4.0, 11.4 Hz, 2H), 3.69 (s, 3H), 3.40-3.32 (m, 2H), 3.32-3.14 (m, 2H), 3.14-3.03 (m, 1H), 1.85 (m, 2H), 1.48-1.36 (m, 2H).

## Example 1.19

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-fluoro-benzamide (Compound 22)

A solution of 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-fluoro-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic acid tert-butyl ester (0.035 g, 0.061 mmol) in 4 M HCl in dioxane (2.2 mL) was shaken on a rotary stirrer for 3 hours. The reaction was concentrated and purified by RP-HPLC. Lyophilization afforded a TFA salt as a pale solid (0.021 g, 48%). LCMS m/z (%)=472 (M+H, <sup>35</sup>Cl, 100), 474 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.40 (s, 1H), 7.96 (dd, J=2.6, 9.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.77 (m, 1H), 7.73 (d, J=2.6 Hz, 1H), 7.68 (s, 1H), 7.64-7.57 (m, 1H) 7.47 (dt, J=2.6, 8.8 Hz, 1H), 7.30 (d, J=9.1 Hz, 1H), 4.37-4.22 (m, 2H), 3.69 (s, 3H), 3.42-3.28 (m, 4H), 3.22-3.10 (m, 1H), 2.86-2.70 (m, 2H), 2.05 (d, J=12.1 Hz, 2H), 1.65-1.50 (m, 2H).

## Example 1.20

Preparation of 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-trifluoromethyl-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic Acid Tert-Butyl Ester (Compound 23)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a yellow solid, 59% yield. LCMS m/z (%)=622 (M+H, <sup>35</sup>Cl, 100), 624 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.50 (s, 1H), 8.30-8.24 (m, 2H), 7.97 (d, J=7.8 Hz, 1H), 7.90 (dd, J=2.6, 9.0 Hz, 1H), 7.82-7.76 (m, 1H), 7.70 (d, J=2.6 Hz, 1H), 7.63 (s, 1H), 7.25 (d, J=9.1 Hz, 1H), 4.11-4.00 (m, 2H), 3.81-3.73 (m, 2H), 3.68 (s, 3H), 2.86-2.70 (m, 4H), 1.72-1.66 (m, 2H), 1.57-1.48 (m, 1H), 1.39 (s, 9H), 1.06-0.96 (m, 2H).

## Example 1.21

Preparation of 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-methoxy-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic acid tert-butyl ester (Compound 24)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 37% yield. LCMS m/z (%)=584 (M+H, <sup>35</sup>Cl, 100), 586 (M+H, <sup>37</sup>Cl, 26). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.31 (s, 1H), 7.98 (dd, J=2.4, 9.0 Hz, 1H), 7.72 (d, J=2.6 Hz, 1H), 7.69 (s, 1H), 7.54 (d, J=7.6 Hz, 1H), 7.49-7.43 (m, 2H), 7.28 (d, J=9.1 Hz, 1H), 7.17 (dd, J=2.7, 8.9 Hz, 1H), 4.35-4.20 (m, 2H), 4.00-3.90 (m, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 3.40-3.30 (m, 2H), 3.15-3.03 (m, 1H), 1.92-1.81 (m, 2H), 1.41 (s, 9H), 1.29-1.20 (m, 4H).

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## Example 1.22

Preparation of 2,4-Difluoro-N-[4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 27)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 36% yield. LCMS m/z (%)=470 (M+H, 100). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.44 (s, 1H), 7.80 (dd, J=2.6, 9.0 Hz, 1H), 7.79-7.71 (m, 1H), 7.66 (d, J=2.6 Hz, 1H), 7.53 (d, J=6.2 Hz, 1H), 7.58-7.40 (m, 2H), 7.29-7.20 (m, 2H), 6.35 (d, J=1.8 Hz, 1H), 4.28-4.22 (m, 2H), 3.70 (s, 3H), 3.50-2.74 (m, 9H), 2.14-2.06 (m, 2H), 1.96-1.84 (m, 1H), 1.70-1.66 (m, 2H).

## Example 1.23

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide (Compound 32)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a white solid as a TFA salt, 99% yield. LCMS m/z (%)=484 (M+H, <sup>35</sup>Cl, 100), 486 (M+H, <sup>37</sup>Cl, 43). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.30 (s, 1H), 7.96 (dd, J=2.6, 9.0 Hz, 1H), 7.74 (d, J=2.6 Hz, 1H), 7.68 (s, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.49-7.47 (m, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.29 (d, J=9.1 Hz, 1H), 7.27 (dd, J=1.9, 8.1 Hz, 1H), 4.36-4.23 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.38-3.28 (m, 4H), 3.22-3.11 (m, 1H); 2.86-2.70 (m, 2H), 2.04 (d, J=12.3 Hz, 2H), 1.65-1.50 (m, 2H).

## Example 1.24

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-fluoro-benzamide (Compound 34)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 28% yield. LCMS m/z (%)=486 (M+H, <sup>35</sup>Cl, 100), 488 (M+H, <sup>37</sup>Cl, 38). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.40 (s, 1H), 7.96 (dd, J=2.6, 9.0 Hz, 2H), 7.82 (d, J=7.9 Hz, 1H), 7.80-7.75 (m, 1H), 7.74 (d, J=2.6 Hz, 1H), 7.65-7.57 (m, 1H), 7.47 (dt, J=2.7, 8.4 Hz, 1H), 7.30 (d, J=9.1 Hz, 1H), 4.36-4.22 (m, 2H), 3.69 (s, 3H), 3.54-3.42 (m, 3H), 3.21-3.08 (m, 1H), 2.91-2.73 (m, 4H), 2.11 (d, J=12.7 Hz, 2H), 2.00-1.82 (m, 2H), 1.73-1.56 (m, 2H).

## Example 1.25

Preparation of 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-trifluoromethyl-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic Acid Ethyl Ester (Compound 39)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a yellow oil, 70% yield. LCMS m/z (%)=594 (M+H, <sup>35</sup>Cl, 100), 596 (M+H, <sup>37</sup>Cl, 45). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.49 (s, 1H), 8.29 (bs, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.97 (d, J=7.9 Hz, 1H), 7.90 (dd, J=2.6, 9.0 Hz, 1H), 7.79 (t, J=6.2 Hz, 1H), 7.69 (d, J=2.7 Hz, 1H), 7.63 (s, 1H), 7.25 (d, J=9.1 Hz, 1H), 4.09 (q, J=-5.3 Hz, 2H), 4.02 (q, J=7.1 Hz, 2H), 3.84-3.76 (m, 2H), 3.67 (s, 3H), 2.78-2.76 (m, 4H), 1.74-1.50 (m, 3H), 1.17 (t, J=7.1 Hz, 3H), 1.08-0.98 (m, 2H).



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## Example 1.26

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide (Compound 41)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a tan solid as a TFA salt, 27% yield. LCMS m/z (%)=498 (M+H, <sup>35</sup>Cl, 100), 500 (M+H, <sup>37</sup>Cl, 51). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.31 (s, 1H), 7.97 (dd, J=2.7, 9.0 Hz, 1H), 7.73 (d, J=2.6 Hz, 1H), 7.71 (s, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.49-7.47 (m, 2H), 7.29 (d, J=9.2 Hz, 1H), 7.17 (dd, J=2.6, 8.2 Hz, 1H), 4.34-4.20 (m, 2H), 3.83 (s, 3H), 3.68 (s, 3H), 3.22-3.10 (m, 1H), 2.90-2.73 (m, 4H), 2.55-2.45 (m, 3H), 2.15-2.08 (m, 2H), 2.00-1.75 (m, 2H), 1.71-1.50 (m, 2H).

## Example 1.27

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-((R)-6-oxo-piperidin-3-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide (Compound 49)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 8% yield. LCMS m/z (%)=498 (M+H, <sup>35</sup>Cl, 100), 500 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.31 (s, 1H), 7.96 (dd, J=2.7, 9.1 Hz, 1H), 7.78-7.69 (m, 1H), 7.68-7.64 (m, 1H), 7.56-7.51 (m, 1H), 7.50-7.46 (m, 1H), 7.44 (dd, J=2.3, 7.9 Hz, 1H), 7.28 (d, J=9.1 Hz, 1H), 7.19-7.14 (m, 1H), 4.36-4.24 (m, 1H), 4.12-4.02 (m, 1H), 3.82 (s, 3H), 3.78-3.48 (m, 2H), 3.66 (s, 3H), 3.20-3.10 (m, 1H), 2.96-2.80 (m, 2H), 2.11-2.10 (m, 1H), 1.30-1.18 (m, 3H).

## Example 1.28

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran 4-ylamino)-ethoxy]-phenyl}-3-fluoro-benzamide (Compound 51)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 69% yield. LCMS=473 (M+H, <sup>35</sup>Cl, 100), 475 (M+H, <sup>37</sup>Cl, 19). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.40 (s, 1H), 7.97 (dd, J=2.6, 9.0 Hz, 1H), 7.82 (d, J=7.8 Hz, 1H), 7.77 (dt, J=2.2, 9.9 Hz, 1H), 7.72 (d, J=2.6 Hz, 1H), 7.70 (s, 1H), 7.64-7.57 (m, 1H), 7.46 (dt, J=2.7, 8.8 Hz, 1H), 7.30 (d, J=9.1 Hz, 1H), 4.36-4.23 (m, 2H), 3.86 (dd, J=4.0, 11.4 Hz, 2H), 3.68 (s, 3H), 3.40-3.30 (m, 1H), 3.23-3.05 (m, 4H), 1.79 (d, J=9.6 Hz, 2H), 1.50-1.35 (m, 2H).

## Example 1.29

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(tetrahydro-pyran-4-ylamino)-ethoxy]-phenyl}-3-methoxy-benzamide (Compound 53)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 32% yield. LCMS m/z (%)=485 (M+H, <sup>35</sup>Cl, 100), 487 (M+H, <sup>37</sup>Cl, 36). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.31 (s, 1H), 7.97 (dd, J=2.7, 9.1 Hz, 1H), 7.73 (d, J=2.6 Hz, 1H), 7.69 (s, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.49-7.46 (m, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.28 (d, J=9.1 Hz, 1H), 7.17 (dd, J=2.6, 8.1 Hz,

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1H), 4.35-4.22 (m, 2H), 3.87 (dd, J=4.0, 11.6 Hz, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 3.40-3.14 (m, 2H), 3.25-3.14 (m, 4H), 1.79 (m, 2H), 1.48-1.35 (m, 2H).

## Example 1-30

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(piperidin-4-ylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 60)

The title compound was prepared in a similar manner as described in Example 1.19 to afford a tan solid as an HCl salt, 99% yield. LCMS m/z (%)=522 (M+H, <sup>35</sup>Cl, 100), 524 (M+H, <sup>37</sup>Cl, 42). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.60 (s, 1H), 8.34-8.26 (m, 2H), 8.10-7.94 (m, 2H), 7.80 (t, J=7.8 Hz, 1H), 7.75 (d, J=2.6 Hz, 1H), 7.68 (s, 1H), 7.32 (d, J=9.1 Hz, 1H), 4.44-4.30 (m, 2H), 3.69 (s, 3H) 3.74-3.64 (m, 2H), 3.37-3.27 (m, 2H), 3.21-3.10 (m, 1H), 2.86-2.70 (m, 2H), 2.09 (d, J=12.1 Hz, 2H), 1.83-1.70 (m, 2H).

