Title: PYRAZOLE DERIVATIVES AS MODULATORS OF THE 5-HT2A SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

Abstract: The present invention relates to certain pyrazole derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT2A 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, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychoses, 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-HT2A serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.
PYRAZOLE DERIVATIVES AS MODULATORS OF THE 5-HT\textsubscript{2A} SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

The present invention relates to certain pyrazole derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT\textsubscript{2A} 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, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, 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\textsubscript{2A} serotonin receptor mediated 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.
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."

**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 D2 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-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT2A, 5-HT2B, and 5-HT2C. The human 5-HT2C receptor was first isolated and cloned in 1987, and the human 5-HT2A 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-HT2A and 5-HT2C receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.


SUMMARY OF THE INVENTION

One aspect of the present invention encompasses certain pyrazole derivatives as shown in Formula (Ia):

![Chemical Structure (Ia)]

or a pharmaceutically acceptable salt thereof,

wherein:

- $R_1$ is selected from the group consisting of $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl and $C_{3-7}$ cycloalkyl;
- $R_2$ is selected from the group consisting of H, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkylcarboxamide, $C_{2-6}$ alkynyl, $C_{1-6}$ alkylsulfonamide, carbo-$C_{1-6}$-alkoxy, carboxamide, carboxy, cyano, $C_{3-7}$ cycloalkyl, $C_{2-6}$ dialkylcarboxamide, and halogen;
- $R_3$ is selected from the group consisting of H, $C_{1-6}$ acyl, $C_{1-6}$ acyloxy, $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxo, $C_{1-6}$ alkylcarboxamide, $C_{2-6}$ alkenyl, $C_{1-6}$ alkylsulfonamide, $C_{1-6}$ alkylsulfanyl, $C_{1-6}$ alkylsulfonyl, $C_{1-6}$ alkylthio, $C_{1-6}$ alkyureyl, 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, $C_{1-6}$ haloalkylsulfanyl, $C_{1-6}$ haloalkylsulfonyl, $C_{1-6}$ haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;
- $R_4$, $R_5$, $R_6$, and $R_7$ are each independently selected from the group consisting of H, $C_{1-6}$ acyl, $C_{1-6}$ acyloxy, $C_{2-6}$ alkenyl, $C_{1-6}$ alkoxo, $C_{1-6}$ alkyl, $C_{1-6}$ alkylcarboxamide, $C_{2-6}$ alkenyl, $C_{1-6}$ alkylsulfonamide, $C_{1-6}$ alkylsulfanyl, $C_{1-6}$ alkylsulfonyl, $C_{1-6}$ alkylthio, $C_{1-6}$ alkyureyl, 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, $C_{1-6}$ haloalkylsulfanyl, $C_{1-6}$ haloalkylsulfonyl, $C_{1-6}$ haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;
- $X$ is -NR$_8$C(=O)-, -C(=O)NR$_8$-, -NH$_2$-, -C(=O)-, -O-, -S-, -S(=O)- or -S(=O)$_2$-; wherein $R_8$ is H or $C_{1-6}$ alkyl; and $R_9$ is selected from the group consisting of H, $C_{1-6}$ acyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkylcarboxamide, $C_{2-6}$ alkenyl, $C_{1-6}$ alkylsulfonamide, $C_{1-6}$ alkylsulfanyl, $C_{1-6}$ alkylsulfonyl, $C_{1-6}$ alkylthio, $C_{1-6}$ alkyureyl, 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, $C_{1-6}$ haloalkylsulfanyl, $C_{1-6}$ haloalkylsulfonyl, $C_{1-6}$ haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;
alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alknnyl, C_{1-6} alkylsulfonyl, carbo-C_{1-6} alkoxy, and C_{3-7} cycloalkyl, each optionally substituted with halogen;

Y is -NR_{10}C(=O)NR_{10}, -C(=O)NR_{10}, -NR_{10}S(=O)NR_{10}, -S(=O)NR_{10}, -NR_{10}C(=O)NR_{11}, -NR_{10}C(=O)O-, -OC(=O)NR_{10}, -NR_{12}, -C(=O)NR_{10}, -O-, -S-, -S(=O)NR_{10}, -S(=O)O- or absent; wherein R_{10} and R_{11} are each independently H or C_{1-6} alkyl; and R_{12} is selected from the group consisting of H, C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkenyl, C_{1-6} alkylsulfonyl, carbo-C_{1-6} alkoxy, and C_{3-7} cycloalkyl, each optionally substituted with halogen;

Ar is aryl or heteroaryl each optionally substituted with R_{13} to R_{17} substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} aclyoxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-8} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkenyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfanyl, C_{1-6} alkylsulfonlfy, C_{1-6} alkythio, C_{1-6} alkyureyl, amino, C_{1-6} alkylamino, C_{2-8} dialkylaminio, 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} haloalkylsulfanyl, C_{1-6} haloalkylsulfonlfy, C_{1-6} haloalkylthio, hydroxyl, thiol, nitro and sulfonamide; or two adjacent substituents together with said aryl or said heteroaryl form a C_{5-7} cycloalkyl optionally comprising 1 to 2 oxygen atoms.

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

One aspect of the present invention encompasses methods for modulating the activity of a 5-HT_{2A} serotonin receptor by contacting the receptor with a compound according to any of the embodiments described herein or a pharmaceutical composition thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof.

One aspect of the present invention encompasses methods for treating 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 thereof. In some embodiments, the individual is a cognitively intact elderly individual.

One aspect of the present invention encompasses methods for treating 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 thereof. In some embodiments, the dementia is due to a degenerative disease of the nervous system. In some embodiments, the dementia is Alzheimer's 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 encompasses methods for treating 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 therapeutically effective amount of a dopamine D₂ receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition thereof. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for treating 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 D₂ receptor antagonist and a compound
according to any of the embodiments described herein or a pharmaceutical composition thereof. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for treating schizophrenia in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D₂ receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition thereof. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for treating negative symptoms of schizophrenia induced by the administration of haloperidol to an individual suffering from 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 thereof. In some embodiments, the dopamine D₂ receptor antagonist or haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms. In some embodiments, the dopamine D₂ receptor antagonist or haloperidol and the compound or pharmaceutical composition are administered in a single dosage form.

One aspect of the present invention encompasses methods for treating 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 thereof. 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 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 encompasses methods for treating 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 thereof. 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 encompasses methods for treating 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 thereof. In some embodiments, the individual in need thereof has a lymphoproliferative disorder. In some embodiments, the individual in need thereof has carcinomatosis. In some embodiments, the individual in need thereof is immunocompromised. 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 ≤ 200/mm³. In some embodiments, the HIV-infected individual has AIDS. In some embodiments, the HIV-infected individual has AIDS-related complex (ARC). In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy. In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy after organ transplantation.

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

One aspect of the present invention is the use of a compound of the present invention for the production of a medicament for use in the treatment of a 5-HT_{2A} mediated 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_{2A} mediated 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_{2A} mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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 Alzheimer's 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$_{2A}$ mediated disorder further comprising a dopamine D$_2$ 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$_2$ 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$_{2A}$ mediated disorder further comprising a dopamine D$_2$ receptor antagonist wherein the disorder is infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies. In some embodiments the dopamine D$_2$ 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$_{2A}$ mediated disorder further comprising a
dopamine $D_2$ receptor antagonist wherein the disorder is schizophrenia. In some embodiments the dopamine $D_2$ 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated disorder wherein the disorder is progressive multifocal leukoencephalopathy.

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$_{2A}$ mediated disorder, as described herein, in 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 sleep disorder, as described herein, in 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 platelet aggregation in 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 progressive multifocal leukoencephalopathy 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**

Figure 1 shows the general synthetic scheme for the preparation of compounds of the present invention wherein the “Y” group is absent. Figure 1 shows two general coupling methods between a phenyl boronic acid and an amino pyrazole. The first method shows the introduction of the Ar group after the coupling between the phenyl boronic acid and the amino
pyrazole. The second method in Figure 1 shows that the Ar group can be introduced prior to the coupling with the amino pyrazole. In addition to the different coupling procedures disclosed herein there are a number of other procedures that are described in the art. Further, R₉ can be introduced before or after the coupling step(s) via methods known in the art after, such as an alkylation reaction, reductive alkylation and like reactions.

Figure 2 shows the general synthetic scheme for the preparation of compounds of the present invention wherein the “Y” group is absent. Figure 2 shows two general coupling methods between a phenyl amine and a pyrazole boronic acid. The first method shows the introduction of the Ar group after the coupling between the phenylamino and the pyrazole boronic acid. The second method in Figure 2 shows that the Ar group can be introduced prior to the coupling with the amino pyrazole. Figure 2 also shows one method for preparing the pyrazole boronic acid. In addition to the different coupling procedures disclosed herein there are a number of other procedures that are described in the art. Further, R₉ can be introduced before or after the coupling step(s) via methods known in the art after.

Figure 3 shows two general copper-assisted coupling procedures for the preparation of compounds of the present invention.

Figure 4 shows two general palladium-assisted coupling procedures for the preparation of compounds of the present invention.

Figure 5 shows the preparation of certain compounds of the present invention. Figure 5 shows the coupling step for the preparation of Compound 1, Compound 4 and Compound 47.

Figure 6 shows the general synthetic scheme for the preparation of compounds of the present invention wherein the “Y” group is urea, amide, sulfonamide or carbamate. The first step in Figure 6 shows the coupling of a nitrophenyl boronic acid with amino pyrazole. In the second step the nitro is reduced with, for example, Na₂S₂O₄ or like reagent, to give the aniline intermediate. The resulting aniline intermediate can be modified with a variety of electrophils. A few examples are shown in Figure 6, such as isocyanates, carboxylic acids together with a suitable coupling agent, acid chlorides, sulfonyl chlorides, chloroformates, and like reagents.

Figure 7 shows the general synthetic scheme for the preparation of compounds of the present invention wherein the “X” group is O, S, S(=O), S(=O)₂ or C(=O). When X is O or S, Figure 7 shows the coupling of either a phenol or thiophenol with a pyrazole boronic acid. In the example when X is O, one representative procedure that can be used is described by Evans D.A. in Tetrahedron Letters (1998), 39(19), 2937-2940. In the example when X is S, one representative procedure that can be used is described by Savarin, C. in Organic Letters (2002), 4(24), 4309-4312; this method utilizes a N-thioimide intermediate that can be prepared via the thiophenol and NCS. Once the thioether is obtained it can be oxidized to either the sulfoxide (i.e., S(=O), or the sulfone [i.e., S(=O)₂] using methods known in the art, for example, mCPBA,
H₂O₂, and the like. In the example when X is C(=O), one representative procedure that can be used is described by Urawa, Y. in *Tetrahedron Letters (2003), 44*(2), 271-273.

**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.

**AGONISTS** shall mean moieties that interact and activate the receptor, such as the 5-HT₃A 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 **ANTAGONISTS** 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.

**CHEMICAL GROUP, MOIETY OR RADICAL:**

The term "C₁₆ acyl" denotes a C₁₆ alkyl radical attached to a carbonyl wherein the definition of alkyl has the same definition as described herein; 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 "C₁₆ acyloxy" denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition as described herein; some examples include, but are not limited to, acetoxy, propionyloxy, butanoyloxy, iso-butanoyloxy, sec-butanoyloxy, t-butanoyloxy and the like.

The term "C₂₋₆ 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 mixtures 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-hexanyl, 2,4-hexadienyl and the like.

The term "C₁₋₆ alkoxy" as used herein denotes an alkyl radical, as defined herein, attached directly to an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy, sec-butoxy and the like.

The term "C₁₋₈ 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, some
embodiments are 1 to 3 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., \(-\text{CH(}\text{CH}_3\text{)CH}_2\text{CH}_3\text{)}\), 2-methylbutyl [i.e., \(-\text{CH}_3\text{CH(CH}_3\text{)CH}_2\text{CH}_3\text{)}\), n-hexyl and the like.

The term "C\text{1-6} alkylcarboxamido" or "C\text{1-6} alkylcarboxamide" denotes a single C\text{1-6} alkyl group attached to the nitrogen of an amide group, wherein alkyl has the same definition as found herein. The C\text{1-6} alkylcarboxamido may be represented by the following:

![Diagram of C\text{1-6} alkylcarboxamido](image)

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\text{1-6} alkylsulfinyl" denotes a C\text{1-6} 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\text{1-6} alkylsulfonamide" refers to the groups shown below:

![Diagram of C\text{1-6} alkylsulfonamide](image)

wherein C\text{1-6} alkyl has the same definition as described herein.

The term "C\text{1-6} alkylsulfonyl" denotes a C\text{1-6} alkyl radical attached to a sulfone radical of the formula: -S(\text{O})_2- 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\text{1-6} alkylthio" denotes a C\text{1-6} 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\text{3-S-}), ethylsulfanyl, n-propylsulfanyl, iso-propylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, iso-butylsulfanyl, t-butylsulfanyl, and the like.

The term "C\text{1-6} alkylthiocarboxamide" denotes a thioamide of the following formulae:

![Diagram of C\text{1-6} alkylthiocarboxamide](image)

wherein C\text{1-6} alkyl has the same definition as described herein.
The term “C_{1-6} alkylureyl” denotes the group of the formula: \(-\text{NC}(\text{O})\text{N}-\) wherein one or both of the nitrogens are substituted with the same or different C_{1-6} alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but are not limited to, CH₃NHC(O)NH₂, NH₂C(O)NCH₃⁻, (CH₃)₂NC(O)NH₂, (CH₃)₂NC(O)NH⁻, (CH₃)₂N(O)NCH₃⁻, CH₃CH₂NHC(O)NH⁻, CH₃(CH₂)₂NH⁻, and the like.

The term “C_{2-6} alkylnyl” 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 alkylnyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term “alkynyl” includes di- and triynes.

The term “amino” denotes the group –NH₂.

The term “C_{1-6} 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, iso-butylamino, t-butylamino, and the like. Some embodiments are “C_{1-2} alkylamino.”

The term “aryl” denotes an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term “benzyl” denotes the group –CH₂C₆H₅.

The term “carbo-C_{1-6}-alkoxy” refers to a 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, carboxopropoxy, carboxisopropoxy, carboxobutoxy, 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 –CONH₂.

The term “carboxy” or “carboxyl” denotes the group –CO₂H; also referred to as a carboxylic acid group.

The term “cyano” denotes the group –CN.

