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(54) **Title**: INDAZOLE AND AZAINDAZOLE SUBSTITUTED COMPOUNDS AS MGLUR4 ALLOSTERIC POTENTIATORS, COMPOSITIONS, AND METHODS OF TREATING NEUROLOGICAL DYSFUNCTION

(57) **Abstract**: Compounds which are useful as allosteric potentiators/positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4); synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of using the compounds, for example, in treating neurological and psychiatric disorders or other disease state associated with glutamate dysfunction.

INDAZOLE AND AZAINDAZOLE SUBSTITUTED COMPOUNDS AS MGLUR4 ALLOSTERIC POTENTIATORS, COMPOSITIONS, AND METHODS OF TREATING NEUROLOGICAL DYSFUNCTION

BACKGROUND

[0001] The amino acid L-glutamate (referred to herein simply as glutamate) is the principal excitatory neurotransmitter in the mammalian central nervous system (CNS). Within the CNS, glutamate plays a key role in synaptic plasticity (e.g., long term potentiation (the basis of learning and memory)), motor control and sensory perception. It is now well understood that a variety of neurological and psychiatric disorders, including, but not limited to, schizophrenia general psychosis and cognitive deficits, are associated with dysfunctions in the glutamatergic system. Thus, modulation of the glutamatergic system is an important therapeutic goal. Glutamate acts through two distinct receptors: ionotropic and metabotropic glutamate receptors. The first class, the ionotropic glutamate receptors, is comprised of multi-subunit ligand-gated ion channels that mediate excitatory post-synaptic currents. Three subtypes of ionotropic glutamate receptors have been identified, and despite glutamate serving as agonist for all three receptor subtypes, selective ligands have been discovered that activate each subtype. The ionotropic glutamate receptors are named after their respective selective ligands: kainate receptors, AMPA receptors and NMDA receptors.

[0002] The second class of glutamate receptor, termed metabotropic glutamate receptors, (mGluRs), are G-protein coupled receptors (GPCRs) that modulate neurotransmitter release or the strength of synaptic transmission, based on their location (pre-or post-synaptic). The mGluRs are family C GPCR, characterized by a large (~560 amino acid) "venus fly trap" agonist binding domain in the amino-terminal domain of the receptor. This unique agonist binding domain distinguishes family C GPCRs from family A and B GPCRs wherein the agonist binding domains are located within the 7-strand transmembrane spanning (7TM) region or within the extracellular loops that connect the strands to this region. To date, eight distinct mGluRs have been identified, cloned and sequenced. Based on structural similarity, primary coupling to intracellular signaling pathways and pharmacology, the mGluRs have been assigned to three groups: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8). Group I mGluRs are coupled through Gαq/11 to increase inositol phosphate and metabolism and resultant increases in intracellular calcium. Group I mGluRs are primarily located post-synaptically and have a modualtory effect on ion channel activity and neuronal excitability. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluRs are primarily located pre-synaptically where they regulate the release of neurotransmitters, such as glutamate. Group II and Group III mGluRs are coupled to Gαi and its associated effectors such as adenylate cyclase.

[0003] mGluR4 belongs to the group III mGluR subfamily and is located in predominantly presynaptic locations in the central nervous system (Benitez et al., 2000; Bradley et al., 1996; Bradley et al., 1999; Mateos et al., 1998; Phillips et al., 1997) where it is functions as an auto- and heteroreceptor to regulate the release of both GABA and glutamate. mGluR4 has also been shown to be expressed at a low level in some postsynaptic locations (Benitez et al., 2000). Numerous reports indicate that mGluR4 is expressed in most brain regions, particularly in neurons known to play key roles in functions of the basal ganglia (Bradley et al., 1999; Corti et al., 2002; Kuramoto et al., 2007; Marino et al., 2003a), learning and memory (Bradley et al., 1996), vision (Akazawa et al., 1994; Koulen et al., 1996; Quraishi et al., 2007), cerebellar functions (Makoff et al., 1996), feeding and the regulation of hypothalamic hormones (Flor et al., 1995), sleep and wakefulness (Noriega et al., 2007) as well as many others. There are now a number of literature reports describing a role for mGluR4 modulation in Parkinson's disease (Battaglia et al., 2006; Lopez et al., 2007; Marino et al., 2005; Marino et al., 2003b; Ossowska et al., 2007; Valenti et al., 2003), anxiety (Stachowicz et al., 2006; Stachowicz et al., 2004), motor effects after alcohol consumption (Blednov et al., 2004), neurogenic fate commitment and neuronal survival (Saxe et al., 2007), epilepsy (Chapman et al., 2001; Pitsch et al., 2007; Snead et al., 2000; Wang et al., 2005) and cancer, particularly medulloblastoma (Iacovelli et al., 2004).

[0004] In addition, there is evidence that activation of mGluR4 receptors (expressed in islets of Langerhans) would inhibit glucagon secretion (Uehara et al., 2004). Thus, activation of mGluR4 may be an effective treatment for disorders involving defects in glucose metabolism such ashypoglycemia, Type 2 diabetes, and obesity.

[0005] Also, there are reports that activation of Group III mGluRs, specifically mGluR4, may be an effective treatment for neuroinflammatory diseases, such as multiple sclerosis and related disorders (Besong et al., 2002).

[0006] Also, that activation of Group III mGluRs, specifically mGlu4 positive allosteric modulators (PAMs), may be an effective treatment for neuroinflammatory diseases, such as multiple sclerosis and related disorders (Besong et al., 2002; Taylor et al., 2003; Fallarino et al., 2010).

[0007] There are two variants of the mGluR4 receptor which are expressed in taste tissues; and thus activation of mGluR4 may be used as taste enhancers, blockade of certain tastes, or taste agents, flavoring agents or other food additives (Kurihara, 2009; Chaudhari et al, 2009).

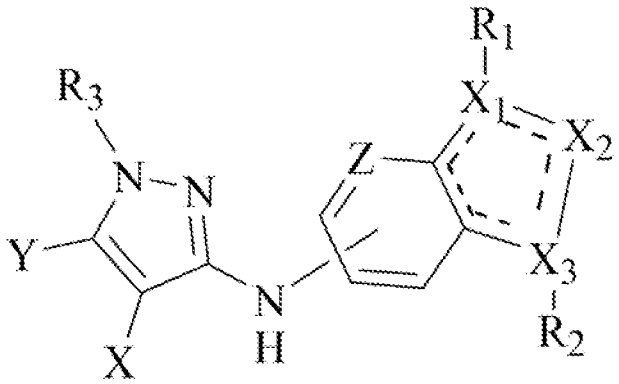
[0008] Despite advances in mGluR4 researh, there is still a scarcity of compounds that effectively potentiate mGluR4 which are also effective in the treatment of neurological and psychiatric disorders associated with glutamatergic neurotransmission dysfunction and diseases, As well as inflammatory central nervous system disorders, medulloblastomas, metabolic disorders and taste enhancing associated with glutamatergic dysfunction and diseases in which mGluR4 receptor is

involved. Further, conventional mGluR4 receptor modulators typically lack satisfactory aqueous solubility and exhibit poor oral bioavailability. These needs and other needs are satisfied by the present invention.

SUMMARY

[0009] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds useful as allosteric modulators of mGluR4 receptor activity, methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction, for example Parkinson's disease, using same. Further disclosed are methods and pharmaceutical compositions useful for treating a disease related to mGluR4 activity. In one aspect, the disclosed compounds can affect the sensitivity of mGluR4 receptors to agonists without binding to the orthosteric agonist binding site or acting as orthosteric agonists themselves. A "receptor allosteric agonist", as used herein, is generally defined as a ligand that functions as both an allosteric modulator and as an agonist on its own (though the latter is usually only at higher concentrations). The presence of a the receptor allosteric agonist (Ago-PAM) activity may offer advantages in various CNS and neurological disorders where the basal glutamatergic tone is low in given brain regions.

[0010] Disclosed are methods for the treatment of a neurotransmission dysfunction or other disease state associated with mGluR4 activity in a mammal comprising the step of administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula (I):



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wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

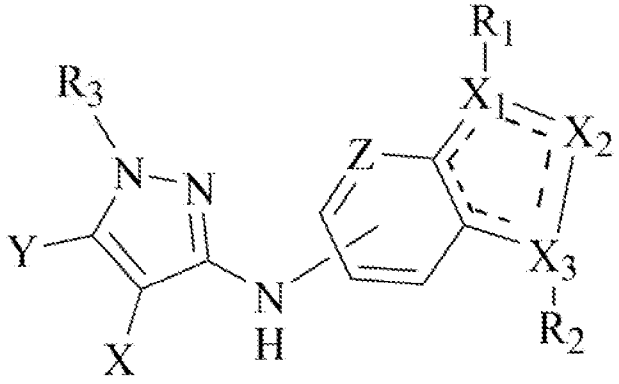
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0011] Also disclosed are methods for potentiating mGluR4 activity in a subject comprising the step of administering to the subject at least one compound at least one compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

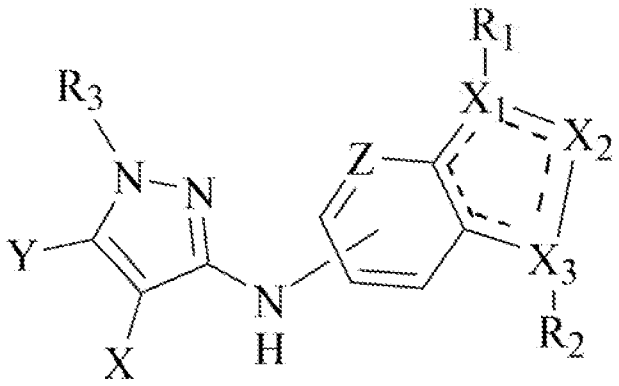
R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3, O-R, O-aryl, O-heteroaryl, NHR, NR_3R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof., in a dosage and amount effective to potentiate mGluR4 receptor activity in the subject.

[0012] Also disclosed are methods of potentiating mGluR4 activity in at least one cell comprising the step of contacting at least one cell with at least one compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

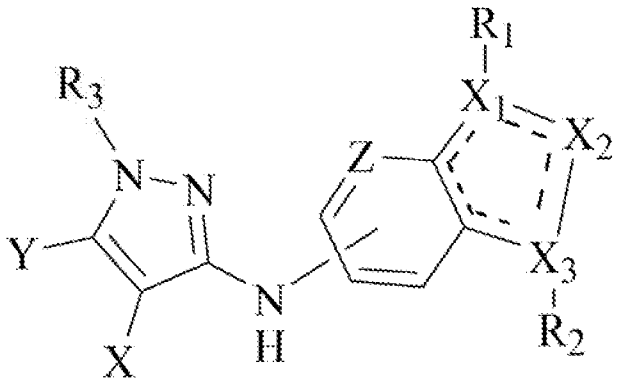
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, in an amount effective to potentiate mGluR4 receptor activity in the at least one cell.

[0013] Also disclosed are compounds having a structure represented by formula (I):



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iwherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

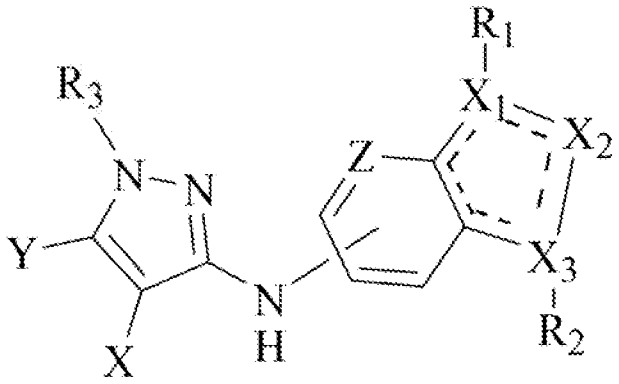
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0014] Also disclosed pharmaceutical compositions comprising a compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_3R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

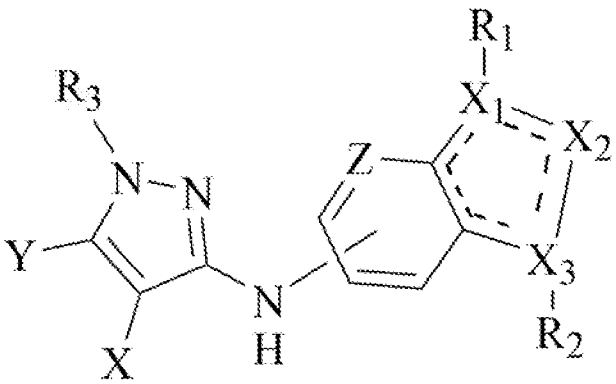
R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0015] Also disclosed are methods for potentiating mGluR4 activity in at least one cell comprising the step of contacting at least one cell with at least one disclosed compound in an amount effective to potentiate mGluR4 receptor activity in at least one cell.

[0016] Also disclosed are methods for potentiating mGluR4 activity in a subject comprising the step of administering to the subject a therapeutically effective amount of at least one disclosed compound in a dosage and amount effective to potentiate mGluR4 receptor activity in the subject.

[0017] Also disclosed are methods for the treatment of a disorder associated with mGluR4 neurotransmission dysfunction or other mGluR4 mediated disease states in a mammal comprising the step of administering to the mammal at least one disclosed compound in a dosage and amount effective to treat the disorder in the mammal.

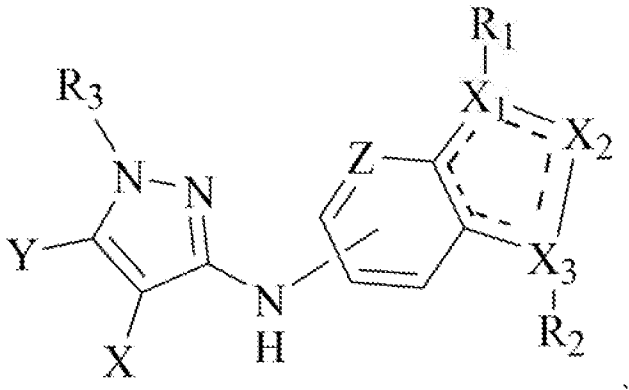
[0018] Also disclosed are methods for making a compound comprising the steps of providing an amine compound having a structure represented by formula (I):



as shown in the Examples below, wherein the variables are defined herein.

[0019] Also disclosed are the products of the disclosed methods of making.