## Example 1.31

Preparation of 4-{2-[2-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(3-fluoro-benzoylamino)-phenoxy]-ethylamino}-piperidine-1-carboxylic Acid Tert-Butyl Ester (Compound 64)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 46% yield. LCMS m/z (%)=572 (M+H, <sup>35</sup>Cl, 100), 574 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.40 (s, 1H), 7.97 (dd, J=2.6, 9.1 Hz, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.79-7.74 (m, 1H), 7.72 (d, J=2.6 Hz, 1H), 7.69 (s, 1H), 7.64-7.57 (m, 1H), 7.47 (dt, J=2.6, 8.8 Hz, 1H), 7.29 (d, J=9.2 Hz, 1H), 4.34 (m, 2H), 4.02-3.87 (m, 2H), 3.68 (s, 3H), 3.41-3.31 (m, 2H), 3.13-3.02 (m, 1H), 1.91-1.80 (m, 2H), 1.40 (s, 9H), 1.30-1.29 (m, 4H).

## Example 1.32

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-hydroxy-ethoxy)-phenyl]-3-methoxy-benzamide (Compound 68)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid, 14% yield. LCMS m/z (%)=402 (M+H, <sup>35</sup>Cl, 100), 404 (M+H, <sup>37</sup>Cl, 33). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.24 (s, 1H), 7.88 (dd, J=2.6, 9.0 Hz, 1H), 7.71 (d, J=2.6 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.48 (m, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.23 (d, J=9.1 Hz, 1H), 7.16 (dd, J=2.4, 8.0 Hz, 1H), 4.11-4.00 (m, 2H), 3.83 (s, 3H), 3.68 (s, 3H), 3.70-3.62 (m, 2H).

## Example 1.33

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-yloxy)ethoxy]-phenyl}-3-methoxy-benzamide (Compound 71)

The title compound was prepared in a similar manner as described in Example 1.18 to afford an orange solid, 41% yield. LCMS m/z (%)=499 (M+H, <sup>35</sup>Cl, 100), 451 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.28 (s, 1H), 7.96 (dd, J=2.5, 9.0 Hz, 1H), 7.72 (m, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.50-7.48 (m, 1H), 7.45 (t, J=7.9 Hz, 1H), 7.31 (dd, J=2.5, 9.1 Hz, 1H), 7.17 (dd, J=2.5, 8.2 Hz,



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1H), 5.16-4.92 (m, 1H), 4.55-4.46 (m, 2H), 3.83 (s, 3H), 3.86-3.64 (m, 2H), 3.66 (s, 3H), 3.50-3.12 (m, 4H), 2.95 (m, 3H), 1.98-1.49 (m, 4H).

## Example 1.34

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1-methyl-piperidin-4-yloxy)-ethoxy]-phenyl}-3-fluoro-benzamide (Compound 73)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt, 87% yield. LCMS m/z (%)=487 (M+H, <sup>35</sup>Cl, 100), 489 (M+H, <sup>37</sup>Cl, 47). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.41 (s, 1H), 7.96 (dd, J=2.6, 9.0 Hz, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.78 (m, 1H), 7.72 (m, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.63-7.57 (m, 1H), 7.46 (dt, J=2.5, 8.7 Hz, 1H), 7.32 (dd, J=2.5, 9.1 Hz, 1H), 5.20-4.92 (m, 1H), 4.56-4.45 (m, 2H), 3.86-3.68 (m, 2H), 3.66 (s, 3H), 3.48-3.13 (m, 4H), 3.01-2.90 (m, 3H), 1.98-1.50 (m, 4H).

## Example 1.35

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-hydroxy-ethoxy)-phenyl]-3-fluoro-benzamide (Compound 76)

The title compound was prepared in a similar manner as described in Example 1.18 to afford a pale solid as a TFA salt. LCMS m/z (%)=390 (M+H, <sup>35</sup>Cl, 100), 392 (M+H, <sup>37</sup>Cl, 33). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.32 (s, 1H), 7.89 (dd, J=2.6, 9.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.79-7.74 (m, 1H), 7.71 (d, J=2.6 Hz, 1H), 7.63 (s, 1H), 7.63-7.56 (m, 1H), 7.45 (dt, J=2.5, 8.3 Hz, 1H), 7.24 (d, J=9.1 Hz, 1H), 4.12-4.00 (m, 2H), 3.71-3.63 (m, 2H), 3.68 (s, 3H).

## Example 1.36

Preparation of N-[4-[2-(2-Hydroxy-ethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethyl-benzamide (Compound 59)

A mixture of N-[4-(2-bromoethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethyl-benzamide (0.500 g, 1.07 mmol), ethanolamine (0.0969 mL, 1.60 mmol) and N,N-diisopropylethylamine (0.372 mL, 2.14 mmol) in 3.0 mL of DMA was heated to 150° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 65% yield. LCMS m/z=449 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.16 (d, J=8.08 Hz, 2H), 7.91 (d, J=8.08 Hz, 2H), 7.75 (s, 1H), 7.48 (s, 1H), 7.23 (d, J=8.89 Hz, 1H), 6.32 (s, 1H), 5.24 (t, J=5.56 Hz, 1H), 4.32 (t, J=5.80 Hz, 2H), 3.70 (s, 3H), 3.55 (q, J=10.61 Hz, 2H), 3.30 (t, J=5.50 Hz, 2H), 2.85 (t, J=5.50 Hz, 2H).

## Example 1.37

N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 3)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.400 g, 0.8 mmol), ethanolamine (0.07 mL, 1 mmol) and

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N,N-diisopropylethylamine (0.3 mL, 2 mmol) in 3.0 mL of DMA was heated to 150° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 52% yield. LCMS m/z (%)=482 (M+H, <sup>35</sup>Cl, 100), 484 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 M DMSO-d<sub>6</sub>) δ 10.61 (s, 1H), 8.27-8.32 (m, 2H), 7.94-8.00 (m, 1H), 7.92 (s, 1H), 7.79 (t, J=7.71 Hz, 1H), 7.74 (d, J=2.78 Hz, 1H), 7.66 (s, 1H), 7.30 (d, J=9.09 Hz, 1H), 5.24 (t, J=4.80 Hz, 1H), 4.27-4.41 (m, 2H), 3.67 (m, 3H), 3.52-3.59 (m, 2H), 3.29 (t, J=5.56 Hz, 2H), 2.82-2.88 (m, 2H).

## Example 1.38

N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-ethylamino-ethoxy)-phenyl]-3-trifluoromethyl-benzamide (Compound 12)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.0900 g, 0.179 mmol), ethylamine (0.0155 mL, 0.269 mmol), N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 88% yield. LCMS m/z (%)=467 (M+H, <sup>35</sup>Cl, 100), 469 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.23-8.36 (m, 2H), 7.90-8.05 (m, 2H), 7.72-7.87 (m, 1H), 7.73 (d, J=2.78 Hz, 1H), 7.67 (s, 1H), 7.31 (d, J=9.09 Hz, 1H), 4.18-4.39 (m, 2H), 3.67 (s, 3H), 3.28 (t, J=5.81 Hz, 2H), 2.75-2.91 (m, 2H), 1.05 (t, J=6.57 Hz, 3H).

## Example 1.39

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-methoxy-ethylamino)-ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 15)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.090 g, 0.179 mmol), 2-methoxyethylamine (0.0202 mL, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 91% yield. LCMS m/z (%)=498 (M+H, <sup>35</sup>Cl, 100), 500 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.23-8.32 (m, 2H), 7.93-8.02 (m, 2H), 7.80 (t, J=7.83 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.67 (s, 1H), 7.29 (d, J=9.09 Hz, 1H), 4.21-4.40 (m, 2H), 3.67 (s, 3H), 3.3-3.4 (m, 4H), 3.29 (s, 3H), 2.96-3.01 (m, 2H), 1.18 (d, J=6.06 Hz, 1H).

## Example 1.40

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(1,1-dimethyl-propylamino)ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 18)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide



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(0.090 g, 0.179 mmol), tert-amylamine (0.0314 mL, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 27% yield. LCMS m/z (%)=509 (M+H, <sup>35</sup>Cl, 100), 511 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.22-8.33 (m, 3H), 7.94-8.02 (m, 2H), 7.80 (t, J=7.71 Hz, 1H), 7.73 (d, J=2.53 Hz, 1H), 7.30 (d, J=9.09 Hz, 1H), 4.15-4.36 (m, 2H), 3.67-3.74 (m, 3H), 3.56-3.66 (m, 2H), 3.21-3.31 (m, 2H), 1.52 (q, J=7.58 Hz, 2M), 1.14 (s, 6H), 0.80 (t, J=7.45 Hz, 3H).

## Example 1.41

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl) (2-isobutylamino-ethoxy)-phenyl]-3-trifluoromethyl-benzamide (Compound 31)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.090 g, 0.179 mmol), iso-butylamine (0.0196 g, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 76% yield. LCMS m/z (%)=495 (M+H, <sup>35</sup>Cl, 100), 497 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.40-8.45 (m, 1H), 8.23-8.32 (m, 2H), 7.94-8.01 (m, 2H), 7.80 (t, J=7.71 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.66 (s, 1H), 7.29 (d, J=9.09 Hz, 1H), 4.24-4.39 (m, 2H), 3.68 (s, 3H), 3.36 (s, 2H), 2.61 (d, J=3.28 Hz, 2H), 1.74-1.89 (m, 1H), 0.86 (dd, J=6.69, 1.89 Hz, 6H).

## Example 1.42

Preparation of N-[4-(2-Benzylamino-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (Compound 36)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.090 g, 0.179 mmol), benzylamine (0.0293 mL, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 74% yield. LCMS m/z (%)=530 (M+H, <sup>35</sup>Cl, 100), 532 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.57 (s, 1H), 8.98-9.05 (m, 1H), 8.22-8.33 (m, 2H), 7.92-8.02 (m, 2H), 7.80 (t, J=7.83 Hz, 1H), 7.74 (d, J=2.78 Hz, 1H), 7.63 (s, 1H), 7.40-7.48 (m, 3H), 7.33-7.40 (m, 2H), 7.31 (d, J=9.09 Hz, 1H), 4.27-4.43 (m, 2H), 4.02 (dd, J=15.92 Hz, 2H), 3.69 (s, 3H), 3.35-3.42 (m, 2H).

## Example 1.43

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-cyclopropylamino-ethoxy)-phenyl]-3-trifluoromethyl-benzamide (Compound 47)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide

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(0.090 g, 0.179 mmol), cyclopropylamine (0.0186 mL, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 84% yield. LCMS m/z (%)=480 (M+H, <sup>35</sup>Cl, 100), 482 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.75-8.90 (m, 1H), 8.23-8.32 (m, 2H), 7.92-8.02 (m, 2H), 7.80 (t, J=7.71 Hz, 1H), 7.73 (d, J=2.78 Hz, 1H), 7.65 (s, 1H), 7.31 (d, J=9.09 Hz, 1H), 4.22-4.40 (m, 2H), 3.68 (s, 4H), 3.34-3.45 (m, 2H), 0.56-0.78 (m, 4H).

## Example 1.44

Preparation of N-{3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-fluoro-ethylamino)ethoxy]-phenyl}-3-trifluoromethyl-benzamide (Compound 58)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.090 g, 0.179 mmol), 2-fluoroethylamine hydrochloride (0.03 g, 0.269 mmol) and N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 25% yield. LCMS m/z (%)=485 (M+H, <sup>35</sup>Cl, 100), 487 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.56 (s, 1H), 8.21-8.33 (m, 2H), 7.93-8.03 (m, 2H), 7.80 (t, J=7.71 Hz, 1H), 7.73 (d, J=2.53 Hz, 1H), 7.66-7.69 (m, 1H), 7.31 (d, J=9.09 Hz, 1H), 4.62-4.72 (m, 1H), 4.56 (t, J=4.67 Hz, 1H), 4.24-4.41 (m, 2H), 3.67 (s, 3H), 3.34-3.43 (m, 2H), 3.08-3.26 (m, 2H), 1.21-1.29 (m, 1H).