The term “C_{3-7} cycloalkyl” denotes a saturated ring radical containing 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. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term “C_{2-6} dialkylamino” denotes an amino substituted with two of the same or different C_{1-6} alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but are not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylethylpropylamino, ethylpropylamino, ethylisopropylamino,
dipropylamino, propylisopropylamino and the like. Some embodiments are “C_{3,4} dialkylamino.”

The term “C_{2,8} dialkylcarboxamido” or “C_{2,8} dialkylcarboxamido” 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 C_{2,8} dialkylcarboxamido may be represented by the following groups:

\[ \text{N} \begin{array}{c} \text{C}_{1,4} \text{ alkyl} \\ \text{C}_{1,4} \text{ alkyl} \end{array} \]

wherein 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 “C_{2,8} dialkylsulfonamide” refers to one of the following groups shown below:

\[ \text{N} \begin{array}{c} \text{S} \\ \text{O} \\ \text{C}_{1,4} \text{ alkyl} \end{array} \]

wherein 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.

The term “C_{1,6} haloalkoxy” denotes a C_{1,6} haloalkyl, as defined herein, which is directly attached to an oxygen atom. Examples include, but are not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term “C_{1,6} haloalkyl” denotes an C_{1,6} alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C_{1,6} haloalkyl can be represented by the formula C_{1,6}L_{2n+1} wherein L is a halogen and “n” is 1, 2, 3, 4, 5 or 6; when more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term “C_{1,6} haloalkylsulfinyl” denotes a C_{1,6} haloalkyl radical attached to a sulfoxide group of the formula: -S(=O)- wherein the haloalkyl radical has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term “C_{1,6} haloalkylsulfonyl” denotes a C_{1,6} haloalkyl radical attached to a sulfone group of the formula: -S(=O)_{2}- wherein haloalkyl has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.
The term "C_{1-4} haloalkythio" denotes a C_{1-4} haloalkyl radical directly attached to a sulfur wherein the haloalkyl has the same meaning as described herein. Examples include, but are not limited to, trifluoromethylthio (i.e., CF_{3}S-, also referred to as trifluoromethylsulfanyl), 1,1-difluoroethythio, 2,2,2-trifluoroethythio and the like.

The term "halogen" or "halo" denotes to a fluoro, chloro, bromo or iodo group.

The term "heteroaryl" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings wherein at least one ring carbon is replaced with a heteroatom selected from, but are not limited to, the group consisting of O, S and N wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl. Examples of heteroaryl groups include, but are not limited to, pyridyl, benzofuranyl, pyrazanyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoazole, benzothiazoled, 1H-benzimidazolo, isoquinoline, quinazoline, quinoxaline and the like. In some embodiments, the heteroaryl atom is O, S, N, or NH, examples include, but are not limited to, pyrrole, indole, and the like. Other examples include, but are not limited to, those in TABLE 1, TABLE 2, and the like.

The term "hydroxyl" refers to the group -OH.

The term "nitro" refers to the group -NO_{2}.

The term "phenoxy" refers to the group C_{6}H_{5}O-.

The term "phenyl" refers to the group C_{6}H_{5}-.

The term "thiol" denotes the group -SH.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and without limitation, a Pharmaceutical Composition is a Composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

CONTACT or CONTACTING shall mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" a 5-HT_{2A} 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 5-HT_{2A} receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a 5-HT_{2A} receptor.

IN NEED OF TREATMENT as used herein refers to 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.
INDIVIDUAL as used herein refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

INHIBIT or INHIBITING, in relationship to the term “response” shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall 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.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

As used herein, the terms MODULATE or MODULATING shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

PHARMACEUTICAL COMPOSITION shall 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.

THERAPEUTICALLY EFFECTIVE AMOUNT as used herein refers to 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).

5 COMPounds OF THE INVENTION:

One aspect of the present invention encompasses certain pyrazole derivatives as shown in Formula (Ia):

![Formula Image]

or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, X, Y and Ar have the same definitions as described herein, supra and infra.

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., R₁, R₂, R₃, R₄, R₅, R₆, R₇, X, Y and Ar) 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 (i.e., 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.

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 individual enantiomers and mixtures thereof, unless stated or shown otherwise.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ic):

![Formula (Ic)](image)

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ie):

![Formula (Ie)](image)

In some embodiments, \( Y \) is bonded at the 2-position on the phenyl ring as shown in the following formula:
Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ig):

In some embodiments, \( Y \) is bonded at the 3-position on said phenyl ring.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (II):

In some embodiments, \( Y \) is bonded at the 4-position on said phenyl ring.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ik):

In some embodiments, \( R_1 \) is \( \text{C}_{1-6} \) alkyl.
In some embodiments, \( R_1 \) is \( \text{CH}_3 \).
In some embodiments, \( R_2 \) is selected from the group consisting of \( \text{H} \) and halogen.
In some embodiments, \( R_2 \) is \( \text{H} \).
In some embodiments, \( R_2 \) is \( \text{F, Cl or Br} \).
In some embodiments, when \( R_1 \) is \( \text{CH}_3 \), \( X \) is \( \text{O} \), and \( Y \) is \( \text{O} \) bonded at the 4-position of the phenyl ring, then \( R_3 \) is a group other than \( \text{CH}_3 \), \( \text{CH}_2\text{CH}_3 \) and \( \text{CF}_3 \).
In some embodiments, \( R_3 \) is a group other than carboxyl (i.e. \( \text{CO}_2\text{H} \)).
In some embodiments, when R₁ is CH₃, X is -C(=O)NH, and Y is -NHC(=O)NH-bonded at the 4-position of the phenyl ring, then R₃ is a group other than tert-butyl.

In some embodiments, R₃ is a group other than tert-butyl.

In some embodiments, R₃ is H.

In some embodiments, R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of H, C₁₋₆ alkoxy, C₁₋₆ alkyl, and halogen.

In some embodiments, R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of H, OCH₃, CH₃ and F.

In some embodiments, X is -NHC(=O)-, -C(=O)NH, or -NH-.

In some embodiments, X is -NH-.

In some embodiments, Y is -NHC(=O)NH-, C(=O)-, -O- or absent.

In some embodiments, Y is absent.

In some embodiments, Ar is a group other than 5-tert-butyl-isoxazol-3-yl.

In some embodiments, Ar is aryl or heteroaryl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C₁₋₆ acyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₆ alkylysulfonyl, C₂₋₆ dialkylamino, carbo-C₁₋₆ alkoxy, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, halogen, C₁₋₆ haloalkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkylsulfonyl, hydroxyl, and sulfonamide; or two adjacent substituents together with said aryl or said heteroaryl form a C₅₋₇ cycloalkyl optionally comprising 1 to 2 oxygen atoms.

In some embodiments, Ar is aryl or heteroaryl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C₁₋₆ acyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, amino, halogen, C₁₋₆ haloalkoxy, C₁₋₆ haloalkyl, and nitro; or two adjacent substituents together with said aryl or said heteroaryl form a C₅₋₇ cycloalkyl optionally comprising 1 to 2 oxygen atoms.

In some embodiments, Ar is aryl or heteroaryl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C(=O)CH₃, OCH₃, CH₃, amino, F, Cl, Br, OCF₃, CF₃ and nitro; or two adjacent substituents together with said aryl form a C₅ cycloalkyl comprising 2 oxygen atoms.

In some embodiments, Ar is phenyl, thiophen-2-yl, thiophen-3-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl or quinolin-8-yl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C₁₋₆ acyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, amino, halogen, C₁₋₆ haloalkoxy, C₁₋₆ haloalkyl, and nitro; or two adjacent substituents together with said aryl or said heteroaryl form a C₅₋₇ cycloalkyl optionally comprising 1 to 2 oxygen atoms.

In some embodiments, Ar is phenyl, thiophen-2-yl, thiophen-3-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl or quinolin-8-yl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C(=O)CH₃, OCH₃, CH₃, amino, F, Cl, Br,
OR<sub>3</sub>, Cl<sub>3</sub> and nitro; or two adjacent substituents together with said aryl form a C<sub>5</sub> cycloalkyl comprising 2 oxygen atoms.

In some embodiments, Ar is aryl optionally substituted with R<sub>13</sub> to R<sub>17</sub> substituents selected independently from the group consisting of C<sub>1-6</sub> acyl, C<sub>1-6</sub> alkoxy, C<sub>1-8</sub> alkyl, amino, halogen, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, and nitro; or two adjacent substituents together with said aryl form a C<sub>5-7</sub> cycloalkyl optionally comprising 1 to 2 oxygen atoms.

In some embodiments, Ar is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-n-propylphenyl, 4-tert-butylphenyl, 4-heptylphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 3-acetylphenyl, 4-nitrophenyl, 3-amino-phenyl, 2,3-difluoro-phenyl, 3,5-difluoro-phenyl, 3,4-difluoro-phenyl, 4-fluoro-2-methyl-phenyl, 3-fluoro-4-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 3-fluoro-4-methoxy-phenyl, 3,4-dichlorophenyl, 2-chloro-4-methylphenyl, 3-chloro-4-trifluoromethyl-phenyl, 2,4-bis-trifluoromethyl-phenyl, benzo[1,3]dioxol-5-yl and 2,6-dimethoxy-phenyl.

In some embodiments Ar is heteroaryl having 5-atoms in the aromatic ring examples of which are represented by the following formulæ:

**TABLE 1**

```
\[ \text{FIGURE}\]
```

wherein the 5-membered heteroaryl is bonded at any available position of the ring, for example, an imidazoyl 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 imidazol-5-yl group).

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

**TABLE 2**

```
\[ \text{FIGURE}\]
```
wherein the heteroaryl group is bonded at any ring carbon. In some embodiments, $R_1$ is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, $R_1$ is pyridinyl.

In some embodiments, $Ar$ is heteroaryl, such as one described in Table 1 or Table 2, optionally substituted with $R_{13}$ to $R_{17}$ substituents as described herein.

In some embodiments, $Ar$ is heteroaryl optionally substituted with $R_{13}$ to $R_{17}$ substituents selected independently from the group consisting of C$_{1-6}$ alkoxy and C$_{1-3}$ alkyl.

In some embodiments, $Ar$ is thiophen-2-yl, thiophen-3-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl or quinolin-8-yl each optionally substituted with $R_{13}$ to $R_{17}$ substituents selected independently from the group consisting of C$_{1-6}$ alkoxy and C$_{1-3}$ alkyl.

In some embodiments, $Ar$ is selected from the group consisting of thiophen-2-yl, thiophen-3-yl, 3,5-dimethyl-isoxazol-4-yl, pyridin-3-yl, 6-methoxy-pyridin-3-yl, pyridin-4-yl and quinolin-8-yl.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ic):

wherein:

$n_1$ is C$_{1-6}$ alkyl;

$n_2$ is selected from the group consisting of H and halogen;

$n_3$ is H;

$n_4$, $n_5$, $n_6$, and $n_7$ are each independently selected from the group consisting of H, C$_{1-6}$ alkoxy, C$_{1-3}$ alkyl, and halogen;

$n_8$ is -NH(-O), -C(-O)NH, or -NH$_2$;

$X$ is -NH(-O), -C(-O)NH, or -NH$_2$;

$Y$ is -NH(-O)NH$_{-}$, C(-O)$_{-}$, -O$_{-}$ or absent; and

$Ar$ is aryl or heteroaryl each optionally substituted with $R_{13}$ to $R_{17}$ substituents selected independently from the group consisting of C$_{1-6}$ acyl, C$_{1-6}$ alkoxy, C$_{1-3}$ alkyl, amino, halogen, C$_{1-6}$.
haloalkoxy, C<sub>1-4</sub> haloalkyl, and nitro; or two adjacent substituents together with said aryl or said heteroaryl form a C<sub>5-7</sub> cycloalkyl optionally comprising 1 to 2 oxygen atoms; or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Ie):

![Chemical Structure](image)

wherein:
R<sub>1</sub> is CH<sub>3</sub>;
R<sub>2</sub> is H, F, Cl or Br;
R<sub>3</sub> is H;
R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are each independently selected from the group consisting of H, OCH<sub>3</sub>, CH<sub>3</sub> and F;
X is -NH-;
Y is absent; and
Ar is aryl or heteroaryl each optionally substituted with R<sub>13</sub> to R<sub>17</sub>; substituents selected independently from the group consisting of C(=O)CH<sub>3</sub>, OCH<sub>3</sub>, CH<sub>3</sub>, amino, F, Cl, Br, OCF<sub>3</sub>, CF<sub>3</sub> and nitro; or two adjacent substituents together with said aryl form a C<sub>5</sub> cycloalkyl comprising 2 oxygen atoms; or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Im):

![Chemical Structure](image)

wherein:
R<sub>1</sub> is CH<sub>3</sub>;
R<sub>2</sub> is H, F, Cl or Br;
R<sub>3</sub> is H;
R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are each independently selected from the group consisting of H, OCH<sub>3</sub>, CH<sub>3</sub> and F; and
Ar is aryl or heteroaryl each optionally substituted with R_{13} to R_{17} substituents selected independently from the group consisting of C(=O)CH_3, OCH_3, CH_3, amino, F, Cl, Br, OCF_3, CF_3 and nitro; or two adjacent substituents together with said aryl form a C_5 cycloalkyl comprising 2 oxygen atoms; or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention encompass certain pyrazole derivatives as shown in Formula (Im):

![Chemical Structure](image)

wherein:

R_1 is CH_3;
R_2 is H, F, Cl or Br;
R_3 is H;
R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of H, OCH_3, CH_3 and F; and

Ar is phenyl, thiophen-2-yl, thiophen-3-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl or quinolin-8-yl each optionally substituted with R_{13} to R_{17} substituents selected independently from the group consisting of C(=O)CH_3, OCH_3, CH_3, amino, F, Cl, Br, OCF_3, CF_3 and nitro; or two adjacent substituents together with said aryl form a C_5 cycloalkyl comprising 2 oxygen atoms; or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention include compounds illustrated in TABLE A as shown below:

<table>
<thead>
<tr>
<th>Cmpd No.</th>
<th>Chemical Structure</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Biphenyl-4-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Chemical Structure 3" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Chemical Structure 4" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure 5" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-fluorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Chemical Structure 6" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-methylbiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Chemical Structure 7" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chlorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Chemical Structure 8" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-chlorobiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Chemical Structure 9" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methylbiphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-propyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-tert-butyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>12</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-heptyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>13</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>14</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-trifluoromethyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>15</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>16</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>17</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>18</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>19</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>1-{4'-(4-Bromo-2-methyl-2H-pyrazol-3-yl)amino}-biphenyl-3-yl</td>
</tr>
<tr>
<td>20</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-nitro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>21</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>N^\text{\textprime}-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-biphenyl-3,4'-diamine</td>
</tr>
<tr>
<td>22</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2',3'-difluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>23</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',5'-difluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Chemical Structure 24" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',4'-difluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="Chemical Structure 25" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3,3',4'-trifluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Chemical Structure 26" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-2'-methyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Chemical Structure 27" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Chemical Structure 28" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-3'-methyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Chemical Structure 29" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Chemical Structure 30" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',4'-dichloro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>31</td>
<td><img src="image" alt="Chemical Structure 31" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-chloro-5'-methyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>32</td>
<td><img src="image" alt="Chemical Structure 32" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(5'-chloro-2'-methyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>33</td>
<td><img src="image" alt="Chemical Structure 33" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chloro-4'-trifluoromethyl-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>34</td>
<td><img src="image" alt="Chemical Structure 34" /></td>
<td>(2',4'-Bis-trifluoromethyl-biphenyl-4-yl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>35</td>
<td><img src="image" alt="Chemical Structure 35" /></td>
<td>(4'-Fluoro-biphenyl-4-yl)-(2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Chemical Structure 36" /></td>
<td>(2,5-Dimethyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Chemical Structure 37" /></td>
<td>(4-Bromo-1-methyl-1H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-2-yl-phenyl)-amine</td>
</tr>
<tr>
<td>39</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-3-yl-phenyl)-amine</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-[4-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-amine</td>
</tr>
<tr>
<td>41</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-pyridin-3-yl-phenyl)-amine</td>
</tr>
<tr>
<td>42</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-[4-(6-methoxy-pyridin-3-yl)-phenyl]-amine</td>
</tr>
<tr>
<td>43</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-pyridin-4-yl-phenyl)-amine</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-quinolin-8-yl-phenyl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>45</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Benzol[1,3]dioxol-5-yl-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>46</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-phenoxy-phenyl)-amine</td>
</tr>
<tr>
<td>47</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>[4-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-phenylmethanone</td>
</tr>
<tr>
<td>48</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-3-(4-chlorophenyl)-urea</td>
</tr>
<tr>
<td>49</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Biphenyl-2-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>50</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Biphenyl-3-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine</td>
</tr>
<tr>
<td>51</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluorobiphenyl-3-yl)-amine</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>52</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methoxy-biphenyl-3-yl)-amine</td>
</tr>
<tr>
<td>53</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethoxy-biphenyl-3-yl)-amine</td>
</tr>
<tr>
<td>54</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-methoxy-4'-trifluoromethoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>55</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-3-methoxy-biphenyl-4-yl)-amine</td>
</tr>
<tr>
<td>56</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2',6'-dimethoxy-biphenyl-3-yl)-amine</td>
</tr>
<tr>
<td>57</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide</td>
</tr>
<tr>
<td>58</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>4'-Fluoro-biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide</td>
</tr>
</tbody>
</table>
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.

The compounds of the Formula (Ia) of the present invention can be prepared according to the general synthetic schemes in Figures 1 through 7 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, 3rd Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. 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.

INDICATIONS AND METHODS OF TREATMENT

In addition to the foregoing beneficial uses for the modulators of 5-HT\textsubscript{2A} 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 (5-HT\textsubscript{2A} mediated 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.

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 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(2A) 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(2A) 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).

The 5-HT(2A) 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(2A) 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(2A) 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(2A) inverse agonist disclosed herein at a time where such risk exists.

2. Asthma

It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in 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$_{2A}$ 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$_{2A}$ inverse agonist disclosed herein.

3. Agitation


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$_{2A}$ 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 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 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$_{2A}$ 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$_{2A}$ 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-HT₂A 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 (multiple, 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 interhuman 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 D₂ 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-HT₂A 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-HT₂A 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 $D_2$ receptor antagonist and a 5-HT$_{2A}$ 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$_{2A}$ inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infunlute autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine $D_2$ receptor antagonist and a 5-HT$_{2A}$ inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infunlute autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and a 5-HT$_{2A}$ 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 $D_2$ receptor antagonist and a 5-HT$_{2A}$ inverse agonist disclosed herein. Preferably, the dopamine $D_2$ receptor antagonist is haloperidol.

The administration of the dopamine $D_2$ receptor antagonist can be concomitant with administration of the 5-HT$_{2A}$ 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$_{2A}$ 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 the schizophrenia, comprising administering to the patient a 5-HT$_{2A}$ 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—

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*, Oct. 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.


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 (i.e. antihistamine).

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 NREM sleep bouts, particularly Stages 3 and 4, and the length of those sleep bouts are increased, while the number and length of waking 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-HT2A agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT2A 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-HT2A 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, electrocortulogic 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 80-100 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-HT2A 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-HT2A 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 Andrzejeewska-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 Jun; 367(6):607-14, used a 5-HT2A antagonist experimental drug AT-1015, and other non-specific 5-HT2A 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 Nov; 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-HT2 receptor antagonists result in a decrease in intraocular 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-HT2A inverse agonists in the treatment of ocular hypertensin associated with glaucoma. The 5-HT2 receptor antagonist ketanserin (Mastropasqua supra) and sarpogrelate (Takenaka et al., Investig Ophthalmol Vis Sci 36:8734 (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).

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$_{2A}$ 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$_{2A}$ antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT$_{2A}$.

5-HT$_{2A}$ 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$_{2A}$ 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$_{2A}$ inverse agonist disclosed herein.

9. Hypertension


10. Pain

5-HT2A inverse agonists are also effective for the treatment of pain. Sarpgrelate 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-HT2A inverse agonist in humans has been shown to be an effective treatment for lower

Representative Methods of the Invention:

One aspect of the present invention encompasses methods for modulating the activity of a 5-HT2A 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 encompasses 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 encompasses 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 encompasses methods for the treatment of 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 encompasses methods for the treatment of 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 encompasses 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 encompasses 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 encompasses 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 encompasses 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 Alzheimer’s 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 encompasses 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 D₂ receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

One aspect of the present invention encompasses 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 D₂ receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

One aspect of the present invention encompasses methods for the treatment of schizophrenia in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a dopamine D₂ receptor antagonist and a compound according to any of the embodiments described herein or a pharmaceutical composition. In some embodiments, the dopamine D₂ receptor antagonist is haloperidol.

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

One aspect of the present invention encompasses 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 $\leq 200/mm^3$. 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/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°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, OKT8 monoclonal antibody (mAb), anti-CD3 immunotoxin
FN18-CRM9, Campath-1H (anti-CD52) 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, and anti-CD45 RB monoclonal antibody.

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 compound according any embodiments described herein and 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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$_{2A}$ mediated 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_2A mediated 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_2A mediated 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_2A mediated 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 Alzheimer's 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 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_2A mediated disorder further comprising a dopamine D_2 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_2 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_2A mediated disorder further comprising a dopamine D_2 receptor antagonist wherein the disorder is infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies. In some embodiments the dopamine D_2 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_2A mediated disorder further comprising a dopamine D_2 receptor antagonist wherein the disorder is schizophrenia. In some embodiments the dopamine D_2 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_2A mediated 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_2A mediated 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_{2A} mediated 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_{2A} mediated 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_{2A} mediated 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 administration. 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-HT2A 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, and 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 caregiver 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, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further 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 regimen 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 administrated 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 desire 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 homogenous 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 preparations 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, ethanesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, 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.
Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers 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.

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_{2A} 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_{2A} receptor modulators, for the treatment of a 5-HT_{2A} 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_{2A} serotonin receptor mediated disorders diseases 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 throbmin 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-{[2-cyclopropyl-1(5*)-(2-fluorophenyl)-2-oxoethyl]-4(R*)-sulfanyl)piperidin-3-ylidene]acetic acid], abciximab (ReoPro®), epifibatide (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-trimethoxybenzylidine)pyrrolidine-2,5-dione], inhibitors of α-2-antiplasmin such as anti-α-2-antiplasmin antibody and thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, phosphodiesterase (PDE) inhibitors, such as dipyridamole (Persantine®) 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 atorvastatin (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); β-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 antiarrhythmic agents such as for atrial fibrillation, for example, amiodarone 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), streptokinase, 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 β-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 dexamethasone; and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, montelukast and pranleukast.

The compounds of the present invention can also be used in combination with anti-arrhythmogenic agents such as for the treatment of atrial fibrillation, for example, amiodarone or dofetilide.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include antiretrovirals [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®, Trizivir®, Zerit®, Ziagen®, Vired®, Emtricitabine, DAPD, and the like), non-nucleoside reverse transcriptase inhibitors (for example, Viramune®, Rescriptor®, Sustiva®, GW687, DPC083, TMC 125, Emivirine, Capravirine, BMS 561930, UC-781 and other oxathiin carboxanilides, SJ-3366, Alkenyldiaryl methane (ADAM), Tivirapine, Calanolide A, HBV097, Loviride, HEPT Family Derivatives, TIBO Derivatives, and the like), protease inhibitors (for example, Fortovase®, Invirase®, 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, Resobene, FP-23199, Cyanovirin-N, Zintevir (T30177, AR177), L-chicoric acid and derivatives, 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, bycyclam 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, Fuzeon® (T-20, DP 178, enfuviritide) trimers, 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 dietho 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, Leptomycin B, PKF050-638, and the like), transcriptional inhibitors (for example, Temacazine, 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.,

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 (1a) 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 (1a) and the
pharmaceutical agent(s) as a single pharmaceutical composition.

**OTHER UTILITIES**

Another object of the present invention relates to radio-labeled 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>125</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 $^3$H, $^{14}$C, $^{125}$I, $^{35}$S and $^{82}$Br. Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide $^3$H and/or $^{14}$C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$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 nonradio-active 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 [$^3$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 [$^3$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 [$^3$H] - This procedure is usually employed to prepare O-methyl or $N$-methyl [$^3$H] products by treating appropriate precursors with high specific activity methyl iodide ([$^3$H]). 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 $^{125}$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 $^{125}$I labeled

B. Ortho \(^{125}\)iodination of phenols – This procedure allows for the incorporation of \(^{125}\)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 \(^{125}\)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. Pd(PPh\(_3\))4] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkyliditin [e.g., (CH\(_3\))\(_3\)SnSn(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\(_{2A}\) 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\(_{2A}\) 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\(_{2A}\) receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the 5-HT\(_{2A}\) receptor. In one embodiment the labeled compound has an IC\(_{50}\) less than about 500 \(\mu\)M, in another embodiment the labeled compound has an IC\(_{50}\) less than about 100 \(\mu\)M, in yet another embodiment the labeled compound has an IC\(_{50}\) less than about 10 \(\mu\)M, in yet another embodiment the labeled compound has an IC\(_{50}\) less than about 1 \(\mu\)M, and in still yet another embodiment the labeled inhibitor has an IC\(_{50}\) less than about 0.1 \(\mu\)M.

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 Figures 1 through 7 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 (¹H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a 4 nucleus auto switchable probe and z-gradient or a Bruker Avance-400 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 = double of doublet, 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 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was preformed 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 *in vacuo* 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 the intermediate (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine.**

A 500-mL round bottom flask was charged with toluene (80 mL), copper(II) acetate (0.83 g, 4.55 mmol), myristic acid (1.56 g, 6.82 mmol), and p-iodophenylboronic acid (10.14 g, 40.91 mmol) then stirred at room temperature for five minutes. While mixing, 2,6-lutidine (7.14 mL, 61.27 mmol) was added and allowed to stir for an additional 10 minutes. 3-Amino-4-bromo-2-methyl pyrazole (4.00 g, 22.73 mmol) was added then the reaction mixture was stirred at room temperature overnight. Ethyl acetate was added, washed with ammonium hydroxide, water and brine. The ammonium salt formed, suspended in the organic layer, was removed by filtration. The filtrate was washed with water twice, dried over MgSO₄ and filtered. The solvent was removed under reduced pressure to yield a crude yellow oil, that was purified by column
chromatography on silica gel (Biotage hexanes/ethyl acetate, gradient elution) to afford (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine as a yellow solid. Yield: 4.51 g (53%). LCMS m/z (%) = 378 (M+H $^{79}$Br, 100), 380 (M+H $^{81}$Br, 97). $^1$H NMR (400MHz, DMSO-d$_6$): δ 8.13 (s, 1H), 7.59 (s, 1H), 7.46 (dd, J=11.8, 3.0 Hz, 2H), 6.39 (dd, J=11.8, 3.0 Hz, 2H), 6.62 (s, 3H).

Example 1.2: Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',4'-difluoro-biphenyl-4-yl)-amine (Compound 24).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 3,4-difluorophenyl boronic acid (50.1 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The mixture was purged with argon and palladium tetrakis triphenyl phosphine (24.5 mg, 0.02 mmol) was added. The reaction mixture was stirred overnight at 80°C, cooled to ambient temperature, taken up in dimethyl sulfoxide, filtered and purified by semi-prep HPLC (0.05% TFA). The major peak was collected and lyophilized to afford Compound 24 as a white solid. Yield: 21.4 mg (28.0%). LCMS m/z (%) = 364.0 (M+H $^{79}$Br, 100), 366 (M+H $^{81}$Br, 79). $^1$H NMR (400MHz, CDCl$_3$): δ 7.55 (s, 1H), 7.40 (d, J=8.8 Hz, 2H), 7.34-7.29 (m, 1H), 7.25-7.148 (m, 2H), 6.66 (d, J=8.8 Hz, 2H), 5.34 (s, 1H), 3.75 (s, 3H).

Example 1.3:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-chloro-biphenyl-4-yl)-amine (Compound 8).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (50.0 mg, 0.13 mmol), 4-chlorophenyl boronic acid (30.5 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (DME) (1 mL) and water (0.2 mL) under argon atmosphere. Tris(dibenzylideneacetone)dipalladium(0) (5.9 mg, 0.0007 mmol) was added and the mixture was purged with argon then stirred overnight at 80°C. The reaction mixture was cooled to ambient temperature, taken up in ethyl acetate and washed with brine and water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product that was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 8 as a light yellow solid. LCMS m/z (%) = 362.0 (M+H $^{79}$Br $^{35}$Cl, 80), 364.0 (M+H $^{81}$Br $^{35}$Cl, 100), 366.0 (M+H $^{81}$Br $^{37}$Cl, 30).