[0020] Also disclosed are methods for the manufacture of a medicament for potentiating mGluR4 receptor activity in a mammal comprising combining a compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

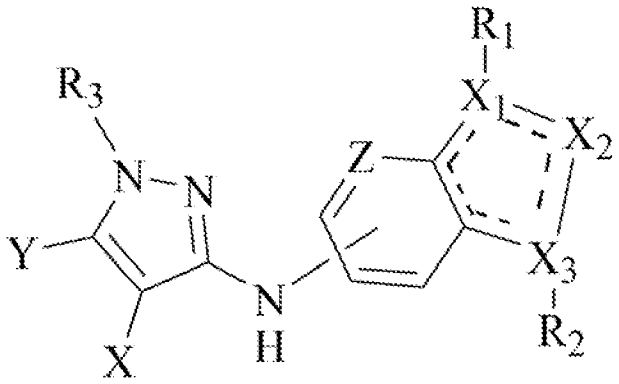
R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0021] Also disclosed are the products of the disclosed methods for the manufacture of a medicament.

[0022] Also disclosed are uses of a compound for potentiating mGluR4 receptor activity in a mammal, wherein the compound has a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

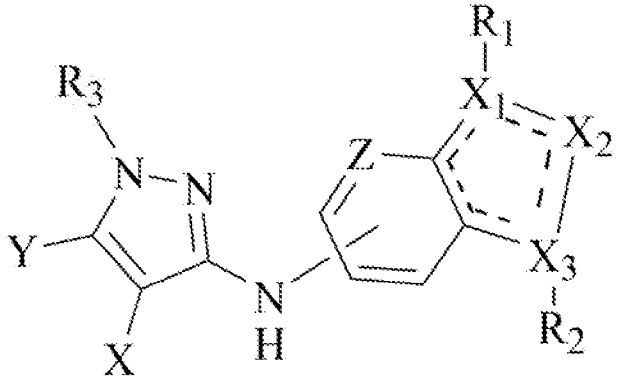
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0023] Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

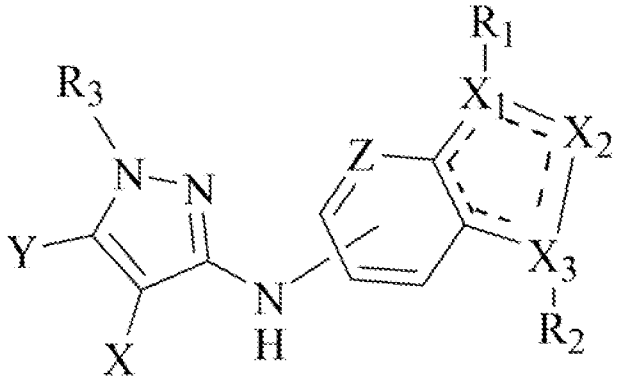
R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3, O-R, O-aryl, O-heteroaryl, NHR, NR_3R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with a drug having a known side-effect of increasing metabotropic glutamate receptor activity.

[0024] Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

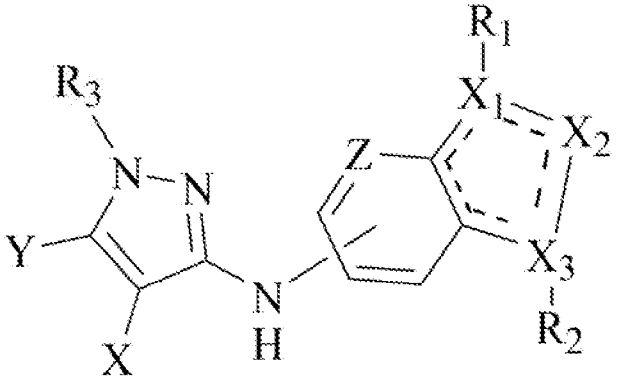
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity.

[0025] Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by a Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

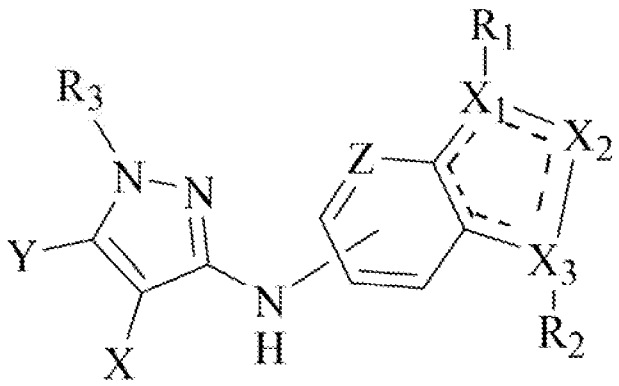
R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3, O-R, O-aryl, O-heteroaryl, NHR, NR_3R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with a drug known to treat the neurotransmission dysfunction or other disease states.

[0026] Also disclosed are kits comprising a compound having a structure represented by Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, and one or more of a drug having a known side-effect of increasing metabotropic glutamate receptor activity, a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or a drug known to treat the neurotransmission dysfunction.

[0027] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION

[0028] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0029] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0030] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which need to be independently confirmed.

I. Definitions

[0031] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0032] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0033] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0034] As used herein, the term "receptor positive allosteric modulator" refers to any exogenously administered compound or agent that directly or indirectly augments the activity of any form (for example, homomeric, heteromeric, oligomeric, or interacting with other proteins or cellular components) of the receptor in the presence or in the absence of the endogenous ligand (such as glutamate, L-serine O-phosphate (L-SOP), other endogenous ligands, other neurotransmitters, etc.) in an animal, in particular a mammal, for example a human. The term "receptor positive allosteric modulator" includes a compound that is a "receptor allosteric potentiator" or a "receptor allosteric agonist," as well as a compound that has mixed activity as both a "receptor allosteric potentiator" and an "mGluR receptor allosteric agonist."

[0035] As used herein, the term "receptor allosteric potentiator" refers to any exogenously administered compound or agent that directly or indirectly augments the response of any form (for example, homomeric, heteromeric, oligomeric, or interacting with other proteins or cellular components) of the receptor produced by the endogenous ligand (such as glutamate, L-serine O-phosphate (L-SOP), other endogenous ligands, other neurotransmitters, etc.) when it binds to an allosteric site of any form of receptor in an animal, in particular a mammal, for example a human. The receptor allosteric potentiator binds to a site other than the orthosteric site (an allosteric site) and positively augments the response of the receptor to an agonist. As it is predicted to induce less desensitization of the receptor, activity of a compound as a receptor allosteric potentiator provides advantages over the use of a pure receptor allosteric agonist. Such advantages can include, for example, increased safety margin, higher tolerability, diminished potential for abuse, and reduced toxicity.

[0036] As used herein, the term "receptor allosteric agonist" refers to any exogenously administered compound or agent that directly augments the activity of any form (for example, homomeric, heteromeric, oligomeric, or interacting with other proteins or cellular components) of the receptor in the absence of the endogenous ligand (such as glutamate, L-serine O-phosphate (L-SOP), other endogenous ligands, other neurotransmitters, etc.) in an animal, in particular a mammal, for example a human. The receptor allosteric agonist binds to the allosteric glutamate site of the receptor and directly influences the orthosteric site of the receptor. the term "receptor positive allosteric modulator" refers to any exogenously administered compound or agent that directly or indirectly augments the activity of the receptor in the presence or in the absence of the endogenous ligand (such as glutamate, L-serine O-phosphate (L-SOP), other endogenous ligands, other neurotransmitters, etc.) in an animal, in particular a mammal, for example a human. The term "receptor positive allosteric

modulator" includes a compound that is a "receptor allosteric potentiator" or a "receptor allosteric agonist," as well as a compound that has mixed activity as both a "receptor allosteric potentiator" and an "mGluR receptor allosteric agonist."

[0037] In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder and/or any other disease state associated with glutamate dysfunction prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for potentiation of metabotropic glutamate receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for partial agonism of metabotropic glutamate receptor activity prior to the administering step. In some aspects, the disclosed methods can further comprise a step of identifying a subject having a need for treatment of a disclosed disorder.

[0038] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

[0039] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0040] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with a disorder treatable by potentiation of mGluR4 activity" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can favorably potentiate mGluR4 activity. As a further example, "diagnosed with a need for potentiation of mGluR4 activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and

found to have a condition characterized by abnormal mGluR4 activity. Such a diagnosis can be in reference to a disorder, such as Parkinson's disease, and the like, as discussed herein.

[0041] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to mGluR4 activity) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0042] As used herein, the term "receptor allosteric agonist", as used herein, is generally defined as a ligand that functions as both an allosteric modulator and as an agonist on its own (though the latter is usually only at higher concentrations).

[0043] As used herein, the term "diagnosed with a need for potentiation of metabotropic glutamate receptor activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by potentiation of metabotropic glutamate receptor activity.

[0044] As used herein, "diagnosed with a need for partial agonism of metabotropic glutamate receptor activity" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by partial agonism of metabotropic glutamate receptor activity.

[0045] As used herein, "diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder or any disease state associated with glutamate dysfunction" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have one or more neurological and/or psychiatric disorder associated with glutamate dysfunction.

[0046] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is,

administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0047] As used herein, the term "effective amount" refers to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0048] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like.

Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. SuiTable 3nert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0049] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting pro¬duct of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more -OCH2CH2O- units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more -CO(CH2)8CO- moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0050] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0051] In defining various terms, "A1," "A2," "A3," and "A4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0052] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, s-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms.

[0053] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" specifically refers to an alkyl group that is substituted with one or more halide, e.g., fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

[0054] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, e.g., an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, e.g., a "halogenated alkoxy," a particular substituted alkenyl can be, e.g., an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0055] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where

at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0056] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by a formula $-(CH_2)_a-$, where "a" is an integer of from 2 to 500.

[0057] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as $-OA^1$ where A^1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as $-OA^1-OA^2$ or $-OA^1-(OA^2)_a-OA^3$, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[0058] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0059] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bound, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0060] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0061] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bound. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0062] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term "aryl" also includes "heteroaryl," which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term "non-heteroaryl," which is also included in the term "aryl," defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." Biaryl refers to two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

[0063] The term "aldehyde" as used herein is represented by a formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, *i.e.*, C=O.

[0064] The terms "amine" or "amino" as used herein are represented by a formula $NA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0065] The term "carboxylic acid" as used herein is represented by a formula —C(O)OH.

[0066] The term "ester" as used herein is represented by a formula —$OC(O)A^1$ or —$C(O)OA^1$, where A^1 can be an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by a formula —$(A^1O(O)C\text{-}A^2\text{-}C(O)O)_a$— or —$(A^1O(O)C\text{-}A^2\text{-}OC(O))_a$—, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0067] The term "ether" as used herein is represented by a formula A^1OA^2, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by a formula —$(A^1O\text{-}A^2O)_a$—, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0068] The term "halide" as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[0069] The term "heterocycle," as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes pyridinde, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole,thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[0070] The term "hydroxyl" as used herein is represented by a formula —OH.

[0071] The term "ketone" as used herein is represented by a formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0072] The term "azide" as used herein is represented by a formula $-N_3$.

[0073] The term "nitro" as used herein is represented by a formula $-NO_2$.

[0074] The term "nitrile" as used herein is represented by a formula -CN.

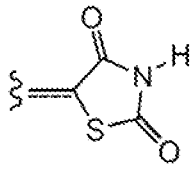
[0075] The term "silyl" as used herein is represented by a formula $-SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0076] The term "sulfo-oxo" as used herein is represented by a formulas $-S(O)A^1$, $-S(O)_2A^1$, $-OS(O)_2A^1$, or $-OS(O)_2OA^1$, where A^1 can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by a formula $-S(O)_2A^1$, where A^1 can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by a formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by a formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0077] The term "thiol" as used herein is represented by a formula -SH.

[0078] The term "organic residue" defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms

[0079] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure



regardless of whether thiazolidinedione is used to prepare the compound. In some aspects the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[0080] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some aspects, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[0081] "Inorganic radicals," as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include,

but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Typically, inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[0082] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0083] As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compounds disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0084] The term "hydrolysable residue" is meant to refer to a functional group capable of undergoing hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, residues of acid halides or activated carboxylic acids, residues of trialkylsilyl halides, residues of alkyloxymethyl halides, and various other protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

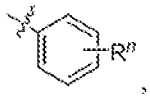
[0085] The term "leaving group" refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, brosylate, and halides.

[0086] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

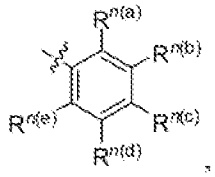
[0087] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described

herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers. Additionally, unless expressly described as "unsubstituted", all substituents can be substituted or unsubstituted.

[0088] In some aspects, a structure of a compound can be represented by a formula:



which is understood to be equivalent to a formula:



wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance. Likewise, when a group R is defined as four substituents, R is understood to represent four independent substituents, R^a, R^b, R^c, and R^d. Unless indicated to the contrary, the substituents are not limited to any particular order or arrangement.

[0089] The following abbreviations are used herein. DMF: dimethyl formamide. EtOAc: ethyl acetate. THF: tetrahydrofuran. DIPEA or DIEA: diisopropylethylamine. HOBt: 1-hydroxybenzotriazole. EDC: 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride. DMSO: dimethylsulfoxide. DMAP: 4-Dimethylaminopyridine. RT: Room temperature. h: Hours. Min: Minutes. DCM: Dichloromethane. MeCN: Acetonitrile. MeOH: methanol. iPrOH: 2-Propanol. n-BuOH: 1-Butanol.

[0090] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and

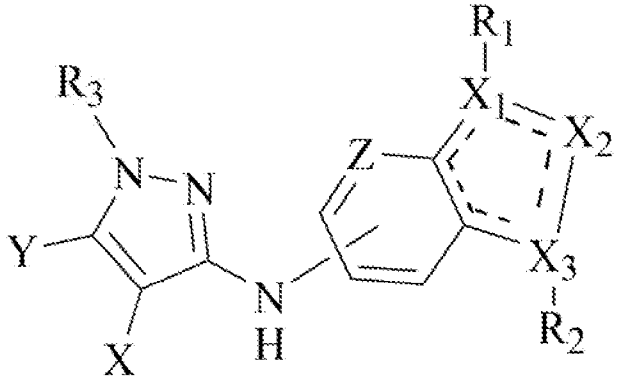
collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific aspect or combination of aspects of the methods of the invention.