## Example 1.45

Preparation of N-[4-[2-(Carbamoylmethyl-amino)-ethoxy]-3-chloro-2-methyl-2H-pyrazol-3-yl]-phenyl]-3-trifluoromethyl-benzamide (Compound 29)

A mixture of N-[4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (0.0900 g, 0.179 mmol), glycine hydrochloride (0.0297 g, 0.269 mmol), N,N-diisopropylethylamine (0.0624 mL, 0.358 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 65% yield. LCMS m/z (%)=496 (M+H, <sup>35</sup>Cl, 100), 498 (M+H, <sup>37</sup>Cl, 40). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.55 (s, 1H), 8.23-8.32 (m, 2H), 7.91-8.01 (m, 2H), 7.80 (t, J=7.83 Hz, 1H), 7.75 (t, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.66 (s, 1H), 7.61 (s, 1H), 7.30 (d, J=9.09 Hz, 1H), 4.21-4.37 (m, 2H), 3.63-3.70 (m, 5H), 1.20-1.29 (m, 2H).

## Example 1.46

Preparation of 2,4-Difluoro-N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 13)

A mixture of N-[4-(2-bromo-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-2,4-difluoro-benzamide (0.100 g,



0.2292 mmol), ethanolamine (0.0138 mL, 0.2292 mmol) and potassium carbonate (0.06366 g, 0.4585 mmol) in 2.0 mL of DMA was heated to 120° C. for 30 minutes under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound in 47% yield. LCMS  $m/z=417$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.43 (s, 1H), 7.70-7.84 (m, 2H), 7.66 (d, J=2.53 Hz, 1H), 7.48 (d, J=2.02 Hz, 1H), 7.40-7.47 (m, 1H), 7.17-7.28 (m, 2H), 6.32 (d, J=1.77 Hz, 1H), 4.27 (t, J=5.18 Hz, 2H), 3.68 (s, 5H), 3.50-3.56 (m, 2H), 3.26-3.36 (m, 2H), 2.85 (s, 2H).

## Example 1.47

Preparation of 3-Fluoro-N-[4-[2-(2-hydroxy-ethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 69)

A mixture of N-[4-(2-bromo-ethoxy)-3-(2-ethyl-2H-pyrazol-3-yl)-phenyl]-3-fluoro-benzamide (0.2770 g, 0.66227 mmol), and N,N-diisopropylethylamine (0.23071 mL, 1.3245 mmol) in 1 mL of DMA was heated to 150° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 37% yield. LCMS  $m/z=399$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.36 (s, 1H), 7.88 (dd, J=8.97, 2.65 Hz, 1H), 7.81 (d, J=7.83 Hz, 1H), 7.73-7.79 (m, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.56-7.64 (m, 1H), 7.49 (d, J=1.77 Hz, 1H), 7.43-7.50 (m, 1H), 7.23 (d, J=8.84 Hz, 1H), 6.23 (d, J=2.35, 1H) 4.28 (t, J=5.31 Hz, 2H), 3.69 (s, 3H), 3.50-3.57 (m, 2H), 3.27-3.37 (m, 2H), 2.79-2.92 (m, 2H).

## Example 1.48

Preparation of N-[4-[2-(2-Hydroxy-ethylamino)ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 43)

A mixture of N-[4-(2-bromo-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (0.700 g, 1.627 mmol), ethanolamine (0.1476 mL, 2.440 mmol) and N,N-diisopropylethylamine (0.5682 mL, 3.254 mmol) in 10 mL of DMA was heated to 150° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 43% yield. LCMS  $m/z=411$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.83-2.89 (m, 2H), 3.27-3.37 (m, 2H), 3.50-3.57 (m, 2H), 3.69 (s, 3H), 3.83 (s, 3H), 4.28 (t, J=5.31 Hz, 2H), 6.32 (d, J=2.35 Hz, 1H) 7.15 (dd, J=7.47, 1.89 Hz, 1H), 7.23 (d, J=8.84 Hz, 1H) 7.43-7.50 (m, 3H), 7.52 (d, J=7.77 Hz, 1H), 7.72 (d, J=2.64 Hz, 1H), 7.88 (dd, J=8.97, 2.65 Hz, 1H), 10.36 (s, 1H).

## Example 1.49

Preparation of Cyclopropanecarboxylic Acid {3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-amide (Compound 65)

A mixture of cyclopropanecarboxylic acid [4-(2-bromo-ethoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-amide (0.2500 g, 0.6271 mmol), ethanolamine (0.03785 mL,

0.6271 mmol) and N,N-isopropylamine (0.2184 mL, 1.254 mmol) in 1 mL of DMA was heated to 150° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 75% yield. LCMS  $m/z=380$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.29 (s, 1H), 7.73 (dd, J=8.97, 2.65 Hz, 1H), 7.64 (s, 1H), 7.54 (d, J=2.53 Hz, 1H), 7.20 (d, J=8.84 Hz, 1H), 5.27 (br. s., 1H), 4.16-4.36 (m, 2H), 3.63 (s, 2H), 3.49-3.56 (m, 4H), 3.28-3.30 (m, 2H), 2.85 (d, J=1.01 Hz, 2H), 1.69-1.80 (m, 1H), 0.79 (d, J=6.32 Hz, 4H).

## Example 1.50

Preparation of 3-Methoxy-N-[4-[2-(2-methoxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 38)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0660 g, 0.15338 mmol), N,N-diisopropylethylamine (0.080366 mL, 0.46015 mmol) and 2-methoxyethanamine (0.020094 mL, 0.23007 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 92% yield. LCMS  $m/z=425$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.27 (s, 1H), 7.88 (dd, J=8.97, 2.65 Hz, 1H), 7.72 (d, J=2.78 Hz, 1H), 7.32-7.58 (m, 4H), 7.14-7.25 (m, 2H), 6.33 (d, J=1.77 Hz, 1H), 4.27 (t, J=5.31 Hz, 5H), 3.84 (s, 3H), 3.69 (s, 3H), 3.42-3.48 (m, 2H), 3.30-3.36 (m, 2H), 2.92-3.01 (m, 2H).

## Example 1.51

Preparation of N-[4-[2-(2-Ethoxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 55)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0644 g, 0.1497 mmol), N,N-diisopropylethylamine (0.07842 mL, 0.4490 mmol), and 2-ethoxyethylamine (0.01334 g, 0.1497 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 85% yield. LCMS  $m/z=439$  (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.28 (s, 1H), 7.88 (dd, J=8.97, 2.65 Hz, 1H), 7.73 (d, J=2.53 Hz, 1H), 7.40-7.60 (m, 4H), 7.22 (d, J=9.09 Hz, 1H), 7.17 (dd, J=8.08, 2.53 Hz, 1H), 6.33 (d, J=2.02 Hz, 1H), 4.28 (t, J=5.31 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.41-3.51 (m, 4H), 3.29-3.37 (m, 2H), 2.96 (br. s., 2H), 1.14 (t, J=6.95 Hz, 3H).

## Example 1.52

Preparation of N-[4-[2-(2-Isopropoxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide (Compound 63)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.06650 g, 0.1545 mmol), 2-aminoethyl isopropyl ether (0.01594 g,



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0.1545 mmol) and N,N-diisopropylethylamine (0.08098 mL, 0.4636 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 69% yield. LCMS m/z=453 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.27 (s, 1H), 7.88 (dd, J=8.97, 2.65 Hz, 1H), 7.72 (d, J=2.78 Hz, 1H), 7.38-7.59 (m, 4H), 7.22 (d, J=9.09 Hz, 1H), 7.14-7.20 (m, 1H), 6.32 (d, J=1.77 Hz, 1H), 4.24-4.32 (m, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.53-3.61 (m, 2H), 3.41-3.51 (m, 2H), 3.27-3.38 (m, 2H), 2.91-2.99 (m, 2H), 1.11 (d, J=6.06 Hz, 6H).

## Example 1.53

## Preparation of N-[4-(2-tert-Butylamino-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide (Compound 66)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0593 g, 0.1378 mmol), tert-butylamine (0.01461 mL, 0.1378 mmol) and N,N-diisopropylethylamine (0.07221 mL, 0.4134 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 89% yield. LCMS m/z=453 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.26 (s, 1H), 7.89 (dd, J=8.97, 2.65 Hz, 1H), 7.73 (d, J=2.53 Hz, 1H), 7.41-7.58 (m, 4H), 7.23 (d, J=9.09 Hz, 1H), 7.17 (dd, J=8.08, 2.53 Hz, 1H), 6.37 (d, J=1.77 Hz, 1H), 4.21 (t, J=5.05 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 3.25 (d, J=5.81 Hz, 2H), 1.21 (s, 9H).

## Example 1.54

## Preparation of N-[4-(2-Isopropylamino-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide (Compound 74)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0557 g, 0.1294 mmol), isopropylamine (0.01109 mL, 0.1294 mmol) and N,N-diisopropylethylamine (0.06782 mL, 0.3883 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 84% yield. LCMS m/z=409 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.27 (s, 1H), 7.89 (dd, J=9.09, 2.53 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.39-7.57 (m, 4H), 7.23 (d, J=8.84 Hz, 1H), 7.17 (dd, J=8.34, 2.53 Hz, 1H), 6.34 (d, J=1.77 Hz, 1H), 4.25 (t, J=5.18 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.26-3.36 (m, 2H), 3.09-3.20 (m, 1H), 1.12 (d, J=6.32 Hz, 6H).

## Example 1.55

## Preparation of 3-Methoxy-N-[3-(2-methyl-2H-pyrazol-3-yl)-4-(2-propylamino-ethoxy)-phenyl]-benzamide (Compound 79)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0510 g,

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0.1185 mmol), n-propylamine (0.009744 mL, 0.1185 mmol) and N,N-diisopropylethylamine (0.06210 mL, 0.3556 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 69% yield. LCMS m/z=409 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.26 (s, 2H), 7.89 (dd, J=9.09, 2.53 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.1-7.57 (m, 4H), 7.22 (d, J=29.09 Hz, 1H), 7.14-7.19 (m, 1H), 6.33 (d, J=2.02 Hz, 1H), 4.26 (t, J=5.05 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.24-3.36 (m, 2H), 2.64-2.79 (m, 2H), 1.41-1.57 (m, 2H), 0.83 (t, J=7.45 Hz, 3H).

## Example 1.56

## Preparation of N-[4-(2-Butylamino-ethoxy)-3-(Z-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide (Compound 26)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0610 g, 0.1418 mmol), n-butylamine (0.01401 mL, 0.1418 mmol) and N,N-diisopropylethylamine (0.07428 mL, 0.4253 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 97% yield. LCMS m/z=423 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.26 (s, 1H), 7.89 (dd, J=8.97, 2.65 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.39-7.57 (m, 4H), 7.23 (d, J=9.09 Hz, 1H), 7.17 (dd, J=8.34, 2.53 Hz, 1H), 6.33 (d, J=1.77 Hz, 1H), 4.26 (t, J=5.05 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.23-3.35 (m, 2H), 2.77 (d, J=5.05 Hz, 2H), 1.39-1.52 (m, 2H), 1.17-1.30 (m, 2H), 0.87 (t, J=7.33 Hz, 3H).