Example 1.4:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine (Compound 4).
A 20-mL scintillation vial was charged with 4-biphenylbromide (233.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 4 as a yellow solid. Yield: 76.2 mg (23.2%). LCMS m/z (%) = 346.0 (M+H\textsuperscript{79}Br, 100), 348 (M+H\textsuperscript{81}Br, 85).

Example 1.5:
Preparation of [4-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-phenyl-methanone (Compound 47).

A 20-mL scintillation vial was charged with 4-benzoylphenylbromide (261.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), cesium carbonate (456.2 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 47 as a yellow solid. LCMS m/z (%) = 356.0 (M+H\textsuperscript{79}Br, 95), 358 (M+H\textsuperscript{81}Br, 100).

Example 1.6:
Preparation of 4'-Fluoro-biphenyl-3-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 60).

Step 1: Preparation of the intermediate N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-3-iodo-benzamide.

A mixture of 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), 3-iodo benzoyl chloride (100.9 μL, 1.2 mmol) and pyridine (104.7 μL, 1.3 mmol) in dichloromethane (2 mL) was heated at 135°C for 10 min under microwaves on a Emrys Synthesizer. The reaction mixture was concentrated and subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 60/40) to give N-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-3-iodo-benzamide as a white solid. LCMS m/z (%) = 406 (M+H\textsuperscript{79}Br, 100), 408 (M+H\textsuperscript{81}Br, 97).

Step 2: Preparation of 4'-Fluoro-biphenyl-3-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 60).

A 20-mL scintillation vial was charged with N-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-3-iodo-benzamide (52.8 mg, 0.13 mmol), 4-fluorophenyl boronic acid (24.3 mg, 0.2 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.3 mL)
under argon atmosphere. Tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford the Compound 60 as a white solid. LCMS m/z (%) = 374 (M+H $^{79}$Br, 100), 376 (M+H $^{81}$Br, 98).

Example 1.7:
Preparation of Biphenyl-4-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (Compound 1).

Route 1: A general procedure for an N-arylation from the corresponding halides (Buchwald-like coupling)

A 20-mL scintillation vial was charged with 4-biphenylbromide (233.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 1 as a yellow solid. Yield: 76.2 mg (23.2 %). LCMS m/z (%) = 328 (M+H $^{79}$Br, 100), 330 (M+H $^{81}$Br, 97).

Route 2: A general procedure for an N-arylation from the corresponding boronic acids

A mixture of 3-amino-4-bromo-2-methyl pyrazole (35.2 mg, 0.2 mmol), 4-biphenylboronic acid (79.2 mg, 0.4 mmol), copper(II) acetate (36.3 mg, 0.2 mmol) and triethylamine (55.8 µL, 0.4 mmol) in methylene chloride (1.5 mL) was stirred at room temperature under ambient atmosphere for five days. The reaction mixture was filtered and subjected first to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) then to purification by preparative LCMS to afford Compound 1 as a yellow solid. LCMS m/z (%) = 328 (M+H $^{79}$Br, 100), 330 (M+H $^{81}$Br, 97).

Example 1.8:
Preparation of Biphenyl-3-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (Compound 50).

A 20-mL scintillation vial was charged with 3-biphenylbromide (233.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica
gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 50 as a brownish solid.

LCMS m/z (%) = 328 (M+H \(^{79}\)Br, 100), 330 (M+H \(^{81}\)Br, 98).

Example 1.9:

**Preparation of Biphenyl-2-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (Compound 49).**

A 20-mL scintillation vial was charged with 2-biphenylyl bromide (233.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 49 as a brownish solid.

LCMS m/z (%) = 328.0 (M+H \(^{79}\)Br, 100), 330 (M+H \(^{81}\)Br, 98).

Example 1.10: A general procedure for a Suzuki coupling starting from (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine.

**Preparation of (4-bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluoro-biphenyl-4-yl)-amine (Compound 2).**

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)-amine (50.0 mg, 0.13 mmol.), 2-fluorophenyl boronic acid (27.3 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added, then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 2 as a yellow solid. LCMS m/z (%) = 346 (M+H \(^{79}\)Br, 100), 348 (M+H \(^{81}\)Br, 97).

Example 1.11:

**Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-biphenyl-4-yl)-amine (Compound 3).**

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)-amine (50.0 mg, 0.13 mmol), 3-fluorophenyl boronic acid (27.3 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and...
subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 3 as a yellow solid. LCMS m/z (%) = 346 (M+H $^{79}$Br, 100), 348 (M+H $^{81}$Br, 98).

Example 1.12:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine (Compound 4).

A 20-mL scintillation vial was charged with 4'-bromo-4-fluoro-biphenyl (251.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 4 as a yellow solid. Yield: 78.6 mg (22.7 %). LCMS m/z (%) = 346 (M+H $^{79}$Br, 100), 348 (M+H $^{81}$Br, 98).

Example 1.13:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-fluoro-biphenyl-4-yl)-amine (Compound 5).

A 20-mL scintillation vial was charged with 4-bromo-2-fluoro-biphenyl (251.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 5 as a yellow solid. Yield: 144.7 mg (41.8 %). LCMS m/z (%) = 346 (M+H $^{79}$Br, 100), 348 (M+H $^{81}$Br, 98).

Example 1.14:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-methyl-biphenyl-4-yl)-amine (Compound 6).

A 20-mL scintillation vial was charged with 4-bromo-2-methyl-biphenyl (247.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography.
on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 6 as a yellow solid. LCMS m/z (%) = 342 (M+H $^{79}$Br, 100), 344 (M+H $^{81}$Br, 98)

Example 1.15:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methyl-biphenyl-4-yl)-amine (Compound 9).

A 20-mL scintillation vial was charged with 4'-bromo-4-methyl-biphenyl (247.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 9 as a yellow solid. LCMS m/z (%) = 342 (M+H $^{79}$Br, 100), 344 (M+H $^{81}$Br, 98).

Example 1.16:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-propyl-biphenyl-4-yl)-amine (Compound 10).

A 20-mL scintillation vial was charged with 4'-bromo-4-propyl-biphenyl (275.2 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 10 as a yellow solid. Yield: 110.7 mg (30.1 %). LCMS m/z (%) = 370 (M+H $^{79}$Br, 100), 372 (M+H $^{81}$Br, 98).

Example 1.17:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-tert-butyl-biphenyl-4-yl)-amine (Compound 11).

A 20-mL scintillation vial was charged with 4'-bromo-4-tert-butyl-biphenyl (289.2 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography
on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 11 as a yellow solid. Yield: 114.8 mg (29.9%). LCMS m/z (%) = 384 (M+H $^{79}$Br, 100), 386 (M+H $^{81}$Br, 98).

Example 1.18:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-heptyl-biphenyl-4-yl)-amine (Compound 12).
A 20-mL scintillation vial was charged with 4'-bromo-4-heptyl-biphenyl (331.2 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 12 as a yellow solid. Yield: 121.3 mg (28.4%). LCMS m/z (%) = 384 (M+H $^{79}$Br, 100), 386 (M+H $^{81}$Br, 97).

Example 1.19:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methoxy-biphenyl-4-yl)-amine (Compound 13).
A 20-mL scintillation vial was charged with 4'-bromo-4-methoxy-biphenyl (263.1 mg, 1 mmol), 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 13 as a yellow solid. LCMS m/z (%) = 358 (M+H $^{79}$Br, 100), 360 (M+H $^{81}$Br, 98).

Example 1.20:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethyl-biphenyl-4-yl)-amine (Compound 16).
A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)-amine (50.0 mg, 0.13 mmol), 4-trifluoromethylphenyl boronic acid (37.0 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added, then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA).
corresponding fractions were collected and lyophilized to afford Compound 16 as a yellow solid. LCMS m/z (%) = 396 (M+H⁷⁹Br, 100), 398 (M+H⁸¹Br, 98).

**Example 1.21:**

**Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4′-trifluoromethoxy-biphenyl-4-yl)-amine (Compound 18).**

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)amine (50.0 mg, 0.13 mmol), 4-trifluoromethoxyphenyl boronic acid (27.3 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added, then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 18 as a yellow solid. LCMS m/z (%) = 384 (M+H⁷⁹Br, 100), 386 (M+H⁸¹Br, 98).

**Example 1.22:**

**Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-2-yl-phenyl)-amine (Compound 38).**

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)amine (50.0 mg, 0.13 mmol), 2-thiophene boronic acid (25.0 mg, 0.20 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 38 as a light brown solid. Yield: 8.5 mg (19.6%). LCMS m/z (%) = 334 (M+H⁷⁹Br, 100), 336 (M+H⁸¹Br, 97).

**Example 1.23:**

**Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-3-yl-phenyl)-amine (Compound 39).**

A 20-mL scintillation vial was charged with intermediate (4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-phenyl)amine (50.0 mg, 0.13 mmol, 1.0 eq.), 3-thiophene boronic acid (25.0 mg, 0.20 mmol, 1.5 eq.), cesium carbonate (84.7 mg, 0.26 mmol, 2.0 eq.), 1,2-dimethoxyethane (1 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol, 0.10 eq.) was added then the
reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 39 as a light brown solid. Yield: 13.8 mg (31.8%). LCMS m/z (%) = 334 (M+H$^{79}$Br, 100), 336 (M+H$^{81}$Br, 98).

Example 1.24:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-phenoxy-phenyl)-amine
(Compound 46).

A mixture of 3-amino-4-bromo-2-methyl pyrazole (52.8 mg, 0.3 mmol), 4-phenoxyphenyl boronic acid (128.4 mg, 0.6 mmol), copper(II) acetate (54.5 mg, 0.3 mmol) and triethylamine (83.6 µL, 0.6 mmol) in methylene chloride (1.5 mL) was stirred at room temperature under ambient atmosphere for five days. The reaction mixture was filtered and subjected first to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) then to a secondary purification by preparative LCMS to afford Compound 46 as a yellow solid. LCMS m/z (%) = 344 (M+H$^{79}$Br, 100), 346 (M+H$^{81}$Br, 98).

Example 1.25:
Preparation of 1-[3-(4-bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-3-(4-chloro-phenyl)-urea (Compound 48).

Step 1: Preparation of (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-nitro-phenyl)-amine.

A mixture of 3-amino-4-bromo-2-methyl pyrazole (2.0 g, 11.36 mmol), 3-nitrophenyl boronic acid (3.79 g, 22.73 mmol), copper(II) acetate (2.1 g, 11.36 mmol) and triethylamine (3.17 mL, 22.73 mmol) in methylene chloride (50 mL) was stirred at room temperature for five days. The reaction mixture was filtered and subjected to column chromatography on silica gel (Biotage, hexanes/ethyl acetate, gradient elution) to afford (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-nitro-phenyl)-amine as a yellow solid. LCMS m/z (%) = 297 (M+H$^{79}$Br, 100), 299 (M+H$^{81}$Br, 98).

Step 2: Preparation of N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-benzene-1,3-diamine.

A solution of (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-nitro-phenyl)-amine (30.0 mg, 0.1 mmol) in hot ethanol (2 mL) was treated with a solution of sodium hydrosulfite (80.0 mg, 0.4 mmol) in water (0.5 mL), added dropwise. The reaction mixture was heated at 78°C for 20 minutes then concentrated. Ethyl acetate and water were added and extracted. The organic layer was separated, washed with water twice, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure to afford N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-
benzene-1,3-diamine as an oil. Yield: 13.2 mg (50.1%). LCMS m/z (%) = 267 (M+H 79Br, 100), 269 (M+H 81Br, 98).

**Step 3: Preparation of 1-[3-(4-bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-3-(4-chloro-phenyl)-urea (Compound 48).**

A solution of N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-benzene-1,3-diamine (10.0 mg, 0.04 mmol) in methylene chloride (0.5 ml) was treated with 4-chlorophenyl isocyanate (6.2 mg, 0.04 mmol). The reaction mixture was stirred at room temperature overnight. The formed precipitate was collected by filtration, washed with methylene chloride and dried to afford Compound 48 as a pale solid. LCMS m/z (%) = 420 (M+H 79Br 35Cl, 80), 422 (M+H 81Br 35Cl, 100), 424 (M+H 81Br 37Cl, 30).

**Example 1.26:**

**Preparation of (4'-fluoro-biphenyl-4-yl)-(2-methyl-2H-pyrazol-3-yl)-amine (Compound 35).**

A 20-mL scintillation vial was charged with 4'-bromo-4-fluoro-biphenyl (251.1 mg, 1 mmol), 3-amino-2-methyl pyrazole (97.1 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 35 as a yellow solid. LCMS m/z (%) = 268 (M+H, 100).

**Example 1.27:**

**Preparation of (2,5-Dimethyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine (Compound 36).**

A 20-mL scintillation vial was charged with 4'-bromo-4-fluoro-biphenyl (251.1 mg, 1 mmol), 3-amino-2,5-dimethyl pyrazole (111.1 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 36 as a yellow solid. LCMS m/z (%) = 282 (M+H, 100).

**Example 1.28:**

**Preparation of (4-Bromo-1-methyl-1H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine**
(Compound 37).

A 20-mL scintillation vial was charged with 4'-bromo-4-fluoro-biphenyl (251.1 mg, 1 mmol), 3-amino-4-bromo-1-methyl pyrazole (176.0 mg, 1 mmol), sodium tert-butoxide (134.5 mg, 1.4 mmol), tris(dibenzyldieneacetone)dipalladium(0) (45.8 mg, 0.05 mmol), BINAP (62.3 mg, 0.1 mmol) and toluene (2 mL) under nitrogen atmosphere. The reaction mixture was heated at 80°C for 48 hours. It was then allowed to cool to room temperature, taken up in ether/ethyl acetate, filtered and concentrated. The crude material was subjected to column chromatography on silica gel (Biotage, eluent hexanes/ethyl acetate 70/30) to afford Compound 37 as a yellow solid. LCMS m/z (%) = 346 (M+H^79Br, 100), 348 (M+H^81Br, 98).