[0091] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

J. Compounds

[0092] In one aspect, the invention relates to compounds, or pharmaceutically acceptable derivatives thereof, useful as potentiators of mGluR4 activity. In general, it is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using. It is also understood that the variables recived herein can be substituted or unsubstituted, and unless specifically stated otherwise, recitation of the variable contemplates both substituted or unsubstituted forms. It is also understood that the disclosed compounds can all be employed as corresponding pharmaceutical compositions.

[0093] In one aspect, the invention relates to compounds having a structure represented by formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3, O-R, O-aryl, O-heteroaryl, NHR, NR_3R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

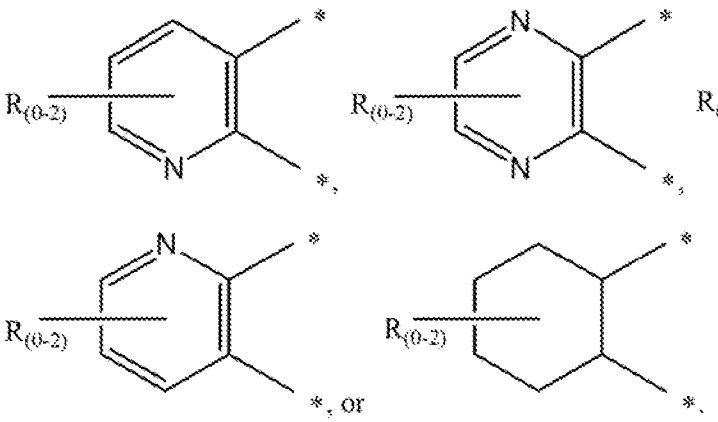
R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine;

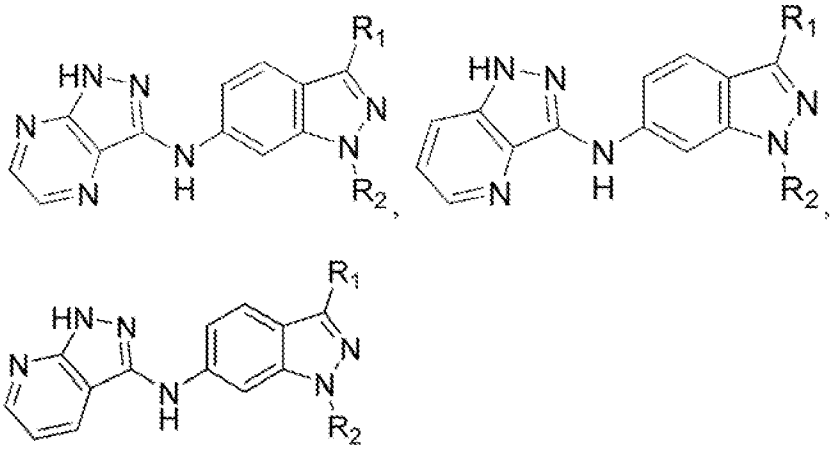
or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

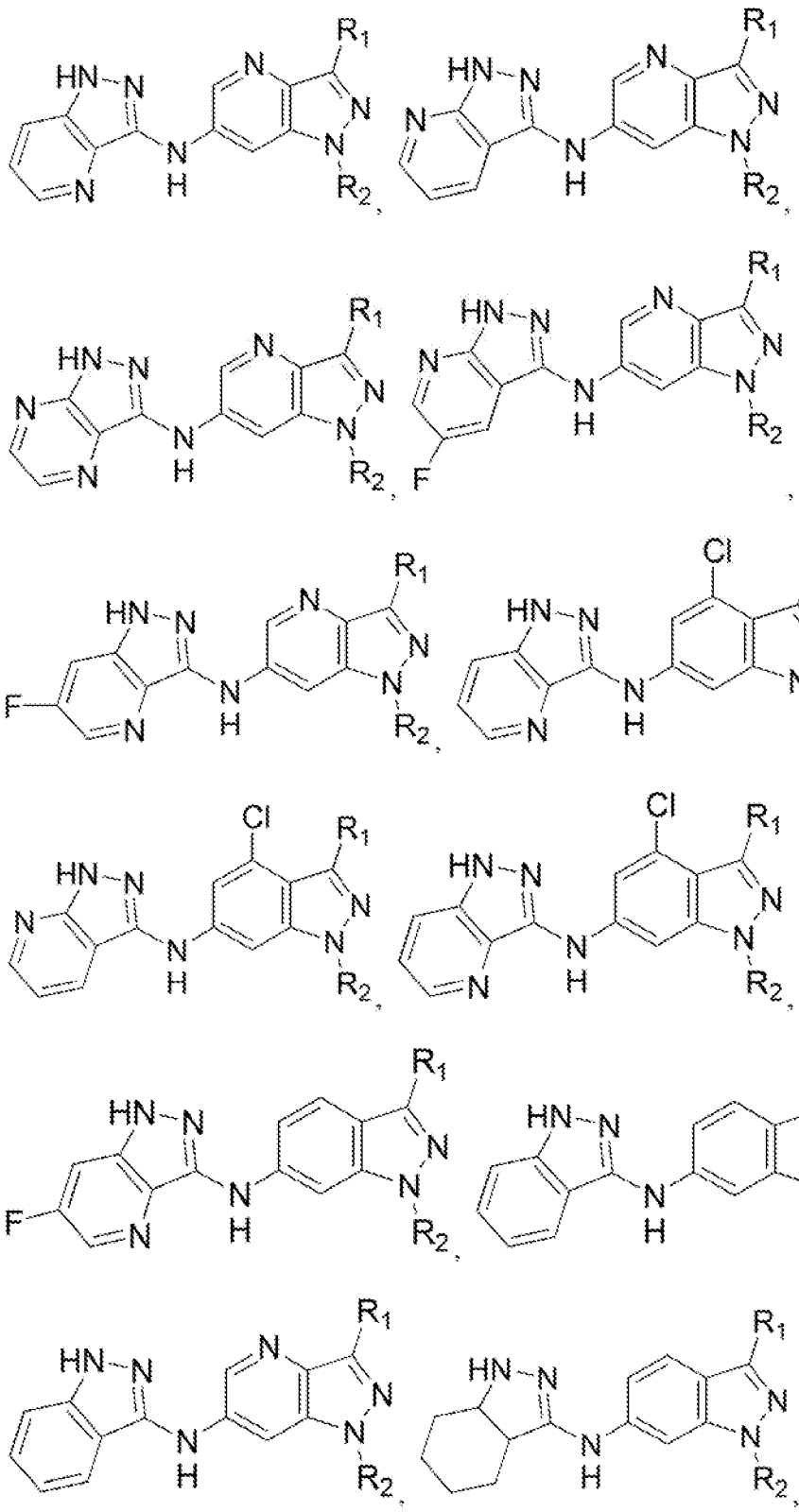
[0094] Also disclosed are compounds of formula (I), wherein X and Y together form:

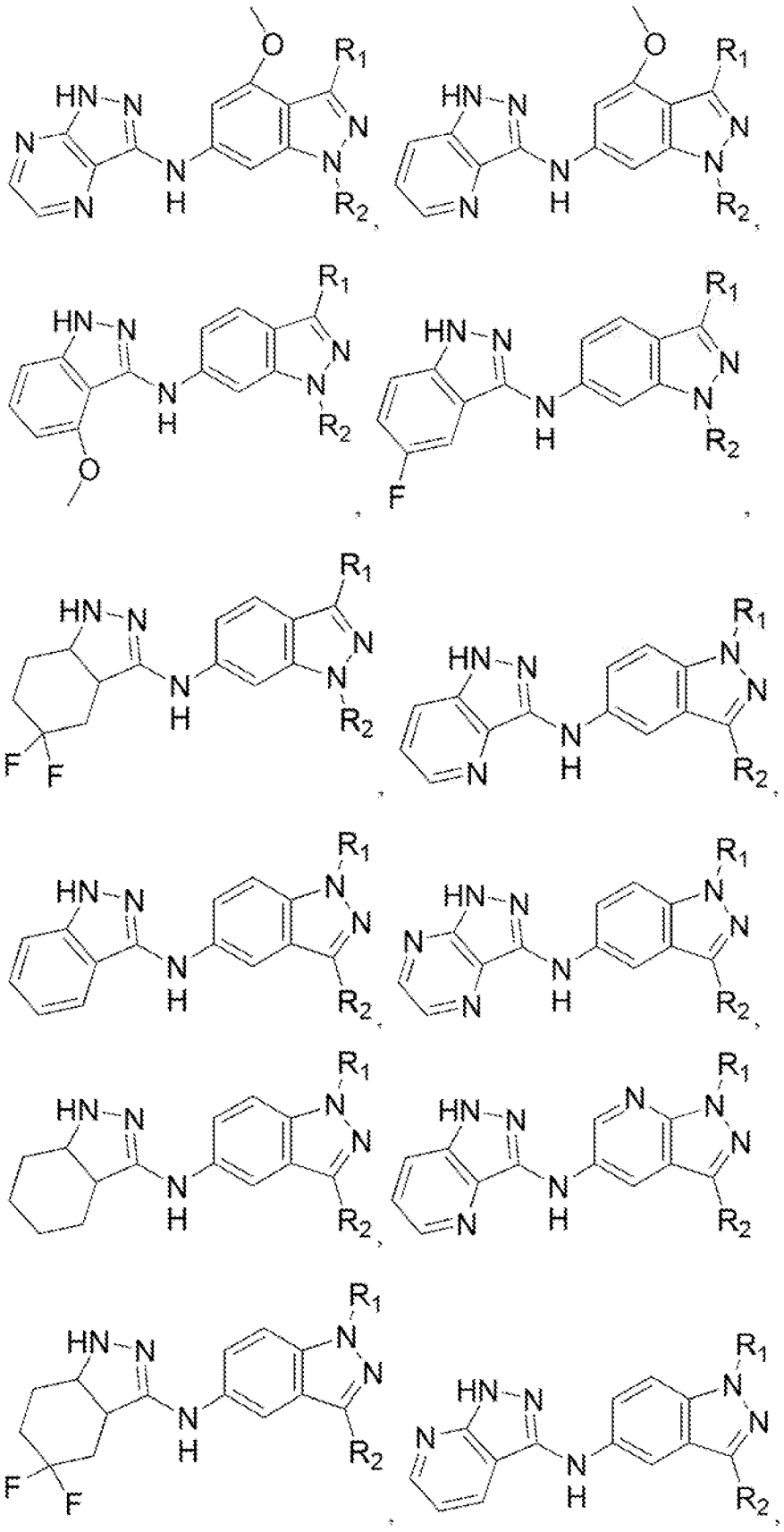


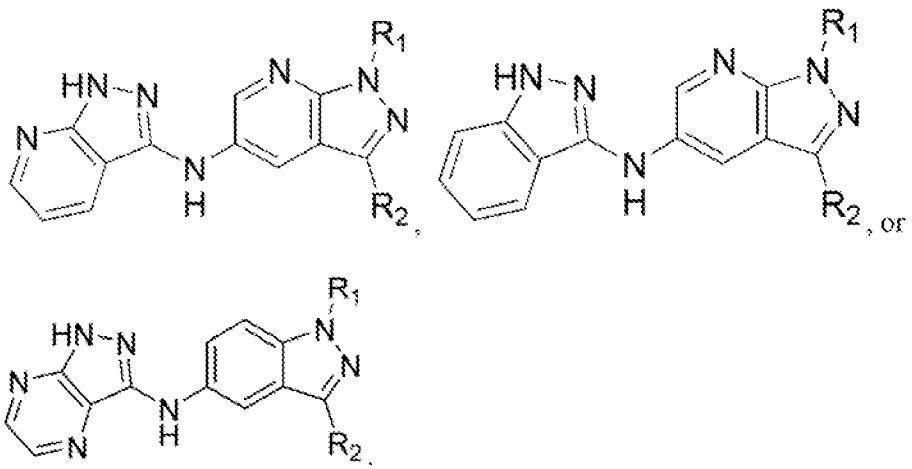
[0095] Also disclosed are compound described above, wherein R, when present, is F. Also disclosed are compounds described above, wherein Z is N, CH, CD, or C-Cl.

[0096] Also disclosed are compounds of the following formula:

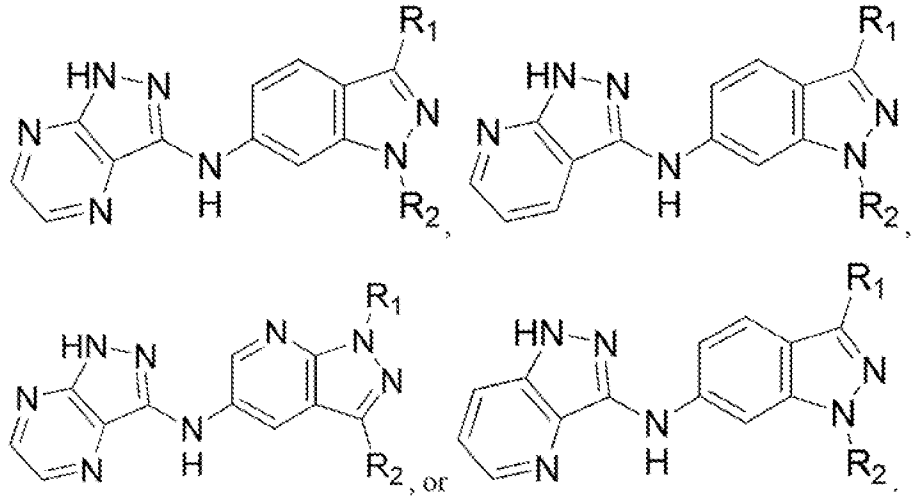






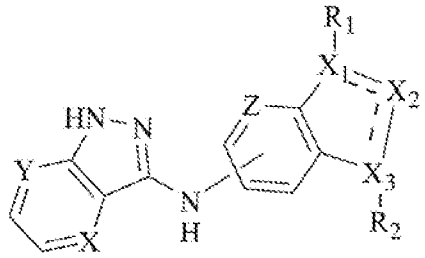


[0097] Also disclosed are compounds of the following formula:

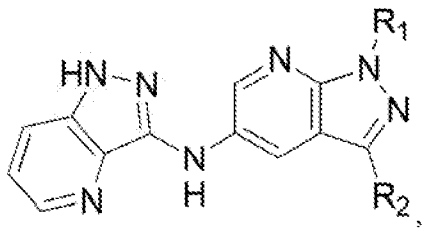


[0098] In certain embodiments, R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0099] Also disclosed are compound of the following formula:

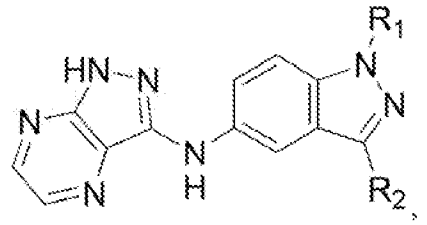


[0100] Also disclosed are compounds of the following formula:



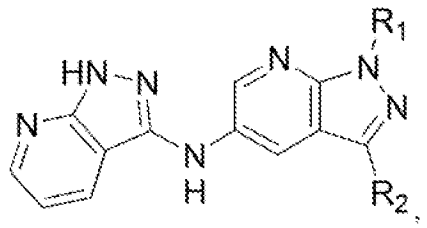
wherein R_1 is H, alkyl, cycloalkyl, heterocycloalkyl, alkyl-cycloalkyl, trifluoroalkyl, hydroxyalkyl, alkyl-alkoxy; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0101] Also disclosed are compounds of the following formula:



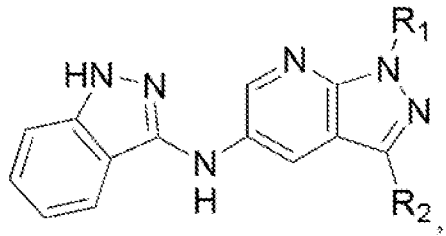
wherein R_1 is H, alkyl, heteroaryl, CO-CF_3, CD_2-alkyl, alkyl-heteroaryl, alkyl-cycloalkyl, cycloalkyl, and R_2 is H, alkyl, alkyl-phenyl, cycloalkyl.