## Example 1.57

## Preparation of N-[4-[2-(2-Fluoro-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxybenzamide (Compound 37)

A mixture of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-methoxybenzamide (0.0645 g, 0.14990 mmol), 2-fluoroethanamine (0.014182 g, 0.22485 mmol) and N,N-diisopropylethylamine (0.07850 mL, 0.44969 mmol) in 1 mL of DMA was heated to 160° C. for 0.5 hours under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was diluted with DMSO and purified by preparative HPLC. The proper fractions were collected and lyophilized to afford a TFA salt of the title compound as a semi-solid in 62% yield. LCMS m/z=413 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 10.27 (s, 1H), 7.89 (dd, J=8.97, 2.65 Hz, 1H), 7.72 (d, J=2.53 Hz, 1H), 7.39-7.60 (m, 4H), 7.10-7.29 (m, 2H), 6.33 (d, J=1.77 Hz, 1H), 4.47-4.73 (m, 2H), 4.28 (t, J=5.31 Hz, 2H), 3.79-3.86 (m, 3H), 3.63-3.72 (m, 3H), 3.38 (s, 2H), 3.20 (s, 2H).

## Example 1.58

## Preparation of 2-(2-(4-Chloro-1-methyl-1R-pyrazol-5-yl)-4-(3-(trifluoromethyl)benzamido)phenoxy)acetic acid (Compound 50)

## Step A: Preparation of tert-Butyl 2-(2-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)benzamido)phenoxy)acetate

To a solution of N-(3-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-hydroxyphenyl)-3-(trifluoromethyl)benzamide (0.396



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g, 1.00 mmol) and potassium carbonate (0.207 g, 1.50 mmol) in acetone (10 mL) was added tert-butyl bromoacetate (0.215 g, 1.10 mmol). The reaction was stirred at 65° C. for 1 hour and then cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with water (x2) and brine, dried over magnesium sulfate and concentrated to a white solid (0.464 g, 91.0%). LCMS m/z (%)=510 (M+H, <sup>35</sup>Cl, 30), 512 (M+H, <sup>37</sup>Cl, 10), 454 (M-tBu+H, <sup>35</sup>Cl, 100). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.47 (s, 9H) 3.80 (s, 3H) 4.52 (s, 2H) 6.87 (d, J=9.09 Hz, 1H) 7.45 (d, J=2.78 Hz, 1H) 7.50 (s, 1H) 7.64 (t, J=7.71 Hz, 1H) 7.78-7.89 (m, 2H) 7.94 (s, 1H) 8.07 (d, J=7.83 Hz, 1H) 8.14 (s, 1H).

Step B: Preparation of 2-(2-(4-Chloro-1-methyl-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)benzamido)phenoxy)acetic Acid

To a solution of tert-butyl 2-(2-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)benzamido)phenoxy)acetate (0.460 g, 0.902 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added water (0.5 mL) and trifluoroacetic acid (5 mL, 56 mmol). The resulting solution was stirred for 18 hours, reduced under vacuum, azeotroped with toluene, and triturated in ether to give the title compound as a white solid (0.290 g, 70.8%). LCMS m/z (%)=454 (M+H, <sup>35</sup>Cl, 100), 456 (M+H, <sup>37</sup>Cl, 30). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.72 (s, 3H) 4.70-4.84 (m, 2H) 7.11 (d, J=9.09 Hz, 1H) 7.63 (s, 1H) 7.72 (d, J=2.53 Hz, 1H) 7.79 (t, J=7.83 Hz, 1H) 7.87 (dd, J=9.22, 2.65 Hz, 1H) 7.97 (d, J=8.34 Hz, 1H) 8.26 (d, J=8.08 Hz, 1H) 8.29 (s, 1H) 10.52 (s, 1H) 13.10 (br. s., 1H).

Step C: Preparation of N-(3-(4-Chloro-1-methyl-1H-pyrazol-5-yl)-4-(2-(2-methoxyethylamino)-2-oxoethoxy)phenyl)-3-(trifluoromethyl)benzamide (Compound 50)

To a solution of 2-(2-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)benzamido)phenoxy)acetic acid (0.060 g, 0.13 mmol) and N,N-diisopropylethylamine (0.034 g, 0.26 mmol) in dichloromethane (1.3 mL) was added BTU (0.075 g, 0.20 mmol) followed by 2-methoxyethylamine (0.015 g, 0.2 mmol). After 1.5 hours the reaction was diluted with ethyl acetate, washed with water, 1 M HCl (x3) and brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (1:1-1:0 EtOAc/hexane) to give a white solid (57.0 mg, 84%). LCMS m/z (%)=511 (M+H, <sup>35</sup>Cl, 100), 513 (M+H, <sup>37</sup>Cl, 30). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.35 (s, 3H) 3.39-3.52 (m, 4H) 3.78 (s, 3H) 4.52 (s, 2H) 6.60 (br. s., 1H) 7.02 (d, J=9.09 Hz, 1H) 7.55 (s, 1H) 7.63-7.67 (m, 2H) 7.74 (dd, J=8.97, 2.91 Hz, 1H) 7.84 (d, J=6.82 Hz, 1H) 7.92 (s, 1H) 8.08 (d, J=6.57 Hz, 1H) 8.14 (s, 1H).

## Example 1.59

Preparation of 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(4-methyl-thiazol-2-ylamino)-ethoxy]-phenyl}-benzamide (Compound 48)

To a solution of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-fluorobenzamide (68.5 mg, 0.164 mmol) and 2-amino-4-methylthiazole (18.7 mg, 0.164 mmol) in DMA (4 mL) was added NaH (56.3 mg, 60% dispersion in mineral oil) and the reaction was stirred for two hours. The resulting material was purified by HPLC. The product was dried under reduced pressure to afford the title compound as a yellow solid (4.0 mg, 5%). LCMS m/z (%)=452 (M+H,

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100). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 10.32 (bs, 1H), 7.89-7.72 (m, 3H), 7.69 (d, J=2.52 Hz, 1H), 7.62-7.56 (m, 1H), 7.48-7.42 (m, 1H), 7.41 (d, J=1.89 Hz, 1H), 7.23 (d, J=9.14 Hz, 1H), 6.45 (bs, 1H), 6.23 (d, J=1.89 Hz, 1H), 4.23-4.18 (m, 2H), 3.70-3.65 (m, 2H), 3.65 (s, 3H), 2.16 (s, 3H).

## Example 1.60

Preparation of 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(1H-tetrazol-5-ylamino)-ethoxy]-phenyl}-benzamide (Compound 54)

To a solution of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-fluorobenzamide (61.0 mg, 0.146 mmol) and 5-amino-1H-tetrazole monohydrate (42.5 mg, 0.500 mmol) in DMA (4 mL) was added NaH (30 mg, 60% dispersion in mineral oil) and the reaction was stirred for two hours. The resulting material was purified by HPLC. The product was dried under reduced pressure to afford the title compound as a white solid (12.5 mg, 20%). LCMS m/z (%)=423 (M+H, 100).

## Example 1.61

Preparation of 3-Fluoro-N-{3-(2-methyl-2H-pyrazol-3-yl)-4-[2-(1H-[1,2,4]triazol-3-ylamino)ethoxy]-phenyl}-benzamide (Compound 42)

To a solution of N-(4-(2-bromoethoxy)-3-(1-methyl-1H-pyrazol-5-yl)phenyl)-3-fluorobenzamide (62.3 mg, 0.149 mmol) and 3-amino-1H-1,2,4-triazole (38.8 mg, 0.461 mmol) in DMA (4 mL) was added NaH (58.8 mg, 60% dispersion in mineral oil) and the reaction was stirred for two hours. The resulting material was purified by HPLC. The product was dried under reduced pressure to afford the title compound as a white solid (30.2 mg, 48%). LCMS m/z (%)=422 (M+H, 100).

## Example 1.62

Preparation of 3-Bromo-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 2)

Step A: Preparation of N-(4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl)acetamide

A mixture of N-(4-hydroxy-3-(2-methyl-2H-pyrazol-3-yl)phenyl)acetamide (1.16 g, 5.00 mmol), cesium carbonate (3.26 g, 10.00 mmol), and 2-bromoethyl methyl ether (0.666 mL, 7.00 mmol) in 10 mL of DMF was heated to 110° C. for 15 minutes under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated under reduced pressure, and the residue was taken up in water and extracted three times with dichloromethane. The combined extracts were dried with sodium sulfate, filtered, and evaporated to dryness to afford the title compound (1.23 g, 85.0% yield) as a tan solid which was used without further purification. LCMS m/z (%) 290.1 (M+H, 100%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.01 (s, 3H) 3.22 (s, 3H) 3.55-3.60 (m, 2H) 3.65 (s, 3H) 4.06-4.12 (m, 2H) 6.22 (d, J=1.77 Hz, 1H) 7.10 (d, J=9.09 Hz, 1H) 7.43 (d, J=2.02 Hz, 1H) 7.49 (d, J=2.78 Hz, 1H) 7.59 (dd, J=8.97, 2.65 Hz, 1H) 9.90 (s, 1H).

Step B: Preparation of 4-(2-Methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)aniline

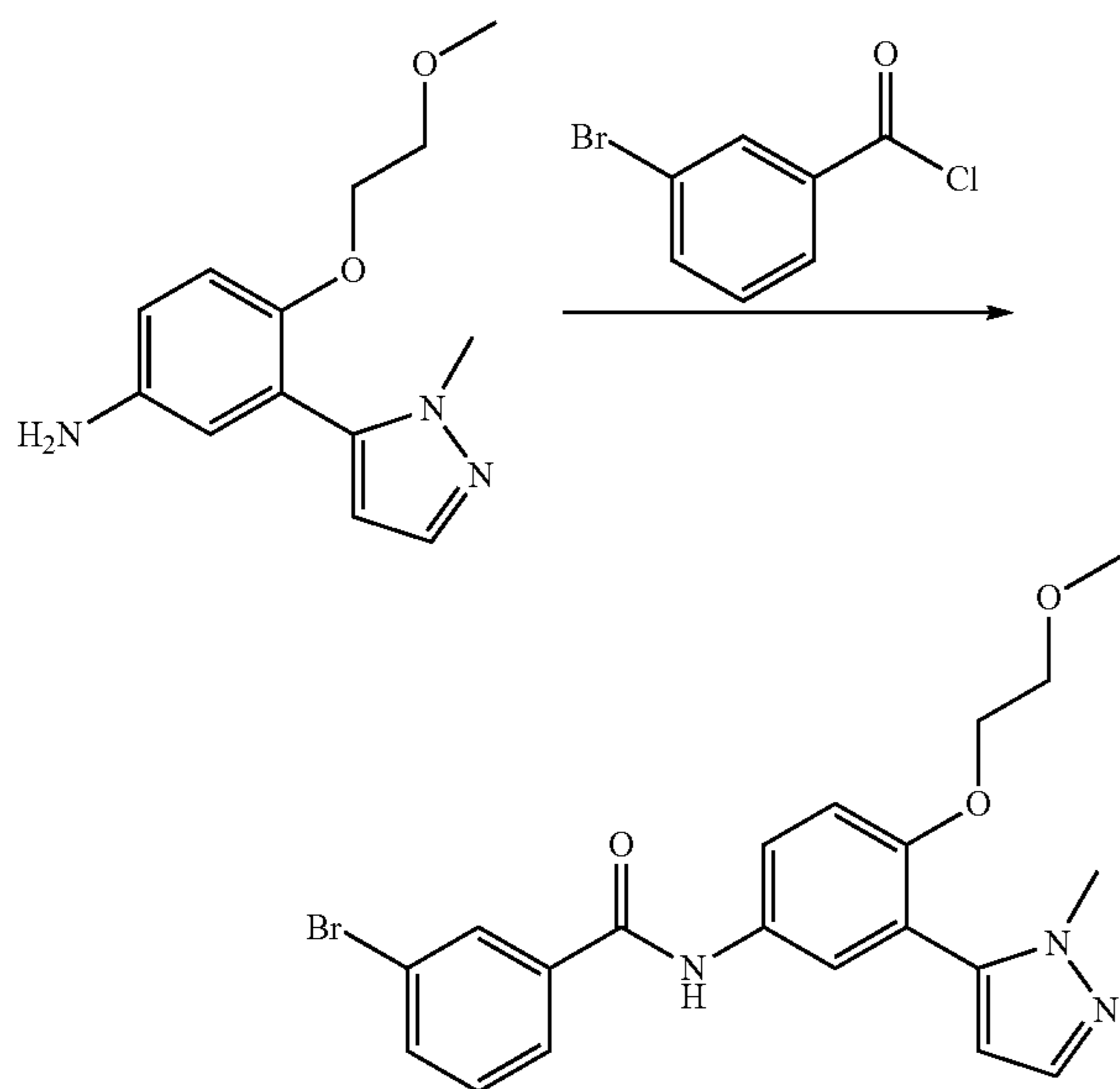
To a suspension of N-(4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl)acetamide (289 mg, 1.0 mmol) in