Example 1.29:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chloro-biphenyl-4-yl)-amine
(Compound 7).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 3-chlorophenyl boronic acid (66.2 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added, then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 7 as a white solid. Yield: 28.7 mg (28.7%). LCMS m/z (%) = 362 (M+H^79Br^35Cl, 90), 364 (M+H^81Br^35Cl, 100), 366 (M+H^81Br^37Cl, 30). ^1H NMR (400MHz, CDCl3): δ 3.59 (s, 3H), 5.17 (s, 1H), 6.51 (dd, J=6.8, 2.0 Hz, 2H), 7.11 (dd, J=1.4 Hz, 1.4 Hz, 1H) 7.16 (t, J=7.16 Hz, 1H), 7.24 (dd, J=6.6, 1.4 Hz, 1H), 7.29 (dd, J=6.8, 1.6 Hz, 2H), 7.34 (dd, J=1.8, 1.8 Hz, 1H), 7.40 (s, 1H).

Example 1.30:

Preparation of (4'-Bromo-biphenyl-4-yl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine
(Compound 62).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 4-bromophenyl boronic acid (85.0 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added, then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 62 as a white solid. Yield: 12.6 mg (12.0...
%. LCMS m/z (%) = 406 (M+H\(^{79}\)Br\(^{79}\)Br, 51), 408 (M+H\(^{79}\)Br\(^{81}\)Br, 100), 410 (M+H\(^{81}\)Br\(^{81}\)Br, 49). \(^1\)H NMR (400MHz, CDCl\(_3\)): 3.75 (s, 3H), 5.33 (s, 1H), 6.67 (dd, J=6.8, 1.6Hz, 1H) 7.26 (s, 1H), 7.40 (dd, J=6.6, 1.8 Hz, 2H), 7.44 (dd, J=6.8, 2.0 Hz, 2H), 7.52 (dd, J=6.6, 1.8 Hz, 2H), 7.55 (s, 1H).

Example 1.31:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-trifluoromethyl-biphenyl-4-yl)-amine (Compound 14).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 2-trifluoromethylphenyl boronic acid (80.4 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 14 as a white solid. Yield: 26.7 mg (26%). LCMS m/z (%) = 396 (M+H\(^{79}\)Br, 100), 398 (M+H\(^{81}\)Br, 98). \(^1\)H NMR (400MHz, CDCl\(_3\)): 3.74 (s, 3H), 5.32 (s, 1H), 6.64 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H) 7.32 (d, J=8.0 Hz, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.56-7.52 (m, 1H), 7.54 (s, 1H), 7.73 (d, J=7.6, 1H).

Example 1.32:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethyl-biphenyl-4-yl)-amine (Compound 15).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 3-trifluoromethylphenyl boronic acid (80.4 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 15 as a white solid. Yield: 18.2 mg (17.7 %). LCMS m/z (%) = 396 (M+H\(^{79}\)Br, 100), 398 (M+H\(^{81}\)Br, 80). \(^1\)H NMR (400MHz, CDCl\(_3\)): 3.76 (s, 3H), 5.37 (s, 1H), 6.70 (dd, J=5.6, 3.6 Hz, 2H), 7.49 (dd, J=6.8, 2.0 Hz, 2H), 7.54-7.52 (m, 2H), 7.56 (s, 1H), 7.70 (dd, J=3.6, 3.6 Hz, 1H), 7.78 (s, 1H).

Example 1.33:
Preparation of (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethoxy-biphenyl-4-yl)-amine (Compound 17).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 3-trifluoromethoxyphenyl boronic acid (87.2 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 17 as a white solid. Yield: 23.1 mg (21.6 %). LCMS m/z (%) = 412 (M+H^{79}Br, 100), 414 (M+H^{81}Br, 98). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \delta 3.76 (s, 3H), 5.35 (s, 1H), 6.69 (dd, J=6.6, 4.6 Hz, 2H), 7.15 (d, J=8.0 Hz, 1H), 7.44-7.37 (m, 3H), 7.47 (dd, J=4.4, 4.4 Hz, 2H), 7.55 (s, 1H).

Example 1.34:
Preparation of 1-[4'-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-biphenyl-3-yl]-ethanone (Compound 19).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 4-acetylphenyl boronic acid (69.4 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 19 as a white solid. Yield: 28.2 mg (29.3 %). LCMS m/z (%) = 370 (M+H^{79}Br, 90), 372 (M+H^{81}Br, 100). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \delta 2.67 (s, 3H), 3.77 (s, 3H), 5.44 (s, 1H), 6.72 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.54-7.51 (m, 1H), 7.57 (s, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.90 (d, J=7.6 Hz, 1H), 8.15 (dd, J=1.6, 1.6 Hz, 1H).

Example 1.35:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-nitro-biphenyl-4-yl)-amine (Compound 20).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 4-nitrophenyl boronic acid (53.0mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5
mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 20 as a white solid. Yield: 26.7 mg (20.9%). LCMS m/z (%) = 373 (M+H<sup>79</sup>Br, 80), 375 (M+H<sup>81</sup>Br, 100). <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 3.77 (s, 3H), 5.40 (s, 1H), 6.71 (dd, J=6.6, 1.8 Hz, 2H), 7.54 (dd, J=6.6, 1.8 Hz, 2H), 7.57 (s, 1H), 7.68 (dd, J=7.0, 1.8 Hz, 2H), 8.27 (dd, J=6.8, 2.0 Hz, 2H).

Example 1.36:

**Preparation of N<sup>4</sup>-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-biphenyl-3,4'-diamine (Compound 21).**

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 3-aminophenyl boronic acid (58.0 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 21 as a white solid. Yield: 3.7 mg (4.2%). LCMS m/z (%) = 343 (M+H<sup>79</sup>Br, 100), 345 (M+H<sup>81</sup>Br, 90). <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 1.60 (s, 2H), 3.74 (s, 3H), 5.29 (s, 1H), 6.65 (d, J=8.4 Hz, 2H), 6.61-6.69 (m, 1H), 6.88 (s, 1H), 6.95 (d, J=7.6 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 7.45 (d, J=8.4 Hz, 2H), 7.53 (s, 1H).

Example 1.37:

**Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2',3'-difluoro-biphenyl-4-yl)-amine (Compound 22).**

A 20-mL scintillation vial was charged with intermediate (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 2,3-difluorophenyl boronic acid (50.1 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 22 as a white solid. Yield: 40.3 mg (52.7%). LCMS m/z (%) = 364 (M+H<sup>79</sup>Br, 100), 366 (M+H<sup>81</sup>Br, 98). <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 3.75 (s, 3H), 5.39 (s, 1H), 6.68 (dd, J=6.8, 2.0 Hz, 2H), 7.18-7.08 (m, 3H), 7.44 (dd, J=8.4, 1.6 Hz, 2H), 7.55 (s, 1H).
Example 1.38:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',5'-difluoro-biphenyl-4-yl)-amine (Compound 23).

A 20-mL scintillation vial was charged with intermediate (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol, 1.0 eq.), 3,5-difluorophenyl boronic acid (50.1 mg, 0.32 mmol, 1.5 eq.), cesium carbonate (137.9 mg, 0.42 mmol, 2.0 eq.), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol, 0.10 eq.) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 23 as a white solid. Yield: 14.0 mg (18.3%). LCMS m/z (%) = 364 (M+H^79Br, 100), 366 (M+H^81Br, 95). ^1H NMR (400MHz, CDCl3): δ 3.75 (s, 3H), 5.31 (s, 1H), 6.66 (dd, J=6.4, 2.0 Hz, 2H), 7.40-7.27 (m, 3H), 7.43 (dd, J=6.4, 2.0 Hz, 2H), 7.53 (s, 1H).

Example 1.39:
Preparation of 4'-Trifluoromethyl-biphenyl-3-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 61).

A 20-mL scintillation vial was charged with N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-3-iodo-benzamide (52.8 mg, 0.13 mmol, see Example 1.6), 4-trifluoromethylphenyl boronic acid (37.0 mg, 0.2 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.3 mL) under argon atmosphere. Tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon once again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 61 as a white solid. LCMS m/z (%) = 424 (M+H^79Br, 100), 426 (M+H^81Br, 98).

Example 1.40:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-2'-methyl-biphenyl-4-yl)-amine (Compound 26).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 4-flouro-2-methylphenyl boronic acid (48.9 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction
mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 26 as a white solid. Yield: 32.2 mg (42.6 %). LCMS m/z (%) = 360 (M+H37Br, 100), 362 (M+H39Br, 98). 1H NMR (400MHz, CDCl3): δ 2.26 (s, 3H), 3.76 (s, 3H), 5.31 (s, 1H), 6.64 (dd, J=6.6, 1.8 Hz, 2H), 6.99-6.88 (m, 1H), 7.15 (dd, J=6.2, 2.2 Hz, 2H), 7.17-7.14 (m, 1H), 7.54 (s, 1H).

Example 1.41:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methyl-biphenyl-4-yl)-amine (Compound 27).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 3-fluoro-4-methylphenyl boronic acid (48.9 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 27 as a white solid. Yield: 24.8 mg (26.5 %). LCMS m/z (%) = 360 (M+H37Br, 100), 362 (M+H39Br, 98). 1H NMR (400MHz, CDCl3): δ 2.30 (s, 3H), 3.75 (s, 3H), 5.31 (s, 1H), 6.66 (dd, J=6.8, 1.8 Hz, 2H), 7.22-7.12 (m, 3H), 7.44 (dd, J=9.0, 2.2 Hz, 2H), 7.55 (s, 1H).

Example 1.42:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-3'-methyl-biphenyl-4-yl)-amine (Compound 28).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 4-fluoro-3-methylphenyl boronic acid (66.2 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 28 as a white solid. Yield: 18.2 mg (19.4 %). LCMS m/z (%) = 360 (M+H37Br, 100), 362 (M+H39Br, 98). 1H NMR (400MHz, CDCl3): δ 2.35 (s, 3H), 3.79 (s, 3H), 5.38 (s, 1H), 6.71 (dd, J=6.6, 1.8 Hz, 2H), 7.26-7.22 (m, 3H), 7.49 (dd, J=6.6, 1.8 Hz, 2H), 7.59 (s, 1H).
Example 1.43:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methoxy-biphenyl-4-yl)-amine (Compound 29).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazole-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 3-fluoro-4-methoxybiphenyl boronic acid (54.0 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 29 as a white solid. Yield: 16.2 mg (20.5 %). LCMS m/z (%) =376 (M+H\textsuperscript{79}Br, 100), 378 (M+H\textsuperscript{81}Br, 95). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): δ 3.75 (s, 3H), 3.92 (s, 3H), 5.30 (s, 1H), 6.66 (d, J=6.6, 1.8 Hz, 2H), 7.03-6.98 (m, 1H), 7.28-7.23 (m, 2H), 7.37 (dd, J=6.4, 2.0 Hz, 2H), 7.55 (s, 1H).

Example 1.44:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3’,4’-dichloro-biphenyl-4-yl)-amine (Compound 30).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 3,4-dichlorobiphenyl boronic acid (60.5 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 30 as a white solid. Yield: 26.9 mg (32.4 %). LCMS m/z (%) = 396 (M+H\textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{35}Cl, 76), 398 (M+H\textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{37}Cl & \textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{35}Cl, 100), 340 (M+H\textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{37}Cl & \textsuperscript{79}Br\textsuperscript{37}Cl\textsuperscript{37}Cl, 52), 342 (M+H\textsuperscript{81}Br\textsuperscript{37}Cl\textsuperscript{37}Cl, 6). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): δ 3.76 (s, 3H), 5.35 (s, 1H), 6.68 (d, J=8.8 Hz, 2H), 7.35 (dd, J=8.2, 1.8 Hz, 1H), 7.47-7.42 (m, 3H), 7.56 (s, 1H), 7.61 (d, J=2.0 Hz, 1H).

Example 1.45:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2’-chloro-5’-methyl-biphenyl-4-yl)-amine (Compound 31).

A 20-mL scintillation vial was charged with intermediate (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 2-chloro-5-methylbiphenyl boronic acid (54.1 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 31 as a white solid. Yield: 26.9 mg (32.4 %). LCMS m/z (%) = 396 (M+H\textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{35}Cl, 76), 398 (M+H\textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{37}Cl & \textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{35}Cl, 100), 340 (M+H\textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{37}Cl & \textsuperscript{79}Br\textsuperscript{37}Cl\textsuperscript{37}Cl, 52), 342 (M+H\textsuperscript{81}Br\textsuperscript{37}Cl\textsuperscript{37}Cl, 6). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): δ 3.76 (s, 3H), 5.35 (s, 1H), 6.68 (d, J=8.8 Hz, 2H), 7.35 (dd, J=8.2, 1.8 Hz, 1H), 7.47-7.42 (m, 3H), 7.56 (s, 1H), 7.61 (d, J=2.0 Hz, 1H).
mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 31 as a white solid. Yield: 26.9 mg (32.4%). LCMS m/z (%) = 376 (M+H^79Br^35Cl, 80), 378 (M+H^81Br^35Cl, 100), 380 (M+H^81Br^37Cl, 25). ^1^H NMR (400MHz, CDCl3): δ 2.42 (s, 3H), 3.75 (s, 3H), 5.31 (s, 1H), 6.66 (dd, J=6.4, 2.0 Hz, 2H), 7.28 (dd, J=8.4, 2.4 Hz, 1H), 7.39-7.35 (m, 2H), 7.43 (dd, J=6.6, 1.8 Hz, 2H), 7.54 (s, 1H).

Example 1.46:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(5'-chloro-2'-methyl-biphenyl-4-yl)-amine (Compound 32).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 5-chloro-2-methylphenyl boronic acid (54.1 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 32 as a white solid. Yield: 29.2 mg (36.9%). LCMS m/z (%) = 376 (M+H^79Br^35Cl, 80), 378 (M+H^81Br^35Cl, 100), 380 (M+H^81Br^37Cl, 25). ^1^H NMR (400MHz, CDCl3): δ 2.25 (s, 3H), 3.75 (s, 3H), 5.29 (s, 1H), 6.63 (dd, J=7.6, 3.6 Hz, 2H), 7.13 (d, J=4.0 Hz, 2H), 7.25-7.11 (m, 3H), 7.53 (s, 1H).

Example 1.47:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chloro-4'-trifluoromethyl-biphenyl-4-yl)-amine (Compound 33).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 3-chloro-4-trifluoromethyl-phenyl boronic acid (54.1 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 33 as a white solid.
Yield: 29.2 mg (36.9 %). LCMS m/z (%) = 430 (M+H⁺Br⁻Br⁻Cl⁻, 60), 432 (M+H⁺Br⁺Br⁻Cl⁻, 100), 434 (M+H⁺Br⁺Br⁻Cl⁻, 30).