[0102] Also disclosed are compounds of the following formula:



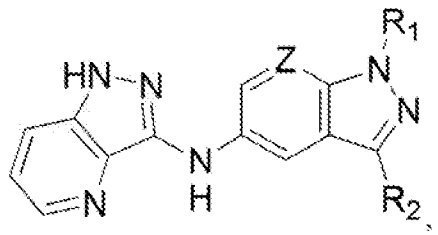
wherein R_1 is alkyl and $R_2$is alkyl.

[0103] Also disclosed are compounds of the following formula:



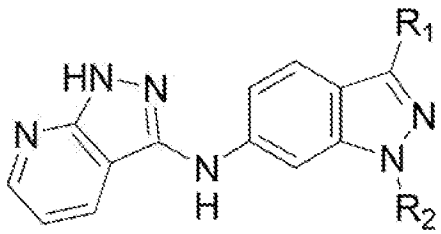
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0104] Also disclosed are compounds of the following formula:



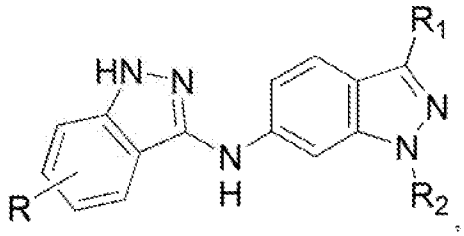
wherein R_1 is H, alkyl, alkene, alkyl-heteroalkyl, alkyl-heterocycloalkyl alkyl, heterocycloalkyl, trifluoroalkyl, alkyl-cycloalkyl, cycloalkyl, alkyl-heteroaryl, heteroaryl, alkyl-acetic acid, CD_3, alkoxy, CD_2-alkyl, alkyl-CO-alkoxy, CF_3, phenyl; fluorophenyl, alkylcarbontrichloride, alkyltricluorocarbon; and R_2 is H, alkyl, Cl, CF_3, heteroaryl, cyclopentene, alkyl-phenyl, trifluoroalkyl, cycloheteroalkyl, amino-alkyl-carboxylate ester; hydoxy, alkyl-cycloalkyl, amino, amino-CO-CF_3, cycloalkyl.

[0105] Also disclosed are compounds of the following formula:



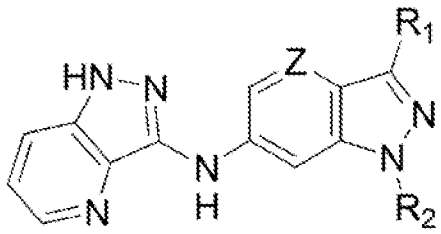
wherein R_1 is H, alkyl, cycloalkyl; and R_2 is H, alkyl, alkyl-cycloalkyl, alkyl-heteroaryl, CD_3.

[0106] Also disclosed are compounds of the following formula:



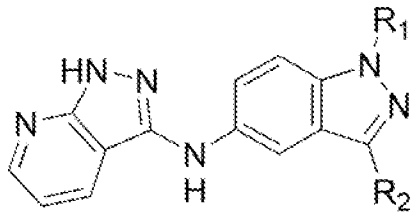
wherein R may be optionally present and when present is O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0107] Also disclosed are compounds of the following formula:



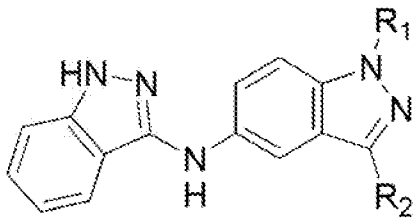
wherein Z is N, C-H, C-Me, C-O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CN, methylsulfonyl, O-alkoxy, O-cycloheteroalkyl, cycloheteroalkyl, alkoxycycloheteroalkyl, halogen; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl, alkyl-acetic acid, heterocycloalkyl, CD_3.

[0108] Also disclosed are compounds of the following formula:



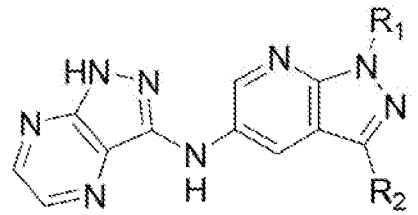
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene.

[0109] Also disclosed are compounds of the following formula:



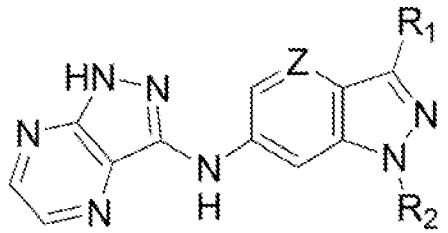
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkoxy, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, cycloheteroalkyl.

[0110] Also disclosed are compounds of the following formula:



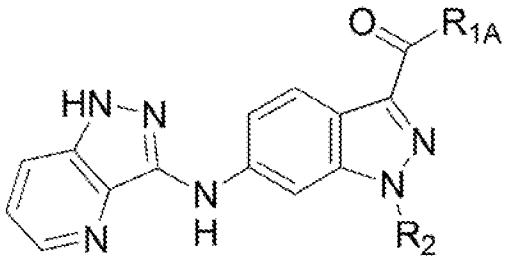
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0111] Also disclosed are compounds of the following formula:



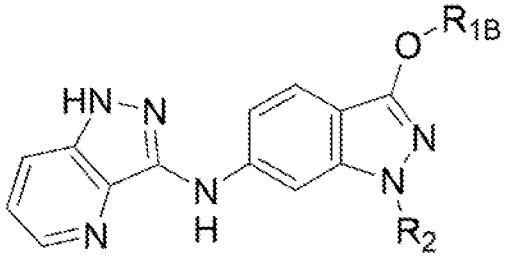
wherein Z is N, CH, CD, C; halogen, C-O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, methylsulfonyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl, CD_3.

[0112] Also disclosed are compounds of the following formula:



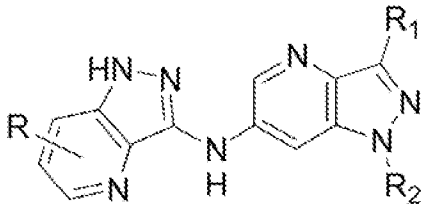
wherein R_{1A} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl-sulfonylmethyl, cycloheteroalkyl, amino-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0113] Also disclosed are compounds of the following formula:



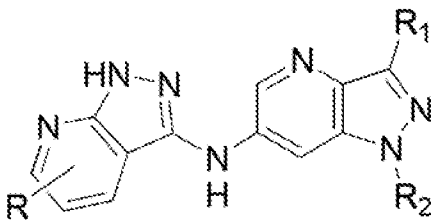
wherein R_{1B} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, cycloheteroalkyl, alkoxy, alkyl-cycloheteroalkyl, alkoxyphenyl, heteroaryl, nitrilepyridine, chloropyridine; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0114] Also disclosed are compounds of the following formula:



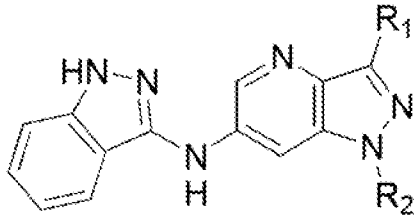
wherein R may be optionally present and when present is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkoxy, hydroxyl, cycloaklyl, methysulfonyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl.

[0115] Also disclosed are compounds of the following formula:



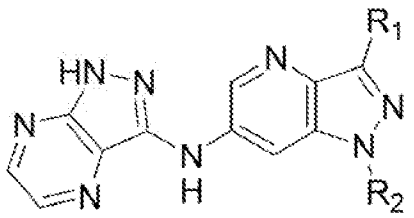
wherein R may be optionally present and when present is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0116] Also disclosed are compounds of the following formula:



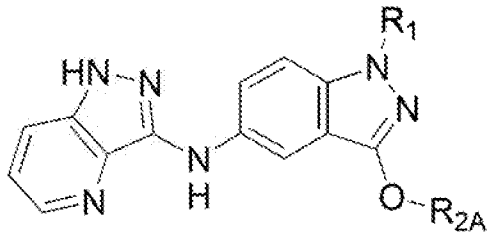
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl.

[0117] Also disclosed are compounds of the following formula:



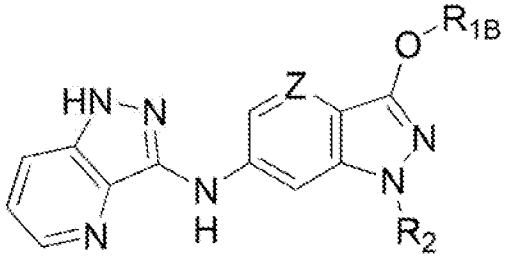
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is alkyl, alkyl-cycloalkyl, alkylheteroaryl.

[0118] Also disclosed are compounds of the following formula:



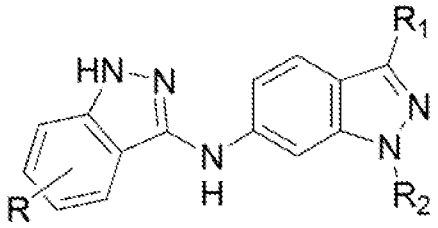
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, heterocycloalkyl , alkoxyphenyl, alkoxyfluorophenyl, heteroaryl, alkylheteroaryl, triflouroalkyl, alkoxyheteroaryl, alkoxy.

[0119] Also disclosed are compounds of the following formula:



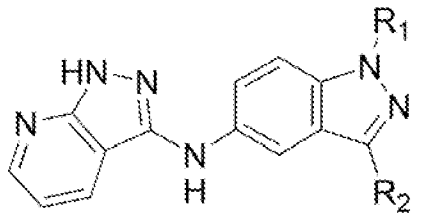
wherein Z is C or C-Cl; R_{18} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, heteroaryl, alkylheteroaryl, alkoxy, CD_3, CD_2alkyl, alkylcycloalkyl, alkylphenyl, alkoxy, alkyl-heterocycloalkyl; and R_2 is heterocycloalkyl, H, alkyl, cycloalkyl, alkyl-cycloalkyl,

[0120] Also disclosed are compounds of the following formula:



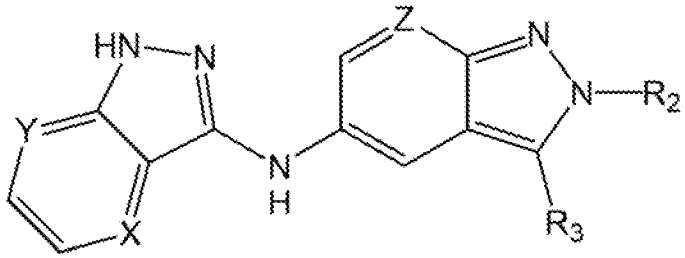
wherein R is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CD_3.

[0121] Also disclosed are compounds of the following formula:



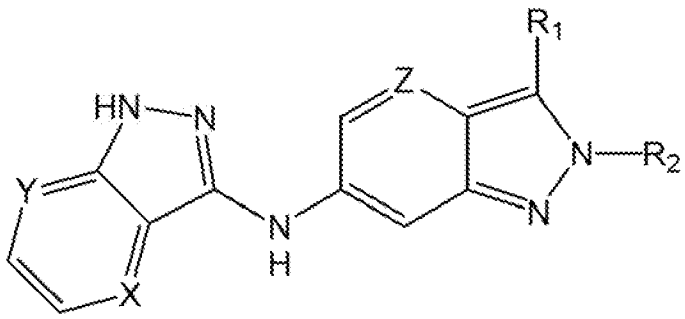
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

[0122] Also disclosed are compounds of the following formula:



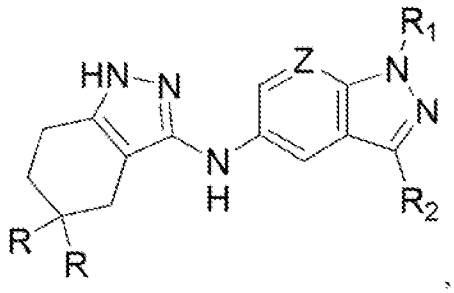
wherein Z is independently N, CH, CD, C-Cl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene, CD_3, alkyl, alkyl-heteroaryl; and R_3 is H, alkyl, cycloalkyl, alkyl-cycloalkyl,

[0123] Also disclosed are compounds of the following formula:



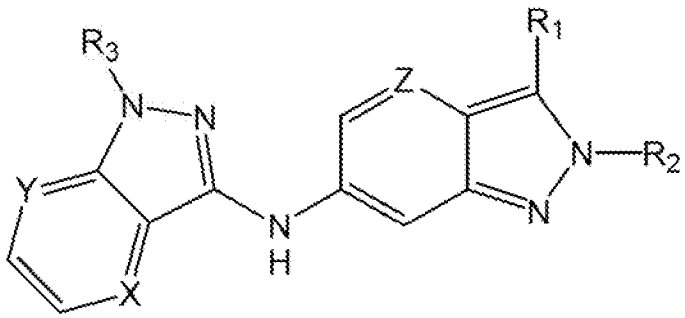
wherein Y is N or CH; Z is C, N, CH, CD, or C-Cl; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene, CD_3, alkyl, alkyl-heteroaryl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl,

[0124] Also disclosed are compounds of the following formula:



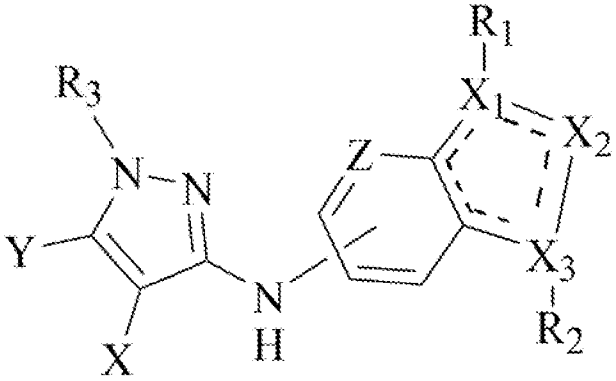
wherein Z is CH, CD, C-Cl, N; each R is optionally present and when present is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CD_3,

[0125] Also disclosed are compounds of the following formula::



wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_3 is alkoxy phenyl, pyridine, nitrilepyridine, chloropyridine.