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MeOH (3 mL) was added a solution of sodium hydroxide (240 mg, 6.0 mmol) in water (0.4 mL) and the mixture was stirred at 160° C. in a microwave oven. After 30 minutes, the mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was taken up in water, and extracted three times with dichloromethane. The extracts were combined, dried with sodium sulfate, filtered, and evaporated to dryness to afford the title compound (231 mg, 93% yield) as a brown oil which was used without further purification. LCMS m/z (%) 248.1 (M+H, 100%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.19 (s, 3H) 3.48-3.53 (m, 2H) 3.63 (s, 3H) 3.89-3.96 (m, 2H) 4.81 (s, 2H) 6.16 (d, J=1.77 Hz, 1H) 6.48 (d, J=3.03 Hz, 1H) 6.62 (dd, J=8.72, 2.91 Hz, 1H) 6.86 (d, J=8.84 Hz, 1H) 7.39 (d, J=1.77 Hz, 1H).

Step C: Preparation of 3-Bromo-N-(4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl)benzamide (Compound 2)



A solution of 3-bromobenzoyl chloride (0.06 mmol), N,N-diisopropylethylamine (14 μL, 0.08 mmol), and 4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)aniline (0.05 mmol) in 0.28 mL DMF was agitated on a mechanical shaker for 2 hours. The product was isolated by RP-HPLC and lyophilized to give the title compound (21.4 mg, 96%). LCMS m/z (%)=432.3 (M+H, <sup>81</sup>Br 100.0), 430.3 (M+H, <sup>79</sup>Br 87.6).

## Example 1.63

Preparation of 4-Chloro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 5)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 19.1 mg, 95%. LCMS m/z (%)=388.3 (M+H, <sup>37</sup>Cl 35.5) 386.2 (M+H, <sup>35</sup>Cl 100.0).

## Example 1.64

Preparation of 3-Chloro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 7)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 17.5 mg, 87%. LCMS m/z

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(%)=388.3 (M+H, <sup>37</sup>Cl 29.0) 386.2 (M+H, <sup>35</sup>Cl 100.0). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.23 (s, 3H) 3.58-3.62 (m, 2H) 3.69 (s, 3H) 4.12-4.16 (m, 2H) 6.27 (d, J=2.02 Hz, 1H) 7.18 (d, J=9.09 Hz, 1H) 7.45 (d, J=1.77 Hz, 1H) 7.57 (t, J=7.96 Hz, 1H) 7.64-7.69 (m, 1H) 7.68 (d, J=2.53 Hz, 1H) 7.82 (dd, J=8.84, 2.78 Hz, 1H) 7.88-7.93 (m, 1H) 8.00 (t, J=1.89 Hz, 1H) 10.33 (s, 1H).

## Example 1.65

Preparation of 2-Chloro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 9)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 17.5 mg, 87%. LCMS m/z (%)=388.3 (M+H, <sup>37</sup>Cl 36.6) 386.2 (M+H, <sup>35</sup>Cl 100.0)

## Example 1.66

Preparation of 4-Fluoro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 11)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 17.2 mg, 90%. LCMS m/z (%)=370.2 (M+H, 100)

## Example 1.67

Preparation of 3-Fluoro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 14)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 17.4 mg, 91%. LCMS m/z (%)=370.2 (M+H, 100). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.23 (s, 3H) 3.58-3.62 (m, 2H) 3.69 (s, 3H) 4.11-4.17 (m, 2H) 6.27 (d, J=1.77 Hz, 1H) 7.18 (d, J=9.09 Hz, 1H) 7.41-7.48 (m, 2H) 7.55-7.62 (m, 1H) 7.69 (d, J=2.53 Hz, 1H) 7.76 (d, J=11.62 Hz, 1H) 7.78-7.84 (m, 2H) 10.30 (s, 1H).

## Example 1.68

Preparation 2-Fluoro-N-[4-(2-methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 17)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 15.3 mg, 80%. LCMS m/z (%)=370.0 (M+H, 100).

## Example 1.69

Preparation of N-[4-(2-Methoxyethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]benzamide (Compound 20)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 11.1 mg, 61%. LCMS m/z (%)=352.4 (M+H, 100).



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## Example 1.70

Preparation of 4-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 25)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 13.9 mg, 70%. LCMS m/z (%)=382.4 (M+H, 100).

## Example 1.71

Preparation of 3-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 30)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 15.7 mg, 79%. LCMS m/z (%)=382.2 (M+H, 100). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.23 (s, 3H) 3.69 (s, 3H) 3.83 (s, 3H) 4.14 (dd, J=5.43, 3.66 Hz, 2H) 6.27 (d, J=1.77 Hz, 1H) 7.13-7.19 (m, 2H) 7.41-7.49 (m, 3H) 7.50-7.55 (m, 1H) 7.69 (d, J=2.78 Hz, 1H) 7.82 (dd, J=8.97, 2.65 Hz, 1H) 10.20 (s, 1H).

## Example 1.72

Preparation of 2-Methoxy-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 35)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 16.5 mg, 83%. LCMS m/z (%)=382.2 (M+H, 100).

## Example 1.73

Preparation of N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethoxybenzamide (Compound 40)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 21.4 mg, 95%. LCMS m/z (%)=436.3 (M+H, 100).

## Example 1.74

Preparation of N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)phenyl]-3-trifluoromethoxybenzamide (Compound 46)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 21.3 mg, 95%. LCMS m/z (%)=436.3 (M+H, 100). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.23 (s, 3H) 3.58-3.63 (m, 2H) 3.69 (s, 3H) 4.12-4.17 (m, 2H) 6.27 (d, J=1.77 Hz, 1H) 7.19 (d, J=8.84 Hz, 1H) 7.45 (d, J=1.77 Hz, 1H) 7.58-7.64 (m, 1H) 7.65-7.72 (m, 2H) 7.82 (dd, J=8.97, 2.65 Hz, 1H) 7.90 (s, 1H) 8.00 (d, J=7.83 Hz, 1H) 10.37 (s, 1H).

## Example 1.75

Preparation of N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethylbenzamide (Compound 52)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 20.9 mg, 96%. LCMS m/z (%)=420.4 (M+H, 100).

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## Example 1.76

Preparation of N-[4-(2-Methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-2-trifluoromethylbenzamide (Compound 57)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 14.7 mg, 67%. LCMS m/z (%)=420.2 (M+H, 100).

## Example 1.77

Preparation of 4-Bromo-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 62)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 20.3 mg, 91%. LCMS m/z (%)=432.3 (M+H, <sup>81</sup>Br 100.0), 430.3 (M+H, <sup>79</sup>Br 79.9). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.23 (s, 3H) 3.60 (dd, J=5.31, 3.79 Hz, 2H) 3.68 (s, 3H) 4.11-4.16 (m, 2H) 6.26 (d, J=1.77 Hz, 1H) 7.17 (d, J=9.09 Hz, 1H) 7.45 (d, J=1.77 Hz, 1H) 7.68 (d, J=2.53 Hz, 1H) 7.73-7.77 (m, 2H) 7.81 (dd, J=8.97, 2.65 Hz, 1H) 7.87-7.93 (m, 2H) 10.30 (s, 1H).

## Example 1.78

Preparation of 3-Cyano-N-[4-(2-methoxy-ethoxy)-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-benzamide (Compound 81)

The title compound was prepared in a similar manner as described in Example 1.62, Step C, 4.3 mg, 22%. LCMS m/z (%)=377.3 (M+H, 100).

## Example 1.79

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-ethylamino-2-methyl-propoxy)-phenyl]-3-trifluoromethylbenzamide (Compound 6)

Step A: Preparation of N-(4-(2-nitro-2-methylpropoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-(trifluoromethyl)benzamide

Cesium carbonate (815 mg, 2.50 mmol) was added to a solution of N-(3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-4-hydroxyphenyl)-3-(trifluoromethyl)benzamide (396 mg, 1.00 mmol) and 2-methyl-2-nitropropyl methanesulfonate (276 mg, 1.40 mmol) in DMA (2.0 mL), and the mixture was stirred at 160° C. After 1 hour, the mixture was allowed to cool to room temperature and poured into water, and the resulting suspension was extracted with dichloromethane. The extract was dried with sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash chromatography (ethyl acetate hexanes 1:2) to afford the title compound (338 mg, 68%) as a yellow oil. LCMS m/z (%)=499.5 (M+H, <sup>37</sup>Cl 31.5), 497.4 (M+H, <sup>35</sup>Cl 100.0). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.51 (s, 3H) 1.57 (s, 3H) 3.64 (s, 3H) 4.01 (d, J=9.85 Hz, 1H) 4.49 (d, J=9.85 Hz, 1H) 7.08 (d, J=8.84 Hz, 1H) 7.49 (d, J=2.53 Hz, 1H) 7.51 (s, 1H) 7.65 (t, J=7.71 Hz, 1H) 7.79-7.89 (m, 3H) 8.07 (d, J=7.83 Hz, 1H) 8.13 (s, 1H).

Step B: Preparation of N-(4-(2-amino-2-methylpropoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-trifluoromethylbenzamide

Acetyl chloride (388 μl, 5.44 mmol) was added dropwise to a solution of N-(4-(2-nitro-2-methylpropoxy)-3-(4-chloro-2-



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methyl-2H-pyrazol-3-yl)phenyl)-3-(trifluoromethyl)benzamide (270 mg, 0.544 mmol) in methanol (5.0 mL). Zinc dust (356 mg, 5.44 mmol) was added, and the mixture was stirred at 23° C. After 1 hour, the mixture was filtered and the filtrate was evaporated to dryness. The residue was taken up in ammonium hydroxide (35%), diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness to afford the title compound as a colorless foam which was used without further purification. LCMS m/z (%) 469.4 (M+H, <sup>37</sup>Cl 46.9), 467.2 (M+H, <sup>35</sup>Cl 86.1), 452.2 (51.6%), 450.1 (100.0%).