Example 1.48:

Preparation of (2',4'-Bis-trifluoromethyl-biphenyl-4-yl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (Compound 34).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (80.0 mg, 0.21 mmol), 2,4-di-(trifluoromethyl)phenyl boronic acid (81.9 mg, 0.32 mmol), cesium carbonate (137.9 mg, 0.42 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (24.5 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 34 as a white solid.

Yield: 40.8 mg (41.9 %). LCMS m/z (%) = 464 (M+H⁺Br⁻, 90), 466 (M+H⁺Br⁺Br⁻, 100). ¹H NMR (400MHz, CDCl₃): δ 3.77 (s, 3H), 5.39 (s, 1H), 6.66 (dd, J=6.6, 1.8 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.0 Hz, 2H), 7.56 (s, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.99(s, 1H).

Example 1.49:

Preparation of (4-Benzol[1,3]dioxol-5-yl-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (Compound 45).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 3,4-dimethoxymethylene phenyl boronic acid (87.8 mg, 0.53 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 45 as a white solid.

Yield: 25.6 mg (12.9 %). LCMS m/z (%) = 372 (M+H⁺Br⁻, 100), 374 (M+H⁺Br⁺Br⁻, 98). ¹H NMR (400MHz, MeOD): δ 3.70 (s, 3H), 5.95 (s, 2H), 6.63 (dd, J=6.4, 4.8 Hz, 2H), 6.83 (d, J=8.0 Hz, 1H), 7.02-7.00 (m, 2H), 7.38 (dd, J=6.8, 2.0, 2H), 7.53 (s, 1H).

Example 1.50:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-(6-chloro-pyridin-3-yl)-phenyl)-amine (Compound 63).
A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 6-chloro-pyridyl-3-boronic acid (83.3 mg, 0.53 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane and (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 63 as a white solid. Yield: 45.5 mg (55 %). LCMS m/z (%) =363 (M+H\textsuperscript{39}Br\textsuperscript{35}Cl, 80), 365 (M+H\textsuperscript{39}Br\textsuperscript{35}Cl, 100), 367 (M+H\textsuperscript{39}Br\textsuperscript{37}Cl, 24). \textsuperscript{1}H NMR (400MHz, MeOD): δ 2.66 (s, 1H), 3.72 (s, 3H), 6.71 (d, J=8.8 Hz, 2H), 7.54-7.46 (m, 4H), 8.01 (dd, J=8.2, 2.6 Hz, 1H), 8.56 (d, J=2.4 Hz, 1H).

Example 1.51:
Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-(6-methoxy-pyridin-3-yl)-phenyl)-amine (Compound 42).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(4-iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 6-methoxy-pyridyl-3-boronic acid (83.3 mg, 0.53 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane and (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 42 as a white solid. Yield: 14.7 mg (15 %). LCMS m/z (%) =359 (M+H\textsuperscript{39}Br, 90), 361 (M+H\textsuperscript{39}Br, 100).

Example 1.52:
Preparation of the intermediate (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-iodo-phenyl)-amine.

A 500-mL round bottom flask was charged with toluene (50 mL), copper(II) acetate (0.62 g, 3.41 mmol), myristic acid (1.17 g, 5.11 mmol), and m-iodophenylboronic acid (5.00 g, 20.18 mmol) then stirred at room temperature for five minutes. While mixing, 2,6-lutidine (1.99 mL, 17.04 mmol) was added and allowed to stir for an additional 10 minutes. 3-amino-4-bromo-2-methyl pyrazole (3.00 g, 17.04 mmol) was added then reaction mixture stirred at room temperature overnight. Ethyl acetate was added, washed with ammonium hydroxide, water and brine. The ammonium salt formed, suspended in the organic layer, was removed by filtration. The filtrate was washed with water twice, dried over MgSO\textsubscript{4} and filtered. The solvent was removed under reduced pressure to yield a crude yellow oil, that was purified by column
chromatography on silica gel (Biotage, hexanes/ethyl acetate, gradient elution) to afford (4-
bromo-2-methyl-2H-pyrazol-3-yl)-(3-iodo-phenyl)-amine as a yellow solid. Yield: 3.25 g (51%
). LCMS m/z (%) = 378 (M+H$^{79}$Br, 100), 380 (M+H$^{81}$Br, 88). $^1$H NMR (400MHz, DMSO-
d$_6$): δ 8.15 (s, 1H), 7.61 (s, 1H), 7.09 (d, J=8.0 Hz, 1H), 6.96 (dd, J=8.0, 8.0 Hz, 1H), 6.90 (dd,
J=1.8, 1.8 Hz, 1H), 6.52 (dd, J=8.0, 1.6 Hz, 1H), 3.63 (s, 3H).

Example 1.53:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluoro-biphenyl-3-yl)-amine
(Compound 51).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-
iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 2-fluorophenyl boronic acid (59.2 mg, 0.42 mmol),
cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL).
The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (30.6
mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction
mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature,
filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions
were collected and lyophilized to afford Compound 51 as a white solid. Yield: 31.1 mg (34.6%
). LCMS m/z (%) =346 (M+H$^{79}$Br, 92), 348 (M+H$^{81}$Br, 100). $^1$H NMR (400MHz, CDCl$_3$): δ
3.67 (s, 3H), 5.24 (s, 1H), 6.56 (dd, J=8.0, 2.0 Hz, 1H), 6.72 (d, J=1.6 Hz, 1H), 7.16-7.02 (m,
3H), 7.28-7.21 (m, 2H), 7.34 (t, J=7.7, 1.7 Hz, 2H), 7.48 (s, 1H).

Example 1.54:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethoxy-biphenyl-3-yl)-
amine (Compound 53).

A 20-mL scintillation vial was charged with (4-bromo-2-methyl-2H-pyrazol-3-yl)-(3-
iodo-phenyl)-amine (100.0 mg, 0.26 mmol), 4-trifluoromethoxyphenyl boronic acid (87.2 mg,
0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water
(0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine)
palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again.
The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient
temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The
 corresponding fractions were collected and lyophilized to afford Compound 53 as a white solid.
LCMS m/z (%) = 412 (M+H$^{79}$Br, 100), 414 (M+H$^{81}$Br, 85). $^1$H NMR (400MHz, CDCl$_3$): δ 3.66
(s, 3H), 5.15 (s, 1H), 6.41 (dd, J=8.0, 2.0 Hz, 1H), 6.57 (t, J=1.8 Hz, 1H), 6.90 (d, J=7.6 Hz, 1H),
7.14-7.07 (m, 3H), 7.37-7.33 (m, 3H).

Example 1.55:
Preparation of the intermediate (4-bromo-2-methoxy-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine.

A 250-mL round bottom flask was charged with toluene (30 mL), copper(II) acetate (0.49 g, 2.70 mmol), myristic acid (0.93 g, 6.82 mmol), and 4-bromo-2-methoxy-phenyl boronic acid (4.99 g, 21.64 mmol) then stirred at room temperature for five minutes. While mixing, 2,6-lutidine (1.58 mL, 13.52 mmol) was added and allowed to stir for an additional 10 minutes. 3-amino-4-bromo-2-methyl pyrazole (2.38 g, 13.52 mmol) was added then reaction mixture stirred at room temperature overnight. Ethyl acetate was added, washed with ammonium hydroxide, water and brine. The ammonium salt formed, suspended in the organic layer, was removed by filtration. The filtrate was washed with water twice, dried over MgSO₄ and filtered. The solvent was removed under reduced pressure to yield a crude yellow oil, that was purified by column chromatography on silica gel (Biotage, hexanes/dichloromethane, gradient elution) to afford (4-bromo-2-methoxy-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine. Yield: 0.14 g (2.8%). LCMS: m/z (%) = 360 (M+H⁷⁹Br⁻⁷⁹Br, 50), 362 (M+H⁷⁹Br⁻⁸¹Br, 100), 364 (M+H⁻⁸¹Br²⁻³¹Br, 55). ¹H NMR (400MHz, MeOD): δ 7.47 (s, 1H), 6.79 (dd, J=12.0, 4.8 Hz, 2H), 6.18 (d, J=2.0 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H).

Example 1.56:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3-methoxy-4'-trifluoromethoxy-biphenyl-4-yl)-amine (Compound 54).

A 20-mL scintillation vial was charged with (4-bromo-2-methoxy-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (60.0 mg, 0.17 mmol), 4-trifluoromethoxyphenyl boronic acid (87.2 mg, 0.42 mmol), cesium carbonate (172.4 mg, 0.53 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenyl-phosphine) palladium(0) (30.6 mg, 0.03 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 54 as a white solid. Yield: 12.1 mg (16.1%). LCMS m/z (%) = 442 (M+H⁻⁷⁹Br, 90), 444 (M+H⁻⁸¹Br, 100).

Example 1.57:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-3-methoxy-biphenyl-4-yl)-amine (Compound 55).

A 20-mL scintillation vial was charged with intermediate (4-bromo-2-methoxy-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (60.0 mg, 0.17 mmol), 3-fluorophenyl boronic acid (46.8 mg, 0.33 mmol), cesium carbonate (108.9 mg, 0.33 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine)
palladium(0) (19.3 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. Then, it was allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 55 as a white solid.

Yield: 39.8 mg (62.4 %). LCMS m/z (%) =376 (M+H\textsuperscript{79}Br, 98), 378 (M+H\textsuperscript{81}Br, 100). \textsuperscript{1}H NMR (400MHz, MeOD): \( \delta \) 3.74 (s, 3H), 3.79 (s, 3H), 6.44 (s, 1H), 6.96 (t, \( J=8.4 \) Hz, 1H), 7.07-7.02 (m, 2H), 7.13 (d, \( J=10.4 \) Hz, 1H), 7.23 (d, \( J=7.6 \) Hz, 1H), 7.37-7.31 (m, 1H), 7.57 (s, 1H), 7.66-7.62 (m, 1H).

Example 1.58:

Preparation of the intermediate (4-bromo-2-fluoro-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine.

A 200-mL round bottom flask was charged with toluene (30 mL), copper(II) acetate (0.52 g, 2.86 mmol), myristic acid (0.98 g, 4.29 mmol), and 4-bromo-2-fluoro-phenyl boronic acid (5.00 g, 22.86 mmol) then stirred at room temperature for five minutes. While mixing, 2,6-lutidine (1.66 mL, 14.29 mmol) was added and allowed to stir for an additional 10 minutes. 3-amino-4-bromo-2-methyl pyrazole (2.52 g, 14.29 mmol) was added then reaction mixture stirred at room temperature overnight. Ethyl acetate was added, washed with ammonium hydroxide, water and brine. The ammonium salt formed, suspended in the organic layer, was removed by filtration. The filtrate was washed with water twice, dried over MgSO\textsubscript{4} and filtered. The solvent was removed under reduced pressure to yield a crude material, that was purified by column chromatography on silica gel (Biotage, hexanes/dichlomethane, gradient elution) to afford (4-bromo-2-fluoro-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine. Yield: 0.07 g (1.4 %). LCMS: m/z (%) = 348 (M+H\textsuperscript{79}Br\textsuperscript{79}Br, 40), 350 (M+H\textsuperscript{79}Br\textsuperscript{81}Br, 100), 352 (M+H\textsuperscript{81}Br\textsuperscript{81}Br, 46). \textsuperscript{1}H NMR (400MHz, MeOD): \( \delta \) 7.43 (s, 1H), 7.19 (d, \( J=10.0 \) Hz, 1H), 7.01 (d, \( J=8.8 \) Hz, 1H), 6.22 (t, \( J=8.8 \) Hz, 1H), 3.62 (s, 3H).

Example 1.59:

Preparation of (4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3,3',4'-trifluoro-biphenyl-4-yl)-amine (Compound 25).

A 20-mL scintillation vial was charged with (4-bromo-2-fluoro-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine (62.0 mg, 0.17 mmol), 3,4-difluorophenyl boronic acid (80.0 mg, 0.51 mmol), cesium carbonate (108.9 mg, 0.33 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.2 mL). The reaction mixture was purged with argon, tetrakis(triphenylphosphine) palladium(0) (19.3 mg, 0.02 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The
corresponding fractions were collected and lyophilized to afford Compound 25 as a white solid. Yield: 35.7 mg (54.9 %). LCMS m/z (%) = 382 (M+H\textsuperscript{79}Br, 100), 384 (M+H\textsuperscript{81}Br, 90). \textsuperscript{1}H NMR (400MHz, MeOD): \(\delta\) 3.76 (s, 3H), 6.47 (dd, J=8.8, 8.8 Hz, 1H), 7.33-7.25 (m, 2H), 7.38-7.37 (m, 1H), 7.41 (dd, J=12.8, 2.0 Hz, 1H), 7.53-7.47 (m, 1H), 7.57 (s, 1H).

Example 1.60:
Preparation of Biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 57).

A 20-mL scintillation vial was charged with 3-amino-4-bromo-2-methyl pyrazole (50 mg, 0.28 mmol), dichloromethane (0.8 mL) followed by the addition of triethylamine (37.4 mg, 0.37 mmol) and 4-biphenyl carbonyl chloride (73.7 mg, 0.34 mmol). The reaction mixture was stirred at room temperature overnight. The solvents were removed under reduced pressure and the residue purified by column chromatography on silica gel (Eluent: ethyl acetate/hexanes = 40/60) to afford Compound 57 as an off-white solid. Yield: 50.8 mg (51 %). LCMS m/z (%) = 356.0 (M+H\textsuperscript{79}Br, 100), 358 (M+H\textsuperscript{81}Br, 85). \textsuperscript{1}H NMR (400MHz, DMSO): \(\delta\) 10.37 (s, 1H), 8.09 (d, J=8.0 Hz, 2H), 7.86 (d, J=8.0 Hz, 2H), 7.75 (d, J=8.0 Hz, 2H), 7.60 (s, 1H), 7.52-7.40 (m, 3H), 3.70 (s, 3H).

Example 1.61:
Preparation of the intermediate N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-benzamide.

Route 1:
A 100-mL round bottom flask was charged with 3-amino-4-bromo-2-methyl pyrazol (1.74 g, 9.90 mmol), anhydrous dichloromethane (30 ml) followed by the addition of triethylamine (0.95 g, 9.35 mmol) and 4-iodo benzoyl chloride (3.17 g, 11.88 mmol). The reaction mixture was stirred at room temperature overnight. The precipitate formed was collected by filtration and washed with hexanes. This crude material was further purified by column chromatography on silica gel (Eluent: ethyl acetate/hexane = 40/60) to produce N-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-benzamide as a white solid. Yield: 3.29 g (81.7 %). LCMS m/z (%) = 406.0 (M+H\textsuperscript{79}Br, 100), 408 (M+H\textsuperscript{81}Br, 97). \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) 10.4 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.87 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 3.68 (s, 3H).