[0126] Also disclosed are compound of the following formula:



wherein the variables are defined above, and X_1 is N and R_1 is alkyl, alkene, CH2-cycloalkyl, cycloalkyl, CH2-CF3, hydroxyalkyl, cycloheteroalkyl, alkyl-alkoxy, heteroaryl, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CD3, CO-CF3, alkyl-CO-O-alkyl.

[0127] In other embodiments, X_1 is CH and R_1 is CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-dioxothian, hydroxyl, alkoxy, cycloalkyl, O-heteroalkyl, alkoxy-heteroalkyl, methylsulfonyl.

[0128] In other embodiments, R_1 is cyclopentylmethyl, cyclobutylmethyl, cyclobutyl, cyclopropyl, cyclohexyl, tetrahydropyran, methoxyethyl.

[0129] In other embodiments, R_1 is pyridine. In other embodiments, R_1 is pyridinepyrazole.

[0130] In other embodiments, R_1 is benzisoxizole, fluoropyridine-substituted isoxazole, cyclopropyl-substituted isozazole, tetrahydropyran, methylquinolone, alkyl, piperidine, alkyl-piperadine, trifluoroethyl, cyclobutyl, methylisoxazole, methylcyclopropyl, methylcyclobutyl, methyldifluorocyclobutyl, alkylmorpholine, methyl oxadiazole, alkyl-methyl benzixoxazole.

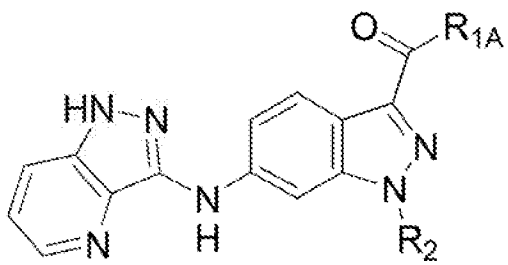
[0131] In other embodiments, R_1 is methylbenzisoxizole.

[0132] In other embodiments, R_1 is methylbenzisoxizole.

[0133] In other embodiments, R_2 is piperazine.

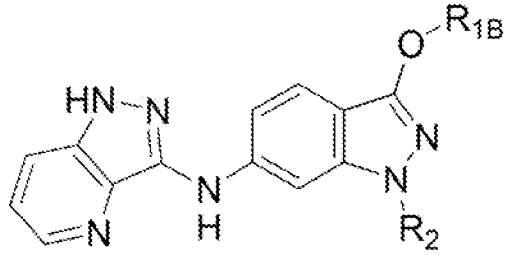
[0134] In other embodiments, R_1 is methylcyclobutyl.

[0135] Also disclosed are compounds of the following formula:



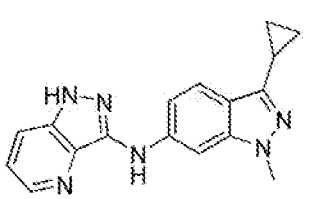
wherein R_{1A} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, difluoropiperidine, piperidine, piperidine-carboxamide, fluoropiperidine, thiazine, dioxothiazine, piperizine, methyl piperizine, morpholino, pyrolidine, methylsulfonylpyrrolidine, fluoropyrrolidine, difluoropyrrolidine, N-cyclobutyl, N-difluorocyclobutyl. R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

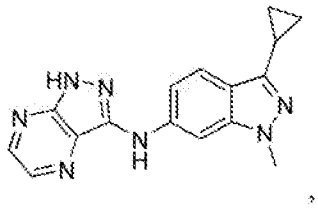
[0136] Also disclosed are compounds of the following formula:



wherein Z is C or C-Cl; R_{1B} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, heteroaryl, alkylheteroaryl, alkoxy, CD_3, CD_2alkyl, alkylcycloalkyl, alkylphenyl, alkoxy, alkyl-heterocycloalkyl, cyclopropyl, difluorocyclopropyl, piperidine, methylpiperidine, oxetane, methyloxetane, thiane, dioxothiane, tetrahydrofuran, pyridine, carbonitrilepyridine, tetrahydropyran, morpholine, morpholinoethoxy; and R_2 is heterocycloalkyl, H, alkyl, cycloalkyl, alkyl-cycloalkyl.

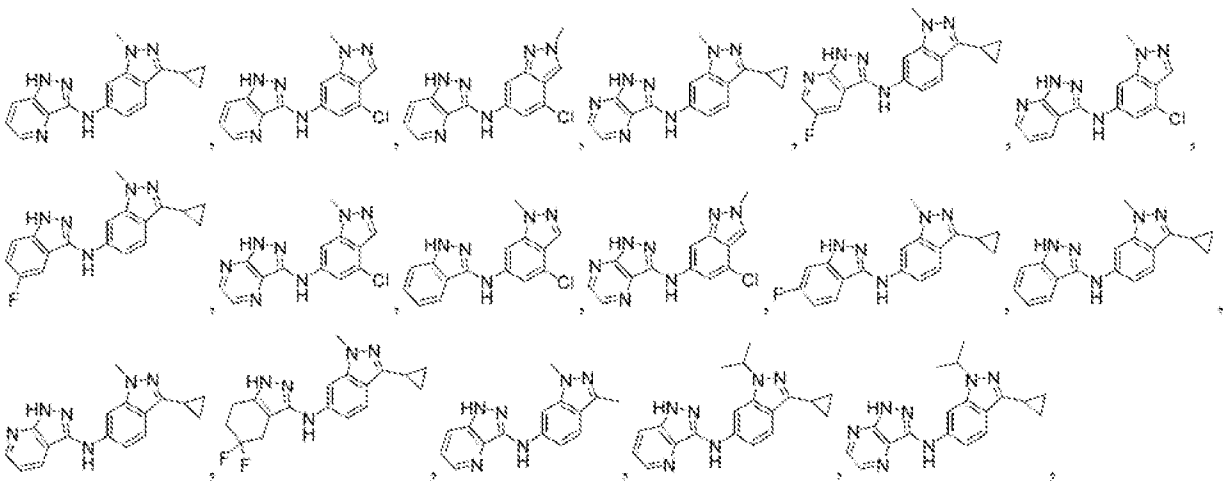
[0137] Also disclosed are compounds of the following formula:

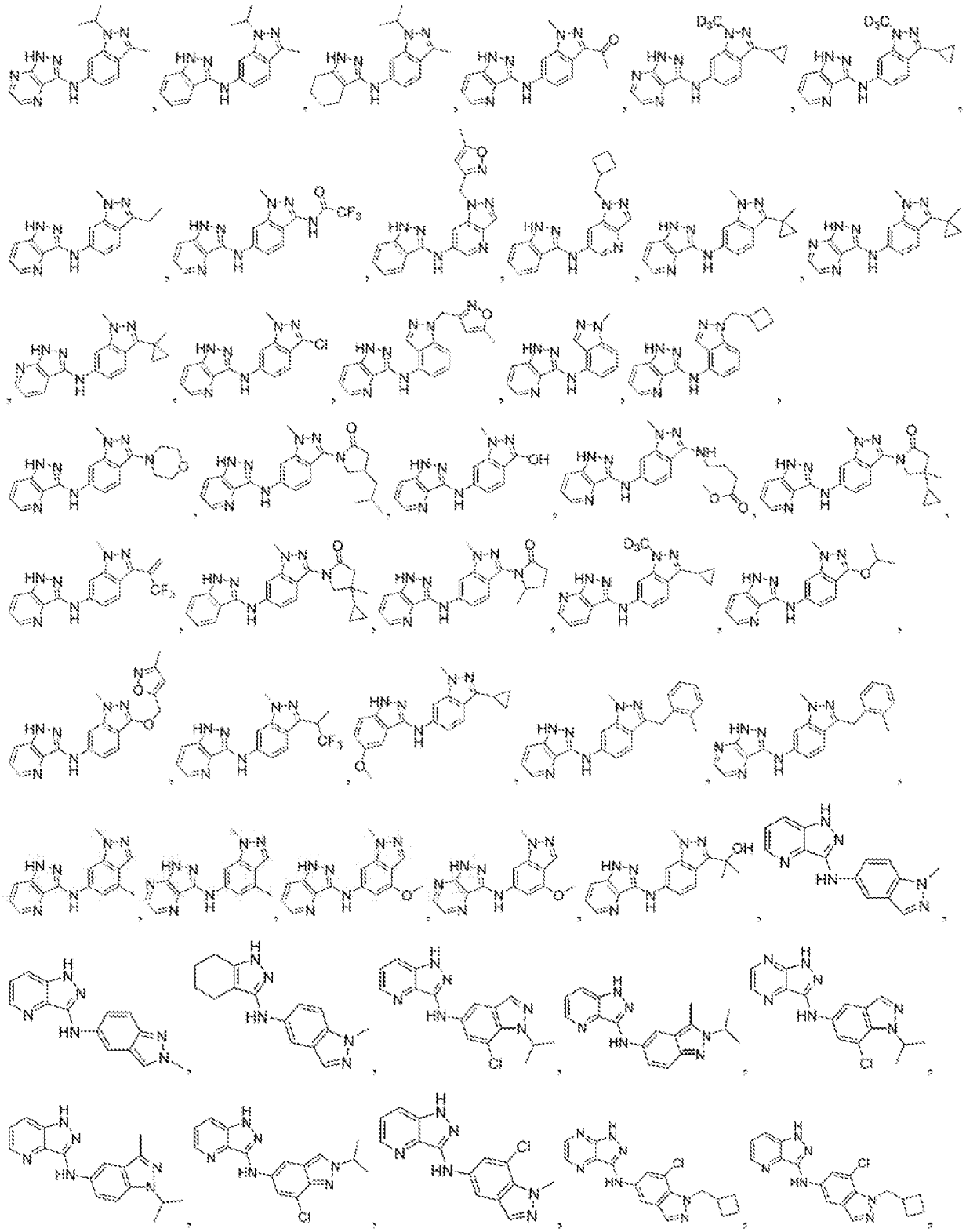


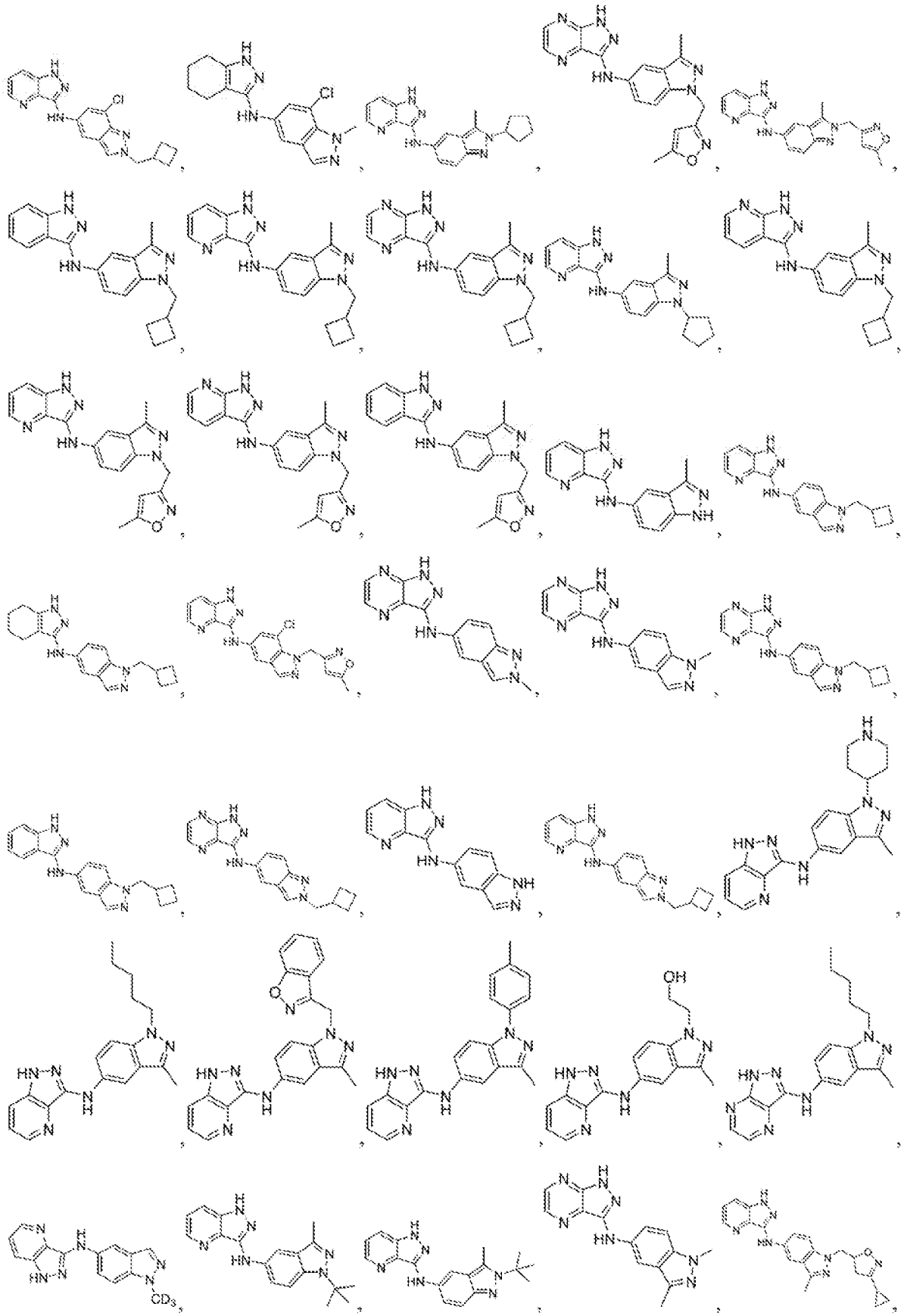


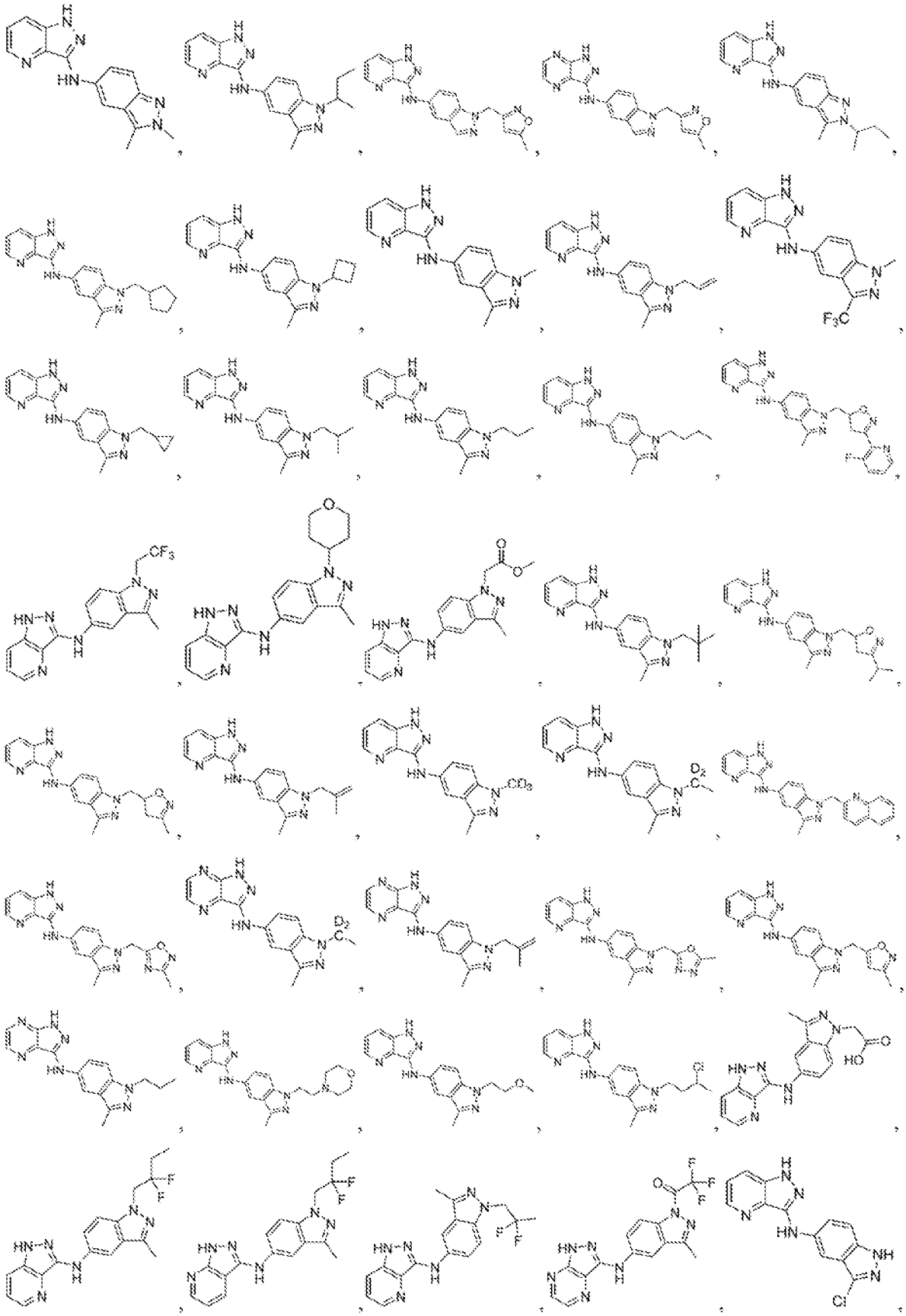
and pharmaceutically acceptable salts thereof.

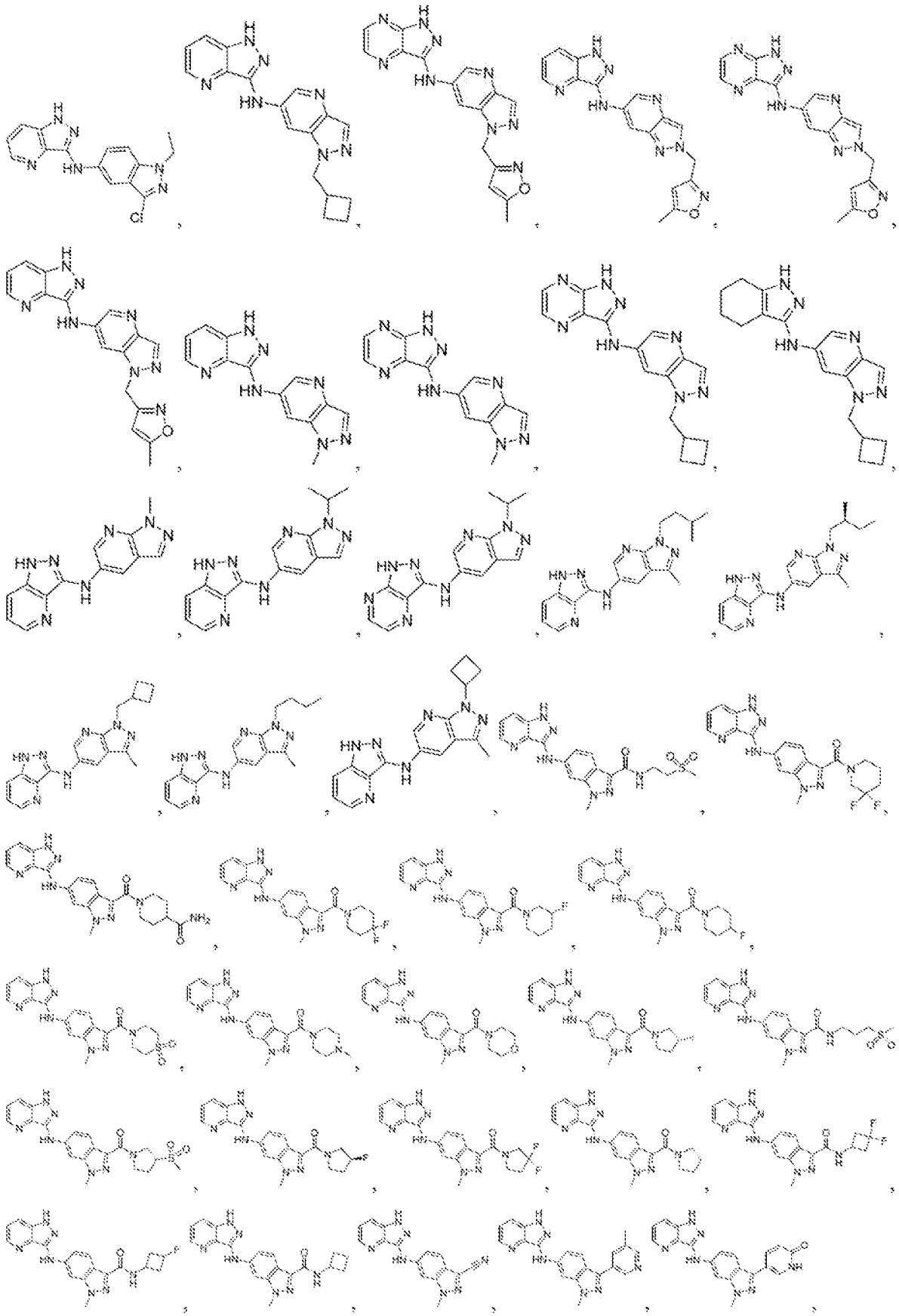
[0138] Also disclosed are compounds of the following formula:

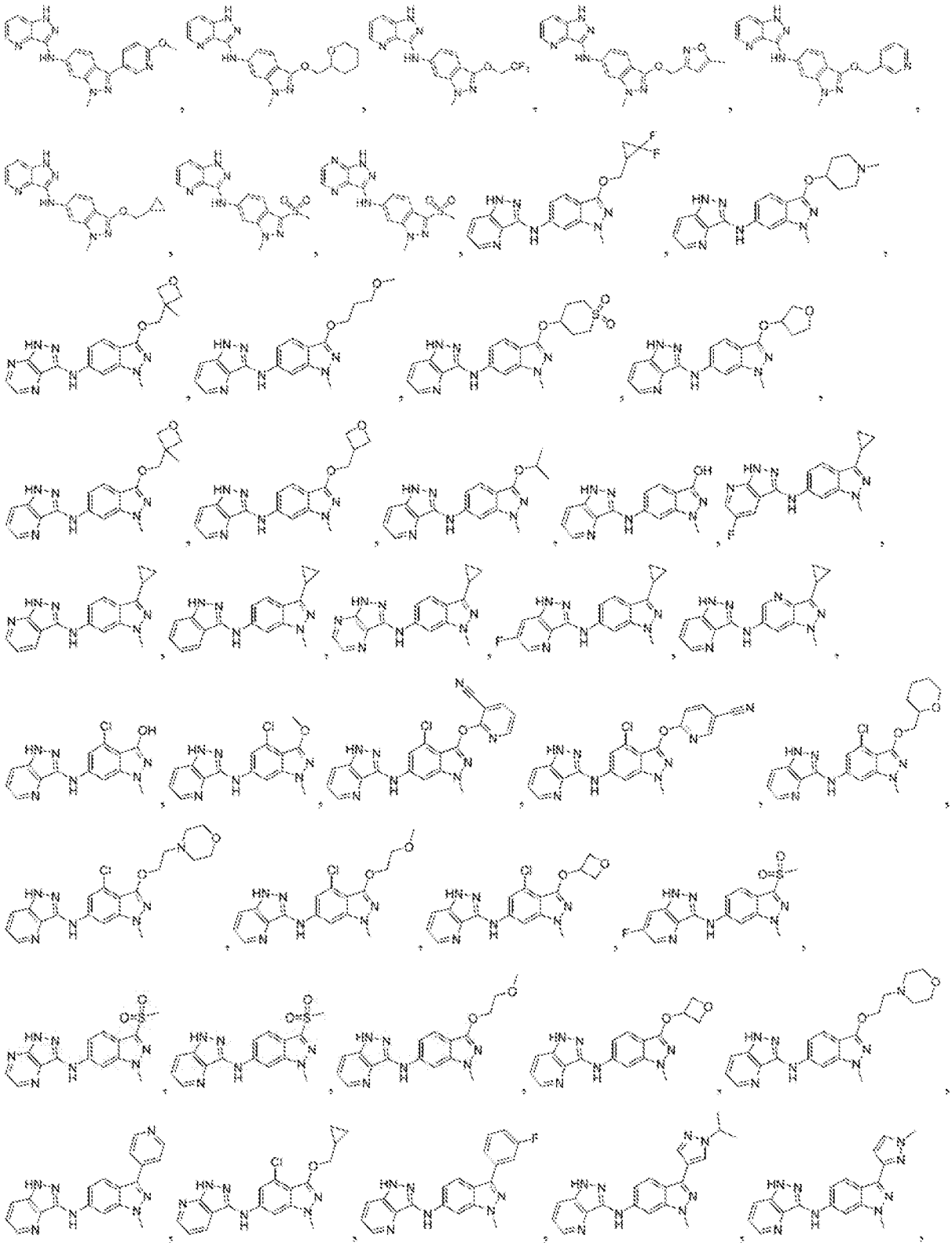


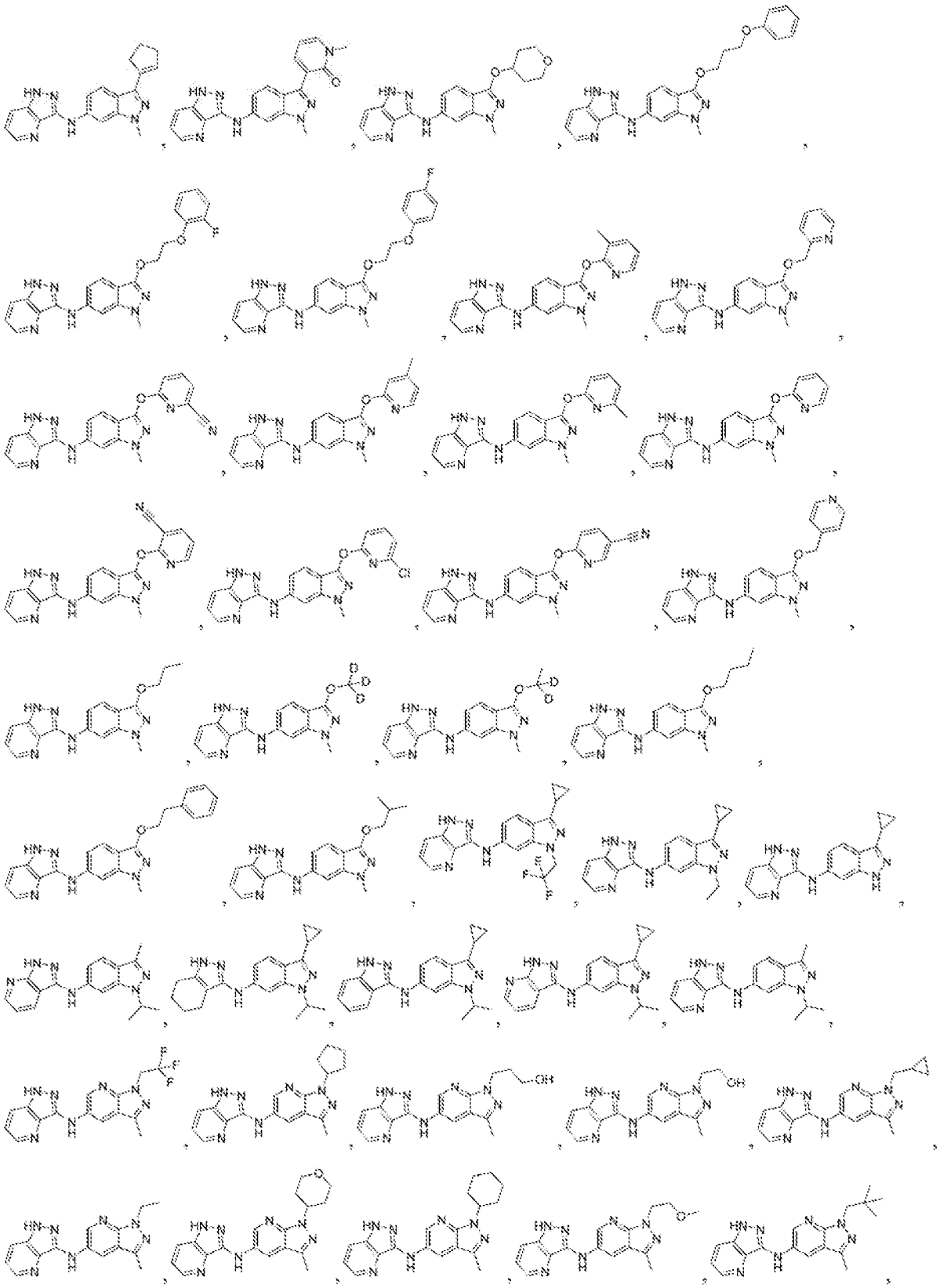


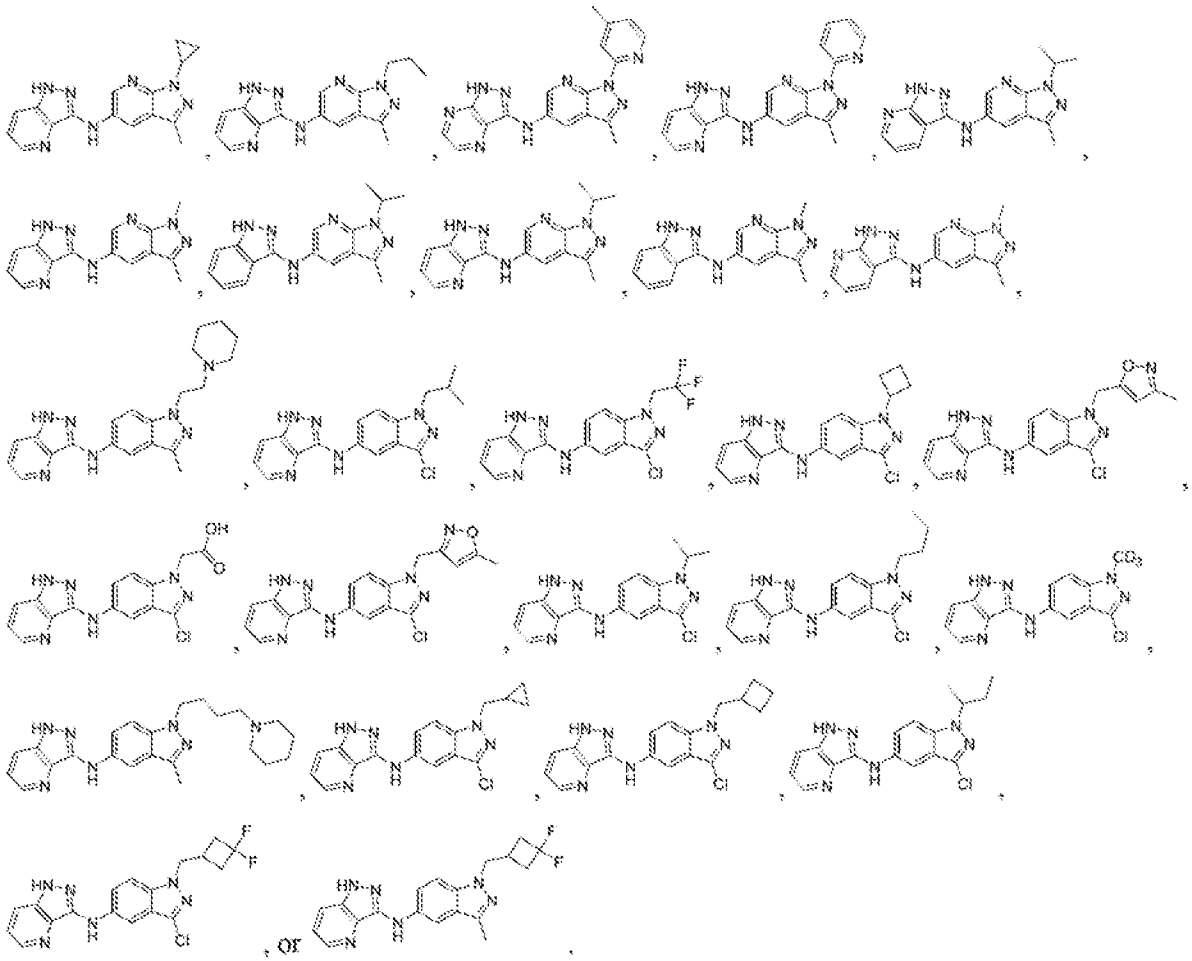












[0139] The compounds disclosed herein can include all salt forms, for example, salts of both basic groups, *inter alia*, amines, as well as salts of acidic groups, *inter alia*, carboxylic acids. The following are non-limiting examples of anions that can form salts with protonated basic groups: chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate, and the like. The following are non-limiting examples of cations that can form salts of acidic groups: ammonium, sodium, lithium, potassium, calcium, magnesium, bismuth, lysine, and the like.

[0140] The analogs (compounds) of the present disclosure are arranged into several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

K. Pharmaceutical compositions

[0141] In one aspect, the invention relates to pharmaceutical compositions comprising the disclosed compounds. That is, a pharmaceutical composition can be provided comprising a

therapeutically effective amount of at least one disclosed compound or at least one product of a disclosed method and a pharmaceutically acceptable carrier.

[0142] In certain aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0143] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric, ferrous, lithium, magnesium, manganese (-ic and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0144] As used herein, the term "pharmaceutically acceptable non-toxic acids" includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[0145] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical

carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[0146] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds. The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[0147] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[0148] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing

agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[0149] The pharmaceutical compositions of the present invention can comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0150] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[0151] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[0152] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[0153] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The

suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[0154] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[0155] A potentiated amount of an mGluR agonist to be administered in combination with an effective amount of a disclosed compound is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day and is expected to be less than the amount that is required to provide the same effect when administered without an effective amount of a disclosed compound. Preferred amounts of a co-administered mGluR agonist are able to be determined by one skilled in the art.

[0156] In the treatment conditions which require potentiation of metabotropic glutamate receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[0157] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy.

[0158] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[0159] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

[0160] Further disclosed herein are pharmaceutical compositions comprising one or more of the disclosed mGluR4 potentiators and a pharmaceutically acceptable carrier.

[0161] Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention.

[0162] The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which disclosed compounds are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

[0163] The weight ratio of the compound of the present invention to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0164] In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0165] Accordingly, the subject compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent may be coadministered, either in concomitant therapy or in a fixed combination.

[0166] In one aspect, the compound can be employed in combination with anti- Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, NSAIDS's (non-steroidal anti-inflammatory drugs) including ibuprofen, vitamin E, and anti-amyloid antibodies. In a further aspect, the subject compound may be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, thiothixene, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, Zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

[0167] In a further aspect, the compound can be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

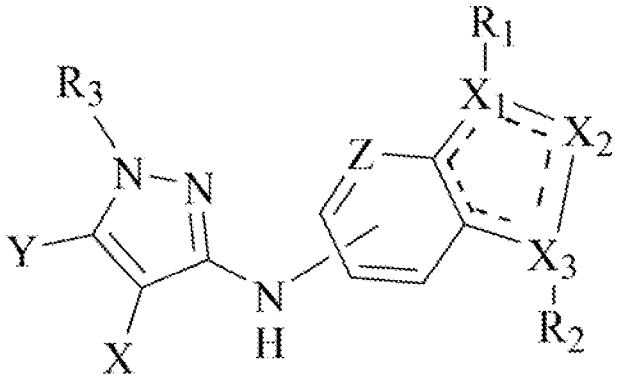
[0168] In a further aspect, the compound can be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the subject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound may be employed in combination with acetophenazine, alentemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

[0169] In one aspect, the compound can be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α- adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HTJA agonists or antagonists, especially 5-HT1A partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide: venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

[0170] In the treatment of conditions which require potentiation of mGluR4 activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15. 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen may be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0171] In one aspect, the invention relates to a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; and a pharmaceutically acceptable carrier.

[0172] In one aspect, the invention relates to pharmaceutical compositions comprising a compound having a structure represented by a compound of the following formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

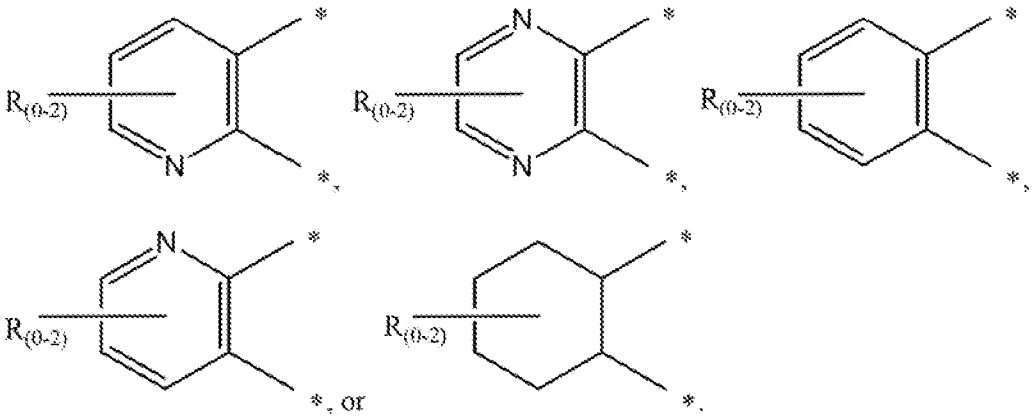
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

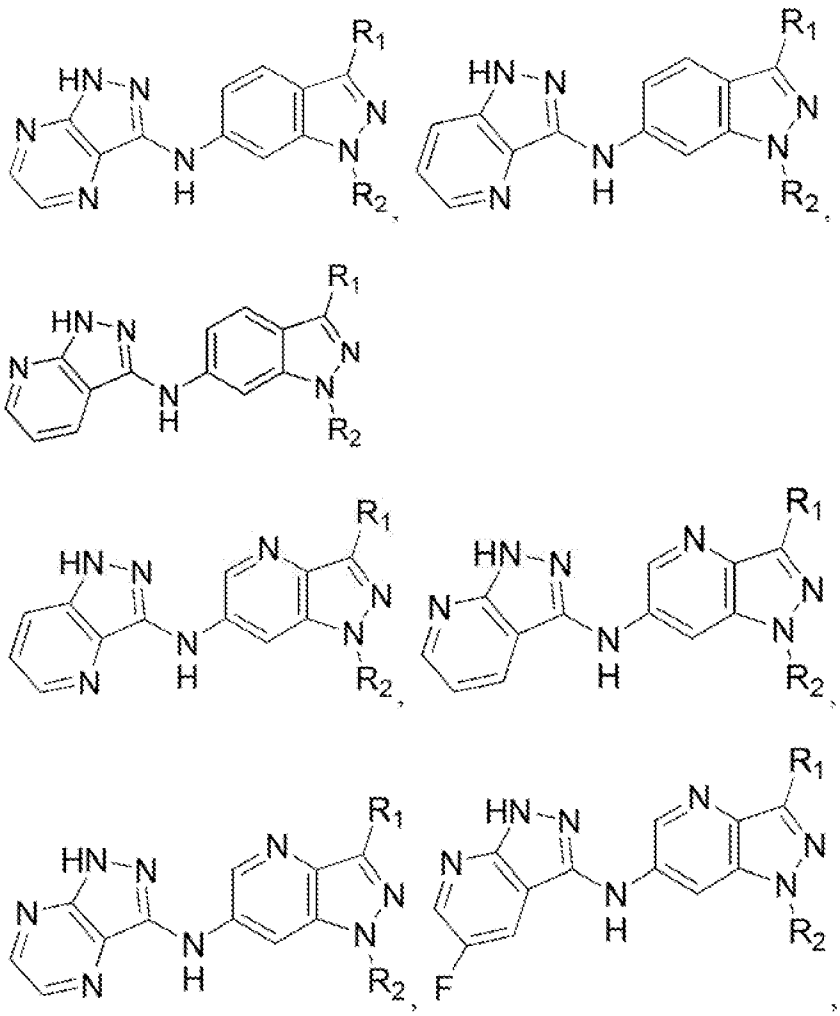
R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