Step C: Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-ethylamino-2-methyl-propoxy)-phenyl]-3-trifluoromethyl-benzamide (Compound 6)

Sodium triacetoxyborohydride (34.2 mg, 161 μmol) was added to a solution of N-(4-(2-amino-2-methylpropoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-(trifluoromethyl)benzamide (53.8 mg, 115 μmol) and acetaldehyde (5.08 mg, 115 μmol) in THF (0.5 mL), and the mixture was stirred at room temperature. After 4 hours, the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The extract was evaporated to dryness, the residue was redissolved in methanol, and the product was isolated by preparative HPLC. The trifluoroacetate salt was dissolved in a mixture of ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated to dryness to afford the title compound (12.5 mg, 22%). LCMS m/z (%)=497.5 (M+H, <sup>37</sup>Cl 45.4), 495.3 (M+H, <sup>35</sup>Cl 100.0%). <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ 1.00 (t, J=7.07 Hz, 3H) 1.07 (s, 6H) 2.42-2.51 (m, 2H) 3.71 (s, 3H) 3.85-3.88 (m, J=9.35 Hz, 1H) 3.90 (d, J=9.09 Hz, 1H) 7.22 (d, J=9.09 Hz, 1H) 7.58 (s, 1H) 7.67 (d, J=2.78 Hz, 1H) 7.73 (t, J=7.83 Hz, 1H) 7.85-7.92 (m, 2H) 8.21 (d, J=7.83 Hz, 1H) 8.27 (s, 1H).

## Example 1.80

Preparation of N-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-(2-methyl-Z-propylamino-propoxy)-phenyl]-3-trifluoromethyl-benzamide (Compound 67)

Sodium triacetoxyborohydride (34 mg, 161 μmol) was added to a solution of N-(4-(2-amino-2-methylpropoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-(trifluoromethyl)benzamide (53.8 mg, 115 μmol) and propionaldehyde (6.7 mg, 115 μmol) in THF (0.5 mL), and the mixture was stirred at room temperature. After 4 hours, the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The extract was evaporated to dryness, the residue was redissolved in methanol, and the products were isolated by preparative HPLC. Product containing fractions were combined and concentrated in a vacuum centrifuge to one fourth of the original volume. The solution was made alkaline with saturated sodium bicarbonate, the product was extracted with dichloromethane, and the extract was evaporated to dryness. The residue was dissolved in a solution of acetyl chloride (16 μL, 230 μmol) in methanol (1 mL) and evaporated to dryness. The residue was dissolved in water and lyophilized to give the title compound (30 mg, 48%) as the hydrochloride salt. LCMS m/z (%)=511.4 (M+H, <sup>37</sup>Cl 60.5), 509.3 (M+H, <sup>35</sup>Cl 100.0%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 0.87 (t, J=7.45 Hz, 3H) 1.26 (s, 6H) 1.46-1.58 (m, 2H) 2.53-2.64 (m, 2H) 3.65 (s, 3H) 4.06 (d, J=10.36 Hz, 1H) 4.16 (d, J=10.36 Hz, 1H) 7.33 (d, J=9.09 Hz, 1H) 7.69 (s, 1H) 7.73

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(d, J=2.78 Hz, 1H) 7.80 (t, J=7.83 Hz, 1H) 7.94-8.02 (m, 2H) 8.28 (d, J=8.34 Hz, 1H) 8.31 (s, 1H) 8.65 (s, 2H) 10.59 (s, 1H).

## Example 1.81

Preparation of N-[4-(2-Butylamino-2-methyl-propoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-trifluoromethyl-benzamide (Compound 75)

Sodium triacetoxyborohydride (34 mg, 161 μmol) was added to a solution of N-(4-(2-amino-2-methylpropoxy)-3-(4-chloro-2-methyl-2H-pyrazol-3-yl)phenyl)-3-(trifluoromethyl)benzamide (53.8 mg, 115 μmol) and butyraldehyde (8 mg, 115 μmol) in THF (0.5 mL), and the mixture was stirred at room temperature. After 4 hours, the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The extract was evaporated to dryness, the residue was redissolved in methanol, and the products were isolated by preparative HPLC. Product containing fractions were combined and concentrated in a vacuum centrifuge to one fourth of the original volume. The solution was made alkaline with saturated sodium bicarbonate, the product was extracted with dichloromethane, and the extract was evaporated to dryness. The residue was dissolved in a solution of acetyl chloride (16 μL, 230 μmol) in methanol (1 mL) and evaporated to dryness. The residue was dissolved in water and lyophilized to give the title compound (24 mg, 37%) as the hydrochloride salt. LCMS m/z (%)=553.6 (M+H, <sup>37</sup>Cl 34.5), 551.6 (M+H, <sup>35</sup>Cl 100.0%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 0.88 (t, J=7.33 Hz, 3H) 1.21-1.34 (m, 2H) 1.26 (s, 6H) 1.40-1.54 (m, 2H) 2.55-2.71 (m, 2H) 3.65 (s, 3H) 4.05 (d, J=10.36 Hz, 1H) 4.15 (d, J=10.36 Hz, 1H) 7.32 (d, J=9.09 Hz, 1H) 7.68 (s, 1H) 7.72 (d, J=2.78 Hz, 1H) 7.80 (t, J=7.71 Hz, 1H) 7.93-8.01 (m, 2H) 8.27 (d, J=7.83 Hz, 1H) 8.30 (s, 1H) 8.58 (s, 2H) 10.58 (s, 1H).

## Example 2

## Receptor Expression

## A. pCMV

Although a variety of expression vectors are available to those in the art, it is preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on Oct. 13, 1998 (10801 University Blvd., Manassas, Va. 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

## B. Transfection Procedure

For the IP accumulation assay (Example 3), HEK293 cells were transfected while for the DOI binding assay (example 4) COS7 cells were transfected. Several protocols well known in the art can be used to transfect cells. The following protocol is representative of the transfection procedures used herein for COS7 or 293 cells.

On day one, COS-7 cells were plated onto 24 well plates, usually 1×10<sup>5</sup> cells/well or 2×10<sup>5</sup> cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 μg cDNA in 50 μL serum-free DMEM/well and then 2 μL lipofectamine in 50 μL serum-free DMEM/well. The solutions ("transfection media") were gently mixed and incubated for 15-30 minutes at room temperature. The cells were washed with 0.5 mL PBS and then 400 μL of serum free media was



mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37° C./5% CO<sub>2</sub>. Then the transfection media was removed and replaced with 1 mL/well of regular growth media.

For 293 cells, on day one, 13×10<sup>6</sup> 293 cells per 150 mm plate were plated out. On day two, 2 mL of serum OptimemI (Invitrogen Corporation) was added per plate followed by addition of 60 μL of lipofectamine and 16 μg of cDNA. Note that lipofectamine must be added to the OptimemI and mixed well before addition of cDNA. While complexes between lipofectamine and the cDNA are forming, media was carefully aspirated and cells were gently rinsed with 5 mL of OptimemI media followed by careful aspiration. Then 12 mL of OptimemI was added to each plate and 2 mL of transfection solution was added followed by a 5 hour incubation at 37° C. in a 5% CO<sub>2</sub> incubator. Plates were then carefully aspirated and 25 mL of Complete Media were added to each plate and cells were then incubated until used.

### Example 3

#### Inositol Phosphate (IP) Accumulation Assays

##### A. 5-HT<sub>2A</sub> Receptor

Compounds of the invention are tested for their ability to activate a 5-HT<sub>2A</sub> receptor clone using an IP accumulation assay. Briefly, HEK293 cells are transiently transfected with a pCMV expression vector containing a human 5-HT<sub>2A</sub> receptor (for the sequence of the receptor see U.S. Pat. No. 6,541,209, SEQ ID NO:24) as described in Example 2. An IP accumulation assay is performed as described below.

##### B. Constitutively active 5-HT<sub>2A</sub> Receptor

Compounds of the invention are tested for their ability to inhibit a constitutively active 5-HT<sub>2A</sub> receptor clone using an IP accumulation assay. Briefly, 293 cells are transiently transfected with a pCMV expression vector containing a constitutively active human 5-HT<sub>2A</sub> receptor (for the sequence of the receptor see U.S. Pat. No. 6,541,209, SEQ ID NO:30) as described in Example 2. The constitutively active human 5-HT<sub>2A</sub> receptor contained the human 5-HT<sub>2A</sub> receptor described in part A except that intracellular loop 3 (IC<sub>3</sub>) and the cytoplasmic tail are replaced by the corresponding human INI 5-HT2C cDNA. An IP accumulation assay is performed as described below.

##### C. IP Accumulation Assay Protocol

On the day after transfections, media is removed and the cells are washed with 5 mL PBS followed by careful aspiration. Cells are then trypsinized with 2 mL of 0.05% trypsin for 20-30 seconds followed by addition of 10 mL of warmed media, gently titrated to dissociate cells, and an additional 13 mL of warmed media is gently added. Cells are then counted and 55,000 cells are added to 96-well sterile poly-D-lysine treated plates. Cells are allowed to attach over a six hour incubation at 37° C. in a 5% CO<sub>2</sub> incubator. Media is then carefully aspirated and 100 μL of warm inositol-free media plus 0.5 μCi <sup>3</sup>H-inositol is added to each well and the plates are incubated for 18-20 hours at 37° C. in a 5% CO<sub>2</sub> incubator.

On the next day, media is carefully aspirated and then 0.1 mL of assay medium is added containing inositol-free/serum free media, 10 μM pargyline, 10 mM lithium chloride, and test compound at indicated concentrations. The plates are then incubated for three hours at 37° C. and then wells are carefully aspirated. Then 200 μL of ice-cold 0.1 M formic acid is added to each well. Plates can then be frozen at this point at -80° C. until further processed. Frozen plates are then thawed over the course of one hour, and the contents of the

wells (approximately 220 μL) are placed over 400 μL of washed ion-exchange resin (AG 1-X8) contained in a Multi Screen Filtration plate and incubated for 10 minutes followed by filtration under vacuum pressure. Resin is then washed nine times with 200 μL of water and then tritiated inositol phosphates (IP, IP2, and IP3) are eluted into a collecting plate by the addition of 200 μL of 1M ammonium formate and an additional 10 minute incubation. The elutant is then transferred to 20 mL scintillation vials, 8 mL of SuperMix or Hi-Safe scintillation cocktails is added, and vials are counted for 0.5-1 minutes in a Wallac 1414 scintillation counter.

### Example 4

#### Binding Assays

Compounds of the invention were tested for their ability to bind to a 5-HT<sub>2A</sub> receptor clone membrane preparation using a radioligand binding assay. Briefly, COS cells were transiently transfected with a pCMV expression vector containing a human 5-HT<sub>2A</sub> receptor (for the sequence of the receptor see U.S. Pat. No. 6,541,209, SEQ ID NO:24) as described in Example 2.

##### A. Preparation of Crude Membrane Preparations for Radioligand Binding Assays

COS7 cells transfected with recombinant human 5-HT<sub>2A</sub> receptors were cultured for 48 hr post transfection, collected, washed with ice-cold phosphate buffered saline, pH7.4 (PBS), and then centrifuged at 48,000×g for 20 min at 4° C. The cell pellet was then resuspended in wash buffer containing 20 mM HEPES pH 7.4 and 0.1 mM EDTA, homogenized on ice using a Brinkman polytron, and recentrifuged at 48,000×g for 20 min. at 4° C. The resultant pellet was then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice, and centrifuged (48,000×g for 20 min at 4° C.). Crude membrane pellets were stored at -80° C. until used for radioligand binding assays.