Route 2: Microwave assisted synthesis
A mixture of 3-amino-4-bromo-2-methyl pyrazole (176.0 mg, 1 mmol), 4-iodo benzoyl chloride (0.10 mL, 1.2 mmol) and pyridine (104.7 \(\mu\)L, 1.3 mmol) in dichloromethane (2 mL) was heated at 135\(^\circ\)C for 10 min under microwaves in an Ermys Synthesizer. The reaction mixture was concentrated and subjected to column chromatography on silica gel (Biotage, eluent...
hexanes/ethyl acetate 60/40) to afford \(N\)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-benzamide as a white solid. LCMS \(m/z\) (%) = 406 (M+H\(^{79}\)Br, 100), 408 (M+H\(^{81}\)Br, 98).

**Example 1.62:** General Procedure for a Suzuki coupling.

Preparation of 4'-Fluoro-biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 58).

A 20-mL scintillation vial was charged with \(N\)-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-benzamide (52.8 mg, 0.13 mmol), 4-fluorophenyl boronic acid (27.3 mg, 0.2 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.3 mL) under argon atmosphere. Tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 58 as a white solid. Yield: 21.8 mg (41.9 %). LCMS \(m/z\) (%) = 374 (M+H\(^{79}\)Br, 100), 376 (M+H\(^{81}\)Br, 98).

**Example 1.63:**

Preparation of 4'-Trifluoromethoxy-biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide (Compound 59).

A 20-mL scintillation vial was charged with \(N\)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-iodo-benzamide (52.8 mg, 0.13 mmol), 4-trifluoromethoxy-phenyl boronic acid (40.2 mg, 0.2 mmol), cesium carbonate (84.7 mg, 0.26 mmol), 1,2-dimethoxyethane (1.5 mL) and water (0.3 mL) under argon atmosphere. Tetrakis(triphenylphosphine) palladium(0) (15.0 mg, 0.013 mmol) was added then the reaction vessel purged with argon once again. The reaction mixture was heated at 80°C overnight. It was then allowed to cool to ambient temperature, filtered and subjected to a purification by prep HPLC (0.05% TFA). The corresponding fractions were collected and lyophilized to afford Compound 59 as a white solid. Yield: 20.4 mg (37.0 %). LCMS \(m/z\) (%) = 440 (M+H\(^{79}\)Br, 100), 442 (M+H\(^{81}\)Br, 98).

**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 October 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 1x10^5 cells/well or 2x10^5 cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 ug 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%CO₂. Then the transfection media was removed and replaced with 1ml/well of regular growth media.

For 293 cells, on day one, 13x10^6 293 cells per 150 mm plate were plated out. On day two, 2 ml of serum OptiMEM (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 OptiMEM 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 5ml of OptiMEM media followed by careful aspiration. Then 12 ml of OptiMEM 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% CO₂ 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-HT₂A receptor

Compounds of the invention are tested for their ability to activate a 5-HT₂A receptor clone using an IP accumulation assay. Briefly, HEK293 cells are transiently transfected with a pCMV expression vector containing a human 5-HT₂A receptor (for the sequence of the receptor see U.S. Patent 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-HT₂A receptor

Compounds of the invention were tested for their ability to inhibit a constitutively active 5-HT₂A receptor clone using an IP accumulation assay. Briefly, 293 cells were transiently transfected with a pCMV expression vector containing a constitutively active human 5-HT₂A receptor and assayed for IP accumulation as described above.
receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:30) as
described in Example 2. The constitutively active human 5-HT_{2A} receptor contained the human
5-HT_{2A} receptor described in part A except that intracellular loop 3 (IC3) and the cytoplasmic tail
were replaced by the corresponding human INI 5-HT_{2C} cDNA. An IP accumulation assay was
performed as described below. Certain compounds of the invention had activity values ranging
from about 10 μM to about 6 nM in this assay.

C. IP Accumulation Assay protocol

On the day after transfections, media was removed and the cells were washed with 5 ml
PBS followed by careful aspiration. Cells were then trypsinized with 2 ml of 0.05% trypsin for 20-
30 seconds followed by addition of 10 mL of warmed media, gently triturated to dissociate cells, and
an additional 13 ml of warmed media was gently added. Cells were then counted and 55,000 cells
were added to 96-well sterile poly-D-lysine treated plates. Cells were allowed to attach over a six
hour incubation at 37°C in a 5% CO2 incubator. Media was then carefully aspirated and 100 μL of
warm inositol-free media plus 0.5 μCi 3H-inositol was added to each well and the plates were
incubated for 18-20 hours at 37°C in a 5% CO2 incubator.

On the next day, media was carefully aspirated and then 0.1 ml of assay medium was
added containing inositol-free/serum free media, 10 μM pargyline, 10 mM lithium chloride, and
test compound at indicated concentrations. The plates were then incubated for three hours at 37°C
and then wells were carefully aspirated. Then 200 μL of ice-cold 0.1M formic acid was added
to each well. Plates can then be frozen at this point at −80°C until further processed. Frozen
plates were then thawed over the course of one hour, and the contents of the wells
(approximately 220 μL) were 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 was then washed nine times with 200 μL of water and then

tritiated inositol phosphates (IP, IP2, and IP3) were eluted into a collecting plate by the addition
of 200ul of 1M ammonium formate and an additional 10 minute incubation. The eluant was then
transferred to 20 ml scintillation vials, 8 mL of SuperMix or Hi-Safe scintillation cocktails was
added, and vials were counted for 0.5-1 minutes in a Wallac 1414 scintillation counter.

30 EXAMPLE 4

Binding Assays

Compounds of the invention are tested for their ability to bind to a 5-HT_{2A} receptor clone
membrane preparation using a radioligand binding assay. Briefly, COS cells are transiently
transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the
sequence of the receptor see U.S. Patent 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$_{2A}$ receptors are cultured for 48 hr post transfection, collected, washed with ice-cold phosphate buffered saline, pH7.4 (PBS), and then centrifuged at 48,000Xg for 20 min at 4°C. The cell pellet is 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 X g for 20 min. at 4°C. The resultant pellet is then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice, and centrifuged (48,000Xg for 20 min at 4°C). Crude membrane pellets are stored at −80°C until used for radioligand binding assays.

B. [$^{125}$I]DOI Radioligand Binding Assay

Radioligand binding assays for human 5-HT$_{2A}$ receptor is conducted using the 5-HT$_{2}$ agonist [$^{125}$I]DOI as radioligand. To define nonspecific binding, 10μM DOI is used for all assays. For competitive binding studies, 0.5 nM [$^{125}$I]DOI is used and compounds are assayed over a range of 0.01 nM to 10 μM. Assays are 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$_2$, and 10 μM pargyline). Assay incubations are performed for 60 min at room temperature and are 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 are then washed several times with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4). Plates are then dried at room temperature and counted in a Wallac microBeta scintillation counter.

EXAMPLE 5

In Vitro Human Platelet Aggregation Assays

Compounds of the invention are tested for their ability to aggregate human platelets.

Aggregation assays are performed using a Chrono-Log Optical aggregometer model 410. Human blood (~100mls) is collected from human donors into glass Vacutainers containing 3.8% sodium citrate (light blue tops) at room temperature. Platelet rich plasma (PRP) is isolated via centrifugation at 100g for 15min at room temperature. After removal of the aqueous PRP layer, the platelet poor plasma (PPP) is prepared via high speed centrifugation at 2400g for 20min. Platelets are counted and their concentration is set to 250,000 cells/µl by dilution with PPP. Aggregation assays are conducted according to the manufacturer’s specifications. Briefly, a suspension of 450µl PRP is stirred in a glass cuvette (1200rpm) and, after baseline is established, 1µM ADP followed by either saline or 1µM 5HT and compound of interest (at desired concentrations) are added and the aggregation response recorded.
EXAMPLE 6

Efficacy of Compounds of the Invention in the Attenuation of DOI-induced hypolocomotion in rats.

In this example, compounds of the invention were 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$_{2A}$/2C receptor agonist that crosses the blood-brain barrier. The standard protocol used is described briefly below.

Animals:

Male Sprague-Dawley rats (Harlan, San Diego, CA) weighing between 200-300g were used for all tests. Rats were housed three to four per cage. These rats were naïve to experimental testing and drug treatment. Rats were handled one to three days before testing to acclimate them to experimental manipulation. Rats were fasted overnight prior to testing.

Compounds:

(R)-DOI HCl (C$_{11}$H$_{16}$INO$_2$HCl) was obtained from Sigma-Aldrich, and was dissolved in 0.9% saline. Compounds of the invention were synthesized at Arena Pharmaceuticals Inc. and were dissolved in 100%PEG400. DOI was injected s.c. in a volume of 1ml/kg, while compounds of the invention were administered p.o. in a volume of 2ml/kg.

Procedure:

The “Motor Monitor” (Hamilton-Kinder, Poway, CA) was used for all activity measurement. This apparatus recorded rears using infrared photobeams.

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

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

Statistics and Results:

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

EXAMPLE 7

In vitro Binding of 5-HT$_{2A}$ 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$_{2A}$ receptor and dopamine D$_2$ 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 $^{125}$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$_{2A}$ receptor and dopamine D$_2$ 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 $^{125}$I-LSD; (b) Buffer plus 1 nanomolar $^{125}$I-LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar $^{125}$I-LSD and 1 micromolar Compound of interest for 30 minutes at room temperature. Sections are then washed 2x 10 minutes at 4°C in Buffer, followed by 20 seconds in distilled H$_2$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$_{2A}$ Receptor Occupancy Studies in Monkey**

In this example, the 5-HT$_{2A}$ receptor occupancy of a compound of the invention can be measured. The study can be carried out in rhesus monkeys using PET and $^{18}$F-altanserin.

**Radioligand:**

The PET radioligand used for the occupancy studies is $^{18}$F-altanserin. Radiosynthesis of $^{18}$F-altanserin is achieved in high specific activities and is suitable for radiolabeling 5-HT$_{2A}$ 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$_{2A}$ 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$_{2A}$ 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 was 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 $^{18}$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 wakefullness 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$_2$/40% O$_2$ 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, MA) 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, RI). 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 CA).

**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% CO₂ 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 1nM to about 100μM, at a concentration of about 10nM to about 100μM, at a concentration of about 1nM to about 10μM, or at a concentration of about 10μM to about 10μM.

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 3X 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 Improvision software.

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 compound of Formula (Ia):

   \[ \text{R}_1 \text{R}_2 \text{N} \text{N} \text{X} \text{R}_4 \text{R}_5 \text{Y} \text{Ar} \]

   (Ia)

   or a pharmaceutically acceptable salt thereof,

   wherein:

   \( \text{R}_1 \) is selected from the group consisting of \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynd and \( C_{3-7} \) cycoalkyl;

   \( \text{R}_2 \) is selected from the group consisting of \( H \), \( C_{2-6} \) alkyl, \( C_{1-4} \) alkyl, \( C_{1-6} \) alkylicarboxamide, \( C_{2-6} \) alkyl, \( C_{1-6} \) alkylsulfonamide, carbo-C(=O)-alkoxy, carboxamide, carboxy, cyano, \( C_{3-7} \) cycoalkyl, \( C_{2-8} \) dialkylcarboxamide, and halogen;

   \( \text{R}_3 \) is selected from the group consisting of \( H \), \( C_{1-6} \) acyl, \( C_{1-6} \) acyloxy, \( C_{2-6} \) alkyl, \( C_{1-6} \) alkylicarboxamide, \( C_{2-6} \) alkyloxy, \( C_{1-6} \) alkyl, \( C_{1-6} \) alkylsulfonamide, \( C_{1-6} \) alkyld, \( C_{1-6} \) alkyld sulfonamide, \( C_{1-6} \) alkylthio, \( C_{1-6} \) alkylureyl, \( C_{1-6} \) alkylamino, \( C_{2-8} \) dialkylamino, carbo-C(=O)-alkoxy, carboxamide, carboxy, cyano, \( C_{3-7} \) cycoalkyl, \( C_{2-8} \) dialkylcarboxamide, \( C_{2-4} \) dialkylsulfonamide, halogen, \( C_{1-6} \) haloalkoxy, \( C_{1-6} \) haloalkyl, \( C_{1-6} \) haloalkysulfanyl, \( C_{1-6} \) haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

   \( \text{R}_4, \text{R}_5, \text{R}_6, \) and \( \text{R}_7 \) are each independently selected from the group consisting of \( H \), \( C_{1-6} \) acyl, \( C_{1-6} \) acyloxy, \( C_{2-6} \) alkyl, \( C_{1-6} \) alkyloxy, \( C_{1-6} \) alkyl, \( C_{1-6} \) alkylsulfonamide, \( C_{2-4} \) alkyl, \( C_{1-6} \) alkylsulfonamide, \( C_{1-6} \) alkyld sulfonamide, \( C_{1-6} \) alkyld thio, \( C_{1-6} \) alkyldureyl, \( C_{1-6} \) alkylamino, amino, \( C_{1-6} \) alkylamino, \( C_{2-8} \) dialkylamino, carbo-C(=O)-alkoxy, carboxamide, carboxy, cyano, \( C_{3-7} \) cycoalkyl, \( C_{2-8} \) dialkylcarboxamide, \( C_{2-8} \) dialkylsulfonamide, halogen, \( C_{1-6} \) haloalkoxy, \( C_{1-6} \) haloalkyl, \( C_{1-6} \) haloalkysulfanyl, \( C_{1-6} \) haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

   \( X \) is \(-NR_4C(=O)-\), \(-C(=O)NR_4-\), \(-NR_9-\), \(-C(=O)-\), \(-O-\), \(-S-\), \(-S(=O)-\) or \(-S(=O)_2-\); wherein \( R_3 \) is \( H \) or \( C_{1-6} \) alkyl; and \( R_9 \) is selected from the group consisting of \( H \), \( C_{1-6} \) acyl, \( C_{2-6} \) alkyl, \( C_{1-6} \) alkyl, \( C_{1-6} \) alkylcarboxamide, \( C_{2-6} \) alkynyl, \( C_{1-6} \) alkylsulfonamide, carbo-C(=O)-alkoxy, and \( C_{3-7} \) cycoalkyl, each optionally substituted with halogen;

   - 100 -
Y is -NR_{10}C(=O)-, -C(=O)NR_{10}, -NR_{10}S(=O)_{2}NR_{10},
-NR_{10}C(=O)NR_{11}, -NR_{10}C(=O)O-, -OC(=O)NR_{10}, -NR_{12}, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)_{2}- or absent; wherein R_{10} and R_{11} are each independently H or C_{1}-
6 alkyl; and R_{12} is selected from the group consisting of H, C_{1-6} acyl, C_{2-6} alkenyl,
C_{1-6} alkyl, C_{1-6} alkylicarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonfyl, carbo-C_{1-6}-
alkoxy, and C_{3-7} cycloalkyl, each optionally substituted with halogen;

Ar is aryl or heteroaryl each optionally substituted with R_{13} to R_{17}

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_{1-8} alkyl, C_{1-6} alkylcarboxamide, C_{2-6}
alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfanyl, C_{1-6} alkylsulfonfyl, C_{1-6}
alkythio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-8} dialkylamino, carbo-C_{1-6}-
alkoxy, carboxamide, carboxy, cyan, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide,
C_{2-8} dialkylsulfonamide, halogen, C_{1-8} haloalkoxy, C_{1-6} haloalkyl, C_{1-8}
ahloalkylsulfanyl, C_{1-8} haloalkylsulfonfyl, C_{1-8} haloalkylthio, hydroxyl, thiol, nitro
and sulfonamide; or two adjacent substituents together with said aryl or said
heteroaryl form a C_{5-7} cycloalkyl optionally comprising 1 to 2 oxygen atoms.