##### B. [<sup>125</sup>I]DOI Radioligand Binding Assay

Radioligand binding assays for human 5-HT<sub>2A</sub> receptor was conducted using the 5-HT<sub>2</sub> agonist [<sup>125</sup>I]DOI as radioligand. To define nonspecific binding, 10 μM DOI was used for all assays. For competitive binding studies, 0.5 nM [<sup>125</sup>I]DOI was used and compounds were assayed over a range of 0.01 nM to 10 μM. Assays were conducted in a total volume of 200 μL in 96-well Perkin Elmer GF/C filter plates in assay buffer (50 mM Tris-HCl, pH 7.4, 0.5 mM EDTA, 5 mM MgCl<sub>2</sub>, and 10 μM pargyline). Assay incubations were performed for 60 min at room temperature and were terminated by rapid filtration under vacuum pressure of the reaction mixture over Whatman GF/C glass fiber filters presoaked in 0.5% PEI using a Brandell cell harvester. Filters were then washing several times with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4). Plates were then dried at room temperature and counted in a Wallac microBeta scintillation counter. Certain compounds of the present invention and their corresponding activity values are shown in the following table.

| Compound No. | IC <sub>50</sub> DOI Binding Assay (nM) |
|--------------|---|
| 15           | 0.082                                   |
| 68           | 0.51                                    |
| 52           | 4.4                                     |
| 50           | 52                                      |



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Certain other compounds of the invention had activity values ranging from about 10  $\mu$ M to about 0.10 nM in this assay.

## Example 5

## In Vitro Human Platelet Aggregation Assays

Compounds of the invention were tested for their ability to aggregate human platelets. Aggregation assays were performed using a Chrono-Log Optical aggregometer model 410. Human blood (~100 mL) was collected from human donors into glass Vacutainers containing 3.8% sodium citrate (light blue tops) at room temperature. Platelet rich plasma (PRP) was isolated via centrifugation at 100 g for 15 min at room temperature. After removal of the aqueous PRP layer, the platelet poor plasma (PPP) was prepared via high speed centrifugation at 2400 g for 20 min. Platelets were counted and their concentration was set to 250,000 cell/ $\mu$ l by dilution with PPP. Aggregation assays were conducted according to the manufacturer's specifications. Briefly, a suspension of 450  $\mu$ l PRP was stirred in a glass cuvette (1200 rpm) and, after baseline was established, 1  $\mu$ M ADP followed by either saline or 1  $\mu$ M 5HT and compound of interest (at desired concentrations) were added and the aggregation response recorded. The concentration of ADP used causes approximately 10-20% of maximal aggregation. The 5-HT concentration corresponded to the concentration which produced maximal potentiation. Percent inhibition of aggregation was calculated from the maximum decrease in optical density of the controls and of the samples containing inhibitors. Only the synergistic effect was assessed. Certain compounds of the invention had activity values ranging from about 10  $\mu$ M to about 5 nM in this assay.

## Example 6

## Efficacy of Compounds of the Invention in the Attenuation of DOI-Induced Hypolocomotion in Rats

In this example, compounds of the invention can be tested for inverse agonist activity by determining whether these compounds could attenuate DOI-induced hypolocomotion in rats in a novel environment. DOI is a potent 5-HT<sub>2A/2C</sub> receptor agonist that crosses the blood-brain barrier. The standard protocol used is described briefly below.

## Animals:

Male Sprague-Dawley rats weighing between 200-300 g are used for all tests. Rats are housed three to four per cage. These rats are naive to experimental testing and drug treatment. Rats are handled one to three days before testing to acclimate them to experimental manipulation. Rats are fasted overnight prior to testing.

## Compounds:

(R)-DOI HCl (C<sub>11</sub>H<sub>16</sub>INO<sub>2</sub>·HCl) can be obtained from Sigma-Aldrich, and is dissolved in 0.9% saline. Compounds of the invention are dissolved in 100% PEG400. DOI is injected s.c. in a volume of 1 mL/kg, while compounds of the invention are administered p.o. in a volume of 2 mL/kg.

## Procedure:

The "Motor Monitor" (Hamilton-Kinder, Poway, Calif.) is used for all activity measurement. This apparatus recorded rears using infrared photobeams.

Locomotor activity testing is conducted during the light cycle (0630-1830) between 9:00 a.m. and 4:00 p.m. Animals are allowed 30 min acclimation to the testing room before testing began.

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In determining the effects of compounds of the invention on DOI-induced hypoactivity, animals are first injected with vehicle or the compound of the invention (50  $\mu$ mol/kg) in their home cages. Sixty minutes later, saline or DOI (0.3 mg/kg salt) is injected. 10 min after DOI administration, animals are placed into the activity apparatus and rearing activity is measured for 10 minutes.

## Statistics and Results:

Results (total rears over 10 minutes) are analyzed by t-test. P<0.05 is considered significant.

## Example 7

In vitro Binding of 5-HT<sub>2A</sub> Receptor

## Animals:

Animals (Sprague-Dawley rats) are sacrificed and brains are rapidly dissected and frozen in isopentane maintained at -42° C. Horizontal sections are prepared on a cryostat and maintained at -20° C.

## LSD Displacement Protocol:

Lysergic acid diethylamide (LSD) is a potent 5-HT<sub>2A</sub> receptor and dopamine D<sub>2</sub> receptor ligand. An indication of the selectivity of compounds for either or both of these receptors involves displacement of radiolabeled-bound LSD from pre-treated brain sections. For these studies, radiolabeled <sup>125</sup>I-LSD (NEN Life Sciences, Boston, Mass., Catalogue number NEX-199) can be utilized; spiperone (RBI, Natick, Mass. Catalogue number s-128) a 5-HT<sub>2A</sub> receptor and dopamine D<sub>2</sub> receptor antagonist, can also utilized. Buffer consists of 50 nanomolar TRIS-HCl, pH 7.4.

Brain sections are incubated in (a) Buffer plus 1 nanomolar <sup>125</sup>I-LSD; (b) Buffer plus 1 nanomolar <sup>125</sup>I-LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar <sup>125</sup>I-LSD and 1 micromolar Compound of interest for 30 minutes at room temperature. Sections are then washed 2x10 minutes at 4° C. in Buffer, followed by 20 seconds in distilled H<sub>2</sub>O. Slides are then air-dried.

After drying, sections are apposed to x-ray film (Kodak Hyperfilm) and exposed for 4 days.

## Example 8

Serotonin 5-HT<sub>2A</sub> Receptor Occupancy Studies in Monkey

In this example, the 5-HT<sub>2A</sub> receptor occupancy of a compound of the invention can be measured. The study can be carried out in rhesus monkeys using PET and <sup>18</sup>F-altanserin. Radioligand:

The PET radioligand used for the occupancy studies is <sup>18</sup>F-altanserin. Radiosynthesis of <sup>18</sup>F-altanserin is achieved in high specific activities and is suitable for radiolabeling 5-HT<sub>2A</sub> receptors in vivo (see Staley et al., Nucl. Med. Biol., 28:271-279 (2001) and references cited within). Quality control issues (chemical and radiochemical purity, specific activity, stability etc) and appropriate binding of the radioligand are verified in rat brain slices prior to use in PET experiments. Drug Doses and Formulations:

Briefly, the radiopharmaceutical is dissolved in sterile 0.9% saline, pH approx 6-7. The compounds of the invention are dissolved in 60% PEG 400-40% sterile saline on the same day of the PET experiment.

Serotonin 5-HT<sub>2A</sub> occupancy studies in humans have been reported for M100,907 (Grunder et al., Neuropsychopharmacology, 17:175-185 (1997), and Talvik-Lofti et al., Psychopharmacology, 148:400-403 (2000)). High occupancies of the



5-HT<sub>2A</sub> receptors have been reported for various oral doses (doses studied ranged from 6 to 20 mg). For example, an occupancy of >90% was reported for a dose of 20 mg (Talvik-Lofti et al., supra), which translates to approx. 0.28 mg/kg. It may therefore be anticipated that an i.v. dose of 0.1 to 0.2 mg/kg of M100,907 is likely to provide high receptor occupancy. A 0.5 mg/kg dose of a Compound of the invention can be used in these studies.

#### PET Experiments:

The monkey is anesthetized by using ketamine (10 mg/kg) and is maintained using 0.7 to 1.25% isoflurane. Typically, the monkey has two i.v. lines, one on each arm. One i.v. line is used to administer the radioligand, while the other line is used to draw blood samples for pharmacokinetic data of the radioligand as well as the cold drugs. Generally, rapid blood samples are taken as the radioligand is administered which then taper out by the end of the scan. A volume of approximately 1 mL of blood is taken per time point, which is spun down, and a portion of the plasma is counted for radioactivity in the blood.

An initial control study is carried out in order to measure baseline receptor densities. PET scans on the monkey are separated by at least two weeks. Unlabeled Compound of the invention is administered intravenously, dissolved in 80% PEG 400:40% sterile saline.

#### PET Data Analysis:

PET data are analyzed by using cerebellum as the reference region and using the distribution volume region (DVR) method. This method has been applied for the analysis of <sup>18</sup>F-altanserin PET data in nonhuman primate and human studies (Smith et al., Synapse, 30:380-392 (1998)).

#### Example 9

##### The Effect of Compounds of the Invention and Zolpidem on Delta Power in Rats

In this example, the effect of Compounds of the invention on sleep and wakefulness can be compared to the reference drug zolpidem. Drugs are administered during the middle of the light period (inactivity period).

Briefly, Compounds of the invention are tested for their effects on sleep parameters and are compared to zolpidem (5.0 mg/kg, Sigma, St. Louis, Mo.) and vehicle control (80% Tween 80, Sigma, St. Louis, Mo.). A repeated measures design is employed in which each rat is to receive seven separate dosings via oral gavage. The first and seventh dosings are vehicle and the second through sixth are the test compounds and zolpidem given in counter-balanced order. Since all dosings are administered while the rats are connected to the recording apparatus, 60% CO<sub>2</sub>/40% O<sub>2</sub> gas is employed for light sedation during the oral gavage process. Rats are fully recovered within 60 seconds following the procedure. A minimum of three days elapses between dosings. In order to test the effect of the compounds on sleep consolidation, dosing occurs during the middle of the rats' normal inactive period (6 hours following lights on). Dosing typically occurs between 13:15 and 13:45 using a 24 hour notation. All dosing solutions are made fresh on the day of dosing. Following each dosing, animals are continuously recorded until lights out the following day (~30 hours).

#### Animal Recording and Surgical Procedures:

Animals are housed in a temperature controlled recording room under a 12/12 light/dark cycle (lights on at 7:00 am) and have food and water available ad libitum. Room temperature (24±2° C.), humidity (50±20% relative humidity) and lighting conditions are monitored continuously via computer

Drugs are administered via oral gavage as described above, with a minimum of three days between dosings. Animals are inspected daily in accordance with NIH guidelines.

Eight male Wistar rats (300±25 g; Charles River, Wilmington, Mass.) are prepared with chronic recording implants for continuous electroencephalograph (EEG) and electromyograph (EMG) recordings. Under isoflurane anesthesia (1-4%), the fur is shaved from the top of the skull and the skin was disinfected with Betadine and alcohol. A dorsal midline incision is made, the temporalis muscle retracted, and the skull cauterized and thoroughly cleaned with a 2% hydrogen peroxide solution. Stainless steel screws (#000) are implanted into the skull and served as epidural electrodes. EEG electrodes are positioned bilaterally at +2.0 mm AP from bregma and 2.0 mm ML and at -6.0 mm AP and 3.0 mm ML. Multi-stranded twisted stainless steel wire electrodes are sutured bilaterally in the neck muscles for recording of the EMG. EMG and EEG electrodes are soldered to a head plug connector that was affixed to the skull with dental acrylic. Incisions are closed with suture (silk 4-0) and antibiotics administered topically. Pain is relieved by a long-lasting analgesic (Buprenorphine) administered intramuscularly once post-operatively. Post-surgery, each animal is placed in a clean cage and observed until it is recovered. Animals are permitted a minimum of one week post-operative recovery before study.

For sleep recordings, animals are connected via a cable and a counter-balanced commutator to a Neurodata model 15 data collection system (Grass-Telefactor, West Warwick, R.I.). The animals are allowed an acclimation period of at least 48 hours before the start of the experiment and are connected to the recording apparatus continuously throughout the experimental period except to replace damaged cables. The amplified EEG and EMG signals are digitized and stored on a computer using SleepSign software (Kissei Comtec, Irvine Calif.).

#### Data Analysis:

EEG and EMG data are scored visually in 10 second epochs for waking (W), REMS, NREMS. Scored data are analyzed and expressed as time spent in each state per half hour. Sleep bout length and number of bouts for each state are calculated in hourly bins. A "bout" consists of a minimum of two consecutive epochs of a given state. EEG delta power (0.5-3.5 Hz) within NREMS is also analyzed in hourly bins. The EEG spectra during NREMS are obtained offline with a fast Fourier transform algorithm on all epochs without artifact. The delta power is normalized to the average delta power in NREMS between 23:00 and 1:00, a time when delta power is normally lowest.

Data are analyzed using repeated measures ANOVA. Light phase and dark phase data are analyzed separately. Both the treatment effect within each rat and the time by treatment effect within each rat is analyzed. Since two comparisons are made, a minimum value of P<0.025 is required for post hoc analysis. When statistical significance is found from the ANOVAs, t-tests are performed comparing all compounds to vehicle and the test compounds to zolpidem.

#### Example 10

##### Efficacy of Compounds of the Invention in the Inhibition of JC Virus Infection of Human Glial Cells

A compound of the invention can be shown to inhibit JC virus infection of human glial cells using the in vitro model of Elphick et al. [Science (2004) 306:1380-1383], essentially as described briefly here.



## Cells and JC Virus

The human glial cell line SVG (or a suitable subclone thereof, such as SVG-A) is used for these experiments. SVG is a human glial cell line established by transformation of human fetal glial cells by an origin defective SV40 mutant [Major et al., Proc. Natl. Acad. Sci. USA (1985) 82:1257-1261]. SVG cells are cultured in Eagle's minimum essential medium (Mediatech Inc., Herndon, Va.) supplemented with 10% heat-inactivated fetal bovine serum, and kept in a humidified 37° C. 5% CO<sub>2</sub> incubator.

The Mad-1/SVEΔ strain of JC virus [Vacante et al., Virology (1989) 170:353-361] is used for these experiments. While the host range of JC virus is typically limited to growth in human fetal glial cells, the host range of Mad-1/SVEΔ extends to human kidney and monkey cell types. Mad-1/SVEΔ is propagated in HEK cells. Virus titer is measured by hemagglutination of human type O erythrocytes.

## Assay for Inhibition of JC Virus Infection

SVG cells growing on coverslips are pre-incubated at 37° C. for 45 min with or without the compound of the invention diluted in media containing 2% FCS. By way of illustration and not limitation, the compound of the invention is used at a concentration of about 1 nM to about 100 μM, at a concentration of about 10 nM to about 100 μM, at a concentration of about 1 nM to about 10 μM, or at a concentration of about 10 nM to about 10 μM.

JC virus (Mad-1/SVEΔ) is then added at an MOI of 1.0 and the cells are incubated for 1 hr at 37° C. in the continued presence of the compound of the invention. The cells are then washed 3× in PBS and fed with growth media containing the compound of the invention. At 72 hr post-infection, V antigen positive cells are scored by indirect immunofluorescence (see below). Controls include the addition of the compound of the invention at 24 and 48 h post-infection. The percentage of infected cells in untreated cultures is set at 100%.

## Indirect Immunofluorescence

For indirect immunofluorescence analysis of V antigen expression, SVG cells growing on coverslips are fixed in ice cold acetone. To detect V antigen expression, the cells are then incubated for 30 min at 37° C. with a 1:10 dilution of hybridoma supernatant from PAB597. The PAB597 hybridoma produces a monoclonal antibody against the SV40 capsid protein VP1 which has been shown to cross-react with JC virus VP1. The cells are then washed and incubated with goat anti-mouse Alexa Fluor 488 secondary antibody for an additional 30 min. After a final wash, the cells are counterstained with 0.05% Evan's blue, mounted onto glass slides using 90% glycerol in PBS and visualized on Nikon E800 epifluorescent scope. Images are captured using a Hamamatsu digital camera and analyzed using Improvion software.

## Example 11

## In Vitro Dog Platelet Aggregation Assays

Approximately 50 mL of blood is pooled from 3 male beagles. The protocol for analyzing the effects of compounds on platelet aggregation are identical to those used for human platelets (see Example 5, supra) except 5 μM ADP and 2 μM 5-HT were used to stimulate amplification of platelet aggregation.

## Example 12

## Ex-Vivo Dog Whole Blood Aggregation

One hour following PO dosing with a test compound whole blood was collected from male beagle dogs in a 5 mL vacu-

tainer with exogenous heparin (5 U/mL) added to vacutainer. Aggregation studies were evaluated by using whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 uL) was added to saline (600 uL) with constant stirring and activated with 5 ug of Collagen (Chronolog Corp.). The serotonin response was obtained by adding 5-HT (Sigma) to final concentration of 2.5 μM. Results: Selected compounds were tested for anti-platelet aggregation activity after single bolus oral dosing. The dose that afforded maximal inhibition of 5-HT amplified platelet aggregation was identified and used for comparison.

## Example 13

## Rat In Vivo Thrombosis, Bleeding, Aggregation, PK Assay

## Thrombosis Formation and Bleeding Time:

This model concomitantly measures thrombus formation, bleeding time, platelet aggregation and drug exposure in a single live dosed rat. Test compounds are administered to male rats (weighing 250-350 g) via PO injection at varying concentrations depending on compound potency ranging from 1 mpk-100 mpk. Animals are then anesthetized using Nembutal approximately 30 min post PO. Once the animal is fully anesthetized using approved surgical techniques the animal's right femoral artery is isolated in 2 different sections approximately 4-6 mm in length, one area for probe placement and one for Ferric Chloride patch positioning. The artery is then allowed to stabilize to allow recovery from the surgery. During stabilization the animal is then intubated and placed on a ventilator (Harvard Apparatus, Inc.) at 75 strokes/min with a volume of 2.5 cubic cm. Following intubation and after stabilization a micro arterial probe (Transonic Systems, Inc) is then placed on the distal isolated femoral artery. Once the probe is in place the flow is monitored using a Powerlab recording system (AD Instruments) to monitor rate of pulsatile flow. A small piece of filter paper soaked in 30% ferric chloride is placed on the area of the artery upstream of the probe for 10 min. After 5 min of Ferric Chloride patch placement the last 3 mm of the rat's tail is removed. The tail is then placed in a saline filled glass vial at 37 degree and the time it took for bleeding to stop is recorded. After the Ferric chloride patch is removed the flow is recorded until the artery is occluded and time to occlusion is recorded.

## Whole Blood Aggregation and PK:

Following measurement of bleeding and time to occlusion 5 mL of blood is obtained for ex-vivo aggregation analysis by cardiac puncture in heparin (5 U/mL). An additional 500 μL of blood is collected in a separate vacutainer for PK analysis (plasma drug concentration). Ex-vivo aggregation studies are evaluated by using whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 μL) is added to saline (600 μL) with constant stirring and activated with 2.55 μg of Collagen (Chronolog Corp.). The serotonin response is obtained by adding 5-HT (Sigma) to final concentration of 2.5 μM. Results: Test compounds or reference compounds with acceptable levels of binding to rat 5-HT<sub>2A</sub> receptors are evaluated for effects of thrombus formation, bleeding and platelet activity in a single model. This allows for the most accurate demonstration of separation of the test compound effects on platelet mediated thrombus formation from effects on bleeding.

Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered



within the scope of the invention. All documents referenced above, including, but are not limited to, printed publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety.

What is claimed is:

1. A method for modulating the activity of a 5-HT<sub>2A</sub> serotonin receptor by contacting the receptor with N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof, *comprising administering to an individual in need thereof a pharmaceutical composition comprising a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.*

2. A method for modulating an activity of a 5-HT<sub>2A</sub> serotonin receptor by contacting the receptor with N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide

wherein the N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide is generated as a result of a metabolic chemical reaction of 3-methoxy-N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide.]

3. A method for treating a 5-HT<sub>2A</sub> associated disorder in an individual comprising administering to the individual in need thereof a *pharmaceutical composition comprising a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.*

4. A method for treating a 5-HT<sub>2A</sub> associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide,

wherein the N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide is generated as a result of a metabolic chemical reaction following administration of 3-methoxy-N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide, or a pharmaceutically acceptable salt thereof, to the individual.]

5. A method for reducing platelet aggregation in an individual comprising administering to the individual in need thereof a *pharmaceutical composition comprising a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.*

6. The method of claim 5, wherein the individual has coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing.

7. A method of reducing platelet aggregation in an individual comprising administering the individual in need thereof a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide,

wherein the N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide is generated as a result of a metabolic chemical reaction following administration of 3-methoxy-N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide, or a pharmaceutically acceptable salt thereof, to the individual.]

8. The method of claim 7, wherein the individual has coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing.]

9. A method for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the individual in need thereof a *pharmaceutical composition comprising a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.*

10. A method of reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the individual in need thereof a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide,

wherein the N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide is generated as a result of a metabolic chemical reaction following administration of 3-methoxy-N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide, or a pharmaceutically acceptable salt thereof, to the individual.]

11. A method for treating a 5-HT<sub>2A</sub> serotonin receptor associated disorder in an individual comprising administering to the individual in need thereof a *pharmaceutical composition comprising a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.*

12. A method for treating a 5-HT<sub>2A</sub> serotonin receptor associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide, or a pharmaceutically acceptable salt thereof,

wherein the N-[4-[2-(2-hydroxy-ethylamino)-ethoxy]-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide is generated as a result of a metabolic chemical reaction of 3-methoxy-N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide, or a pharmaceutically acceptable salt thereof.]

13. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is sleep disorder.

14. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is progressive multifocal leukoencephalopathy.

15. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is hypertension.

16. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is pain.

17. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is claudication.

18. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is peripheral artery disease.

19. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is vasoconstriction.

20. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is vasospasm.

21. The method according to claim 3, wherein said 5-HT<sub>2A</sub> mediated disorder is thrombosis.

22. The method according to claim 6, wherein said 5-HT<sub>2A</sub> mediated disorder is stroke.



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : RE45,337 E  
APPLICATION NO. : 14/091952  
DATED : January 13, 2015  
INVENTOR(S) : Bradley Teergarden et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)  
by 455 days.

Signed and Sealed this  
Sixteenth Day of February, 2016



Michelle K. Lee  
*Director of the United States Patent and Trademark Office*