2. The compound according to claim 1 having Formula (Ic):

![Chemical Structure](image)

(Ic)

3. The compound according to claim 1 or 2, wherein Y is bonded at the 4-position on said
phenyl ring.

4. The compound according to any one of claims 1 to 3, wherein R_{1} is CH_{3}.

5. The compound according to any one of claims 1 to 4, wherein R_{2} is H, F, Cl or Br.

6. The compound according to any one of claims 1 to 5, wherein R_{3} is H.

7. The compound according to any one of claims 1 to 6, wherein R_{4}, R_{5}, R_{6}, and R_{7} are each
independently selected from the group consisting of H, C_{1-6} alkoxy, C_{1-6} alkyl, and
halogen.
8. The compound according to any one of claims 1 to 7, wherein X is -NH-.

9. The compound according to any one of claims 1 to 8, wherein Y is absent.

10. The compound according to any one of claims 1 to 9, wherein Ar is aryl or heteroaryl each optionally substituted with R_{13} to R_{17} substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-4} alky, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonyl, C_{2-8} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfonanyl, hydroxyl, and sulfonamide; or two adjacent substituents together with said aryl or said heteroaryl form a C_{5-7} cycloalkyl optionally comprising 1 to 2 oxygen atoms.

11. The compound according to any one of claims 1 to 9, wherein Ar is selected from the group consisting of phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chlorophenyl, 4-chloro-phenyl, 4-methyl-phenyl, 4-n-propyl-phenyl, 4-tert-butyl-phenyl, 4-heptyl-phenyl, 4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl, 3-acetylphenyl, 4-nitro-phenyl, 3-amino-phenyl, 2,3-difluoro-phenyl, 3,5-difluoro-phenyl, 3,4-difluoro-phenyl, 4-fluoro-2-methyl-phenyl, 3-fluoro-4-methyl-phenyl, 4-fluoro-3-methyl-phenyl, 3-fluoro-4-methoxy-phenyl, 3,4-dichloro-phenyl, 2-chloro-4-methylphenyl, 3-chloro-4-trifluoromethyl-phenyl, 2,4-bis-trifluoromethyl-phenyl, benzo[1,3]dioxol-5-yl and 2,6-dimethoxy-phenyl.

12. The compound according to any one of claims 1 to 9, wherein Ar is selected from the group consisting of thiophen-2-yl, thiophen-3-yl, 3,5-dimethyl-isoxazol-4-yl, pyridin-3-yl, 6-methoxy-pyridin-3-yl, pyridin-4-yl and quinolin-8-yl.

13. The compound according to claim 1 having Formula (Im):

![Chemical Structure Image](image)

(Im)

wherein:
- R_1 is CH_3;
- R_2 is H, F, Cl or Br;
- R_3 is H;
R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of H, OCH₃, CH₃ and F; and

Ar is aryl or heteroaryl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C(=O)CH₃, OCH₃, CH₃, amino, F, Cl, Br, OCF₃, CF₃ and nitro; or two adjacent substituents together with said aryl form a C₅ cycloalkyl comprising 2 oxygen atoms;

or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1 having Formula (Im):

![Formula (Im)](image)

wherein:
R₁ is CH₃;
R₂ is H, F, Cl or Br;
R₃ is H;
R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of H, OCH₃, CH₃ and F; and

Ar is phenyl, thiophen-2-yl, thiophen-3-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl or quinolin-8-yl each optionally substituted with R₁₃ to R₁₇ substituents selected independently from the group consisting of C(=O)CH₃, OCH₃, CH₃, amino, F, Cl, Br, OCF₃, CF₃ and nitro; or two adjacent substituents together with said aryl form a C₅ cycloalkyl comprising 2 oxygen atoms;

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1 wherein the compound is selected from the group consisting of:

Biphenyl-4-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-fluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chloro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-chloro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-propyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-tert-butyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-heptyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methoxy-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-trifluoromethyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-trifluoromethoxy-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethoxy-biphenyl-4-yl)-amine;
1-[4'-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-biphenyl-3-yl]-ethanone;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-nitro-biphenyl-4-yl)-amine;
N^1-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-biphenyl-3,4'-diamine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2',3'-difluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',5'-difluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',4'-difluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',3',4'-trifluoro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-2'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-fluoro-3'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-4'-methoxy-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3',4'-dichloro-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-chloro-5'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(5'-chloro-2'-methyl-biphenyl-4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-chloro-4'-trifluoromethyl-biphenyl-4-yl)-amine;
(2',4'-Bis-trifluoromethyl-biphenyl-4-yl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine;
(4'-Fluoro-biphenyl-4-yl)-(2-methyl-2H-pyrazol-3-yl)-amine;
(2,5-Dimethyl-2H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine;
(4-Bromo-1-methyl-1H-pyrazol-3-yl)-(4'-fluoro-biphenyl-4-yl)-amine;
(4-Benzo[1,3]dioxol-5-yl-phenyl)-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-phenoxy-phenyl)-amine;
[4-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-phenyl-methanone;
1-[4-(4-Bromo-2-methyl-2H-pyrazol-3-ylamino)-phenyl]-3-(4-chloro-phenyl)-urea;
Biphenyl-2-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine;
Biphenyl-3-yl-(4-bromo-2-methyl-2H-pyrazol-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2'-fluoro-biphenyl-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-methoxy-biphenyl-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4'-trifluoromethoxy-biphenyl-3-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3-methoxy-4'-trifluoromethoxy-biphenyl-
4-yl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(3'-fluoro-3-methoxy-biphenyl-4-yl)-
amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(2',6'-dimethoxy-biphenyl-3-yl)-amine;
Biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-amide;
4'-Fluoro-biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-
amide;
4'-Trifluoromethoxy-biphenyl-4-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-
3-yl)-amide;
4'-Fluoro-biphenyl-3-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-3-yl)-
amide; and
4'-Trifluoromethyl-biphenyl-3-carboxylic acid (4-bromo-2-methyl-2H-pyrazol-
3-yl)-amide;
or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 1 wherein the compound is selected from the group
consisting of:
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-2-yl-phenyl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-thiophen-3-yl-phenyl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-[4-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-
amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-pyridin-3-yl-phenyl)-amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-[4-(6-methoxy-pyridin-3-yl)-phenyl]-
amine;
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-pyridin-4-yl-phenyl)-amine; and
(4-Bromo-2-methyl-2H-pyrazol-3-yl)-(4-quinolin-8-yl-phenyl)-amine;
or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

18. A method for treating a 5-HT$_{2A}$ mediated disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

19. The method according to claim 18, wherein said 5-HT$_{2A}$ mediated disorder is 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 said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

20. A method for treating a condition associated with platelet aggregation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

21. A method for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

22. A method for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

23. A method for treating a sleep disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

24. The method according to claim 23, wherein said sleep disorder is a dyssomnia.
25. The method according to claim 23, wherein said sleep disorder is a parasomnia.

26. A method for treating a diabetic-related disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

27. A method for treating progressive multifocal leukoencephalopathy in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

28. A method for treating hypertension in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

29. A method for treating pain in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.

30. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in the treatment of a 5-HT2A mediated disorder.

31. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in the treatment of a 5-HT2A mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

32. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in the treatment of a condition associated with platelet aggregation.

33. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutical composition according to claim 17.
34. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in reducing the risk of blood clot formation in an individual.

35. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in reducing the risk of blood clot formation in an individual suffering from atrial fibrillation.

36. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating a dyssomnia.

37. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating a parasomnia.

38. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating a diabetic-related disorder.

39. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating progressive multifocal leukoencephalopathy.

40. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating hypertension.

41. Use of a compound according to any one of claims 1 to 16 for production of a medicament for use in treating pain.

42. A compound according to any one of claims 1 to 16 for use in a method of treatment of the human or animal body by therapy.

43. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a 5-HT2A mediated disorder in the human or animal body by therapy.

44. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a 5-HT2A mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.
45. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a condition associated with platelet aggregation.

46. A compound according to any one of claims 1 to 16 for use in a method of reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual.

47. A compound according to any one of claims 1 to 16 for use in a method of reducing the risk of blood clot formation in an individual.

48. A compound according to any one of claims 1 to 16 for use in a method of reducing the risk of blood clot formation in an individual suffering from atrial fibrillation.

49. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a dyssomnia.

50. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a parasomnia.

51. A compound according to any one of claims 1 to 16 for use in a method for the treatment of a diabetic-related disorder in the human or animal body by therapy.

52. A compound according to any one of claims 1 to 16 for use in a method for the treatment of progressive multifocal leukoencephalopathy in the human or animal body by therapy.

53. A compound according to any one of claims 1 to 16 for use in a method for the treatment of hypertension.

54. A compound according to any one of claims 1 to 16 for use in a method for the treatment of pain.

55. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 16 and a pharmaceutically acceptable carrier.
General Methods for the preparation of compounds of the invention wherein Y is absent.

- The Ar group added after coupling with amine.
- The Ar group added prior to coupling with amine.

Figure 1
General Methods for the preparation of compounds of the invention wherein Y is absent

The Ar group added after coupling with amine.

Preparation of pyrazole boronic acids

1) n-BuLi/THF
2) Tnisopropyl borate
3) H_3O^+

The Ar group added prior to coupling with amine.
General coupling methods for the preparation of compounds of the invention

Copper coupling reagents

For example: Myristic Acid, Copper Acetate, 2,6 Lutidine, Toluene, r.t.

For example: Cu(OAc)₂, Et₃N / CH₂Cl₂, rt

Figure 3
General coupling methods for the preparation of compounds of the invention

Palladium coupling reagents

Figure 4
Preparation of certain compounds of the invention

Preparation of Compound 1
Cu(OAc)$_2$ / $\text{Et}_3\text{N} / \text{CH}_2\text{Cl}_2$, rt

Preparation of Compound 4
Pd$_2$(dba)$_3$ / BINAP / NaOi-Bu, Toluene, 80°C

Preparation of Compound 47
Pd$_2$(dba)$_3$ / BINAP / Cs$_2$CO$_3$, Toluene, 80°C
General Methods for the preparation of compounds of the invention

Coupling

Ar-NCO

Ar-O(C(O)Cl or equivalent
General Methods for the preparation of compounds of the invention wherein X is O, S, S(=O), S(=O)₂, or C(=O).

When X is O or S:

\[
\begin{align*}
\text{Ar} & \quad \text{R₃} \\
\text{R₄} & \quad \text{X-H} \\
\text{R₅} & \quad \text{Y} \\
\end{align*}
\]

\[
\begin{align*}
\text{R₆} & \quad \text{N} \\
\text{R₇} & \quad \text{N} \\
\end{align*}
\]

\[
\text{R₈} \\
\text{R₉} \\
\text{R₁₀}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{R₃} \\
\text{R₄} & \quad \text{X} \\
\text{R₅} & \quad \text{Y} \\
\end{align*}
\]

\[
\begin{align*}
\text{R₆} & \quad \text{N} \\
\text{R₇} & \quad \text{N} \\
\end{align*}
\]

\[
\text{R₈} \\
\text{R₉} \\
\text{R₁₀}
\]

\[
\text{R₁₁} \\
\text{R₁₂}
\]

\[
\text{For Example: when X = O, Cu(OAc)₂, TEA, CH₂Cl₂; or when X = S, CuI, NCS, THF}
\]

When X is S, conversion to S(=O) and S(=O)₂:

\[
\begin{align*}
\text{Ar} & \quad \text{R₃} \\
\text{R₄} & \quad \text{S} \\
\text{R₅} & \quad \text{R₆} \\
\text{R₇} & \quad \text{R₈} \\
\end{align*}
\]

\[
\begin{align*}
\text{R₉} & \quad \text{N} \\
\text{R₁₀} & \quad \text{N} \\
\end{align*}
\]

\[
\text{R₁₁} \\
\text{R₁₂}
\]

\[
\text{For Example: when X = S, CuI, NCS, THF}
\]

When X is C(=O):

\[
\begin{align*}
\text{Ar} & \quad \text{R₃} \\
\text{R₄} & \quad \text{C(=O)} \\
\text{R₅} & \quad \text{R₆} \\
\text{R₇} & \quad \text{Halo}
\end{align*}
\]

\[
\text{R₈} \\
\text{R₉} \\
\text{R₁₀}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{R₃} \\
\text{R₄} & \quad \text{C(=O)} \\
\text{R₅} & \quad \text{R₆} \\
\text{R₇} & \quad \text{Halo}
\end{align*}
\]

\[
\text{R₈} \\
\text{R₉} \\
\text{R₁₀}
\]

\[
\text{R₁₁} \\
\text{R₁₂}
\]

\[
\text{For Example: a Suzuki-Miyaura Rxn; K₃PO₄, PdCl₂(PPh₃)₂, Toluene}
\]

**Figure 7**