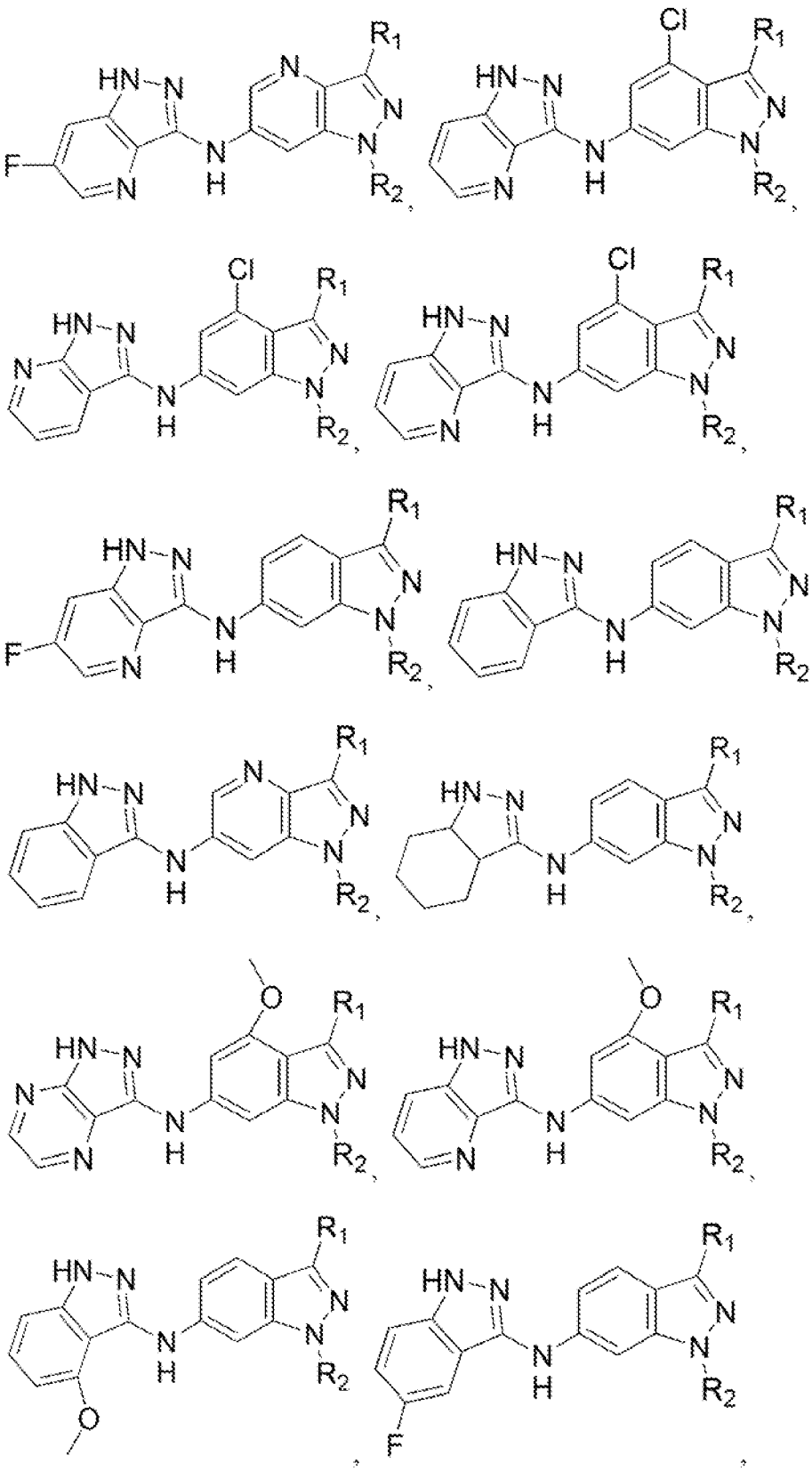
R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

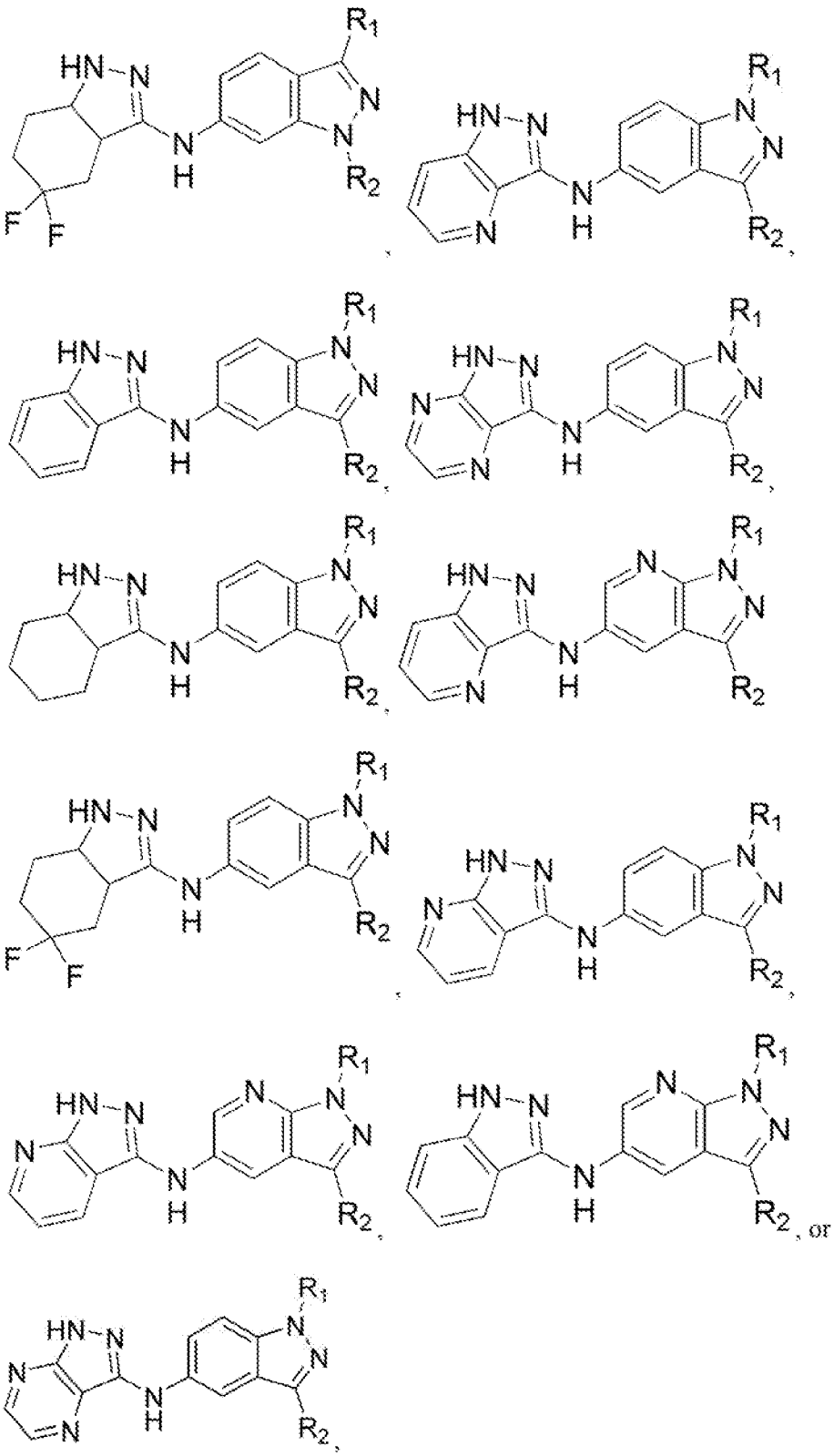
[0173] In another embodiment, in the compound X and Y together form:



[0174] In another embodiment, R, when present, is F. In another embodiment, Z is N, CH, CD, or C-Cl. In another embodiment, the compound is of the following formula:







or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; and a pharmaceutically acceptable carrier.

L. Methods of using the compounds and compositions

[0175] mGluR4 belongs to the group III mGluR subfamily and is located in predominantly in presynaptic locations in the central nervous system where it is functions as an auto- and heteroreceptor to regulate the release of both GABA and glutamate. In addition, mGluR4 is also expressed at a low level in some postsynaptic locations. mGluR4 is expressed in most brain regions, particularly in neurons known to play key roles in the following functions of the CNS:

a) learning and memory;

b) regulation of voluntary movement and other motor functions

c) motor learning

d) emotional responses

e) habit formation, including repetitive tasks and perseverative thought processes

f) reward systems

g) vision and olfaction

h) cerebellar functions;

i) feeding and the regulation of hypothalamic hormones; and

j) sleep and wakefulness.

As such, mGluR4 plays a major role in the modulation of CNS-related diseases, syndromes and non-CNS related diseases or conditions the like, for example,

k) Parkinson's disease, parkinsonism, and other disorders involving akinesia or bradykinesia

l) Dystonia

m) Huntington's diseases and other disorders involving involuntary movements and dyskinesias

n) Tourette`s syndrome and related ticking disorders

o) Obsessive/compulsive disorder and other perseverative behavioral disorders

p) Addictive disorders (including drug abuse, eating disorders, and)

q) Schizophrenia and other psychotic disorders

r) Posttraumatic stress disorder

s) Anxiety disorders;

t) motor effects after alcohol consumption or other drug-induced motor disorders;

u) neurogenic fate commitment and neuronal survival;

v) epilepsy;

w) certain cancers, for example, medulloblastoma;

x) type 2 diabetes, and/or other metabolic disorders; and

y) taste enhancement/blockade.

[0176] The disclosed compounds can act as potentiators of the metabotropic glutamate receptor activity (mGluR4). Therefore, in one aspect, the disclosed compounds can be used to treat one or more mGluR4 associated disorders that result in dysfunction in a mammal.

[0177] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which compounds of formula I or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound will be more efficacious than either as a single agent.

1. Treatment methods

[0178] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with glutamate dysfunction. Thus, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[0179] Also provided is a method for the treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[0180] Examples of disorders associated with glutamate dysfunction include: acute and chronic neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, multiple sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, addictive behavior, including addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), obesity, psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, conduct disorder, diabetes and other metabolic disorders, taste alteration, and cancer.

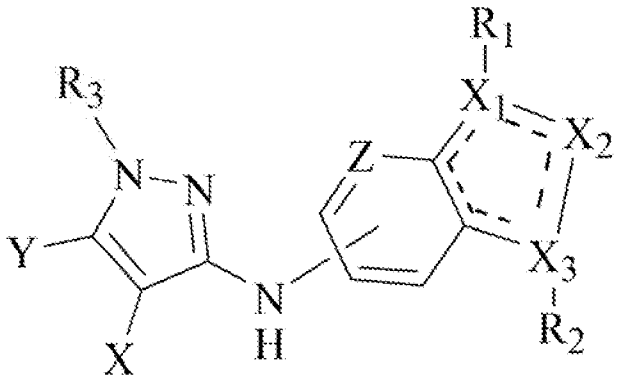
[0181] Anxiety disorders that can be treated or prevented by the compositions disclosed herein include generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. Addictive behaviors include addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.) and substance tolerance.

[0182] Thus, in some aspects of the disclosed method, the disorder is dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression.

[0183] Also provided is a method for treating or prevention anxiety, comprising: administering to a subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

(1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified.

[0184] In one aspect, the invention relates to methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of administering to the mammal at least one compound of the present invention in a dosage and amount effective to treat the dysfunction in the mammal. In certain embodiments, the compound has a structure represented by formula:



wwherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

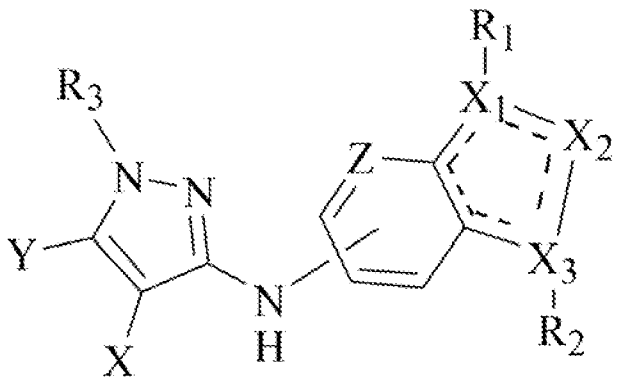
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof

[0185] In one aspect, the invention relates to methods for potentiating mGluR4 activity in a subject comprising the step of administering to the subject at least one compound of the present invention in a dosage and amount effective to treat the dysfunction in the mammal. In certain embodiments, the compound has a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

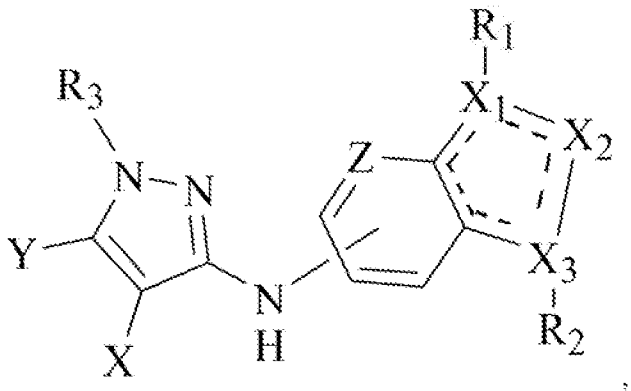
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, in a dosage and amount effective to potentiate mGluR4 receptor activity in the subject.

[0186] In one aspect, the invention relates to methods of potentiating mGluR4 activity in at least one cell comprising the step of contacting the at least one cell with at least one compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-

dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, in an amount effective to potentiate mGluR4 receptor activity in the at least one cell.

[0187] In certain aspects, a subject, for example a mammal or a human, has been diagnosed with the dysfunction prior to the administering step. In further aspects, a disclosed method can further comprise the step of identifying a subject, for example a mammal or a human, having a need for treatment of a dysfunction. In further aspects, a subject, for example a mammal or a human, has been diagnosed with a need for potentiation of mGluR4 receptor activity prior to the administering step. In further aspects, a disclosed method can further comprise the step of identifying a subject, for example a mammal or a human, having a need for potentiation of mGluR4 receptor activity. In further aspects, a cell (e.g., a mammalian cell or a human cell) has been isolated from a subject, for example a mammal or a human, prior to the contacting step. In further aspects, contacting is via administration to a subject, for example a mammal or a human.

[0188] In one aspect, the invention relates to methods for potentiating mGluR4 activity in at least one cell comprising the step of contacting the at least one cell with at least one disclosed compound in an amount effective to potentiate mGluR4 receptor activity in the at least one cell.

[0189] In one aspect, the invention relates to methods for potentiating mGluR4 activity in a subject comprising the step of administering to the subject a therapeutically effective amount of at least one disclosed compound in a dosage and amount effective to potentiate mGluR4 receptor activity in the subject.

[0190] In one aspect, the invention relates to methods for the treatment of a disorder associated with mGluR4 neurotransmission dysfunction or other disease state in a mammal comprising the step of administering to the mammal at least one disclosed compound in a dosage and amount effective to treat the disorder in the mammal.

[0191] The disclosed compounds can be used to treat a wide range of neurological and psychiatric disorders and other disease states associated with glutamate dysfunction. Non-limiting examples of these diseases includes movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease), dystonia, epilepsy, chorea, neurogenerative diseases such as dementia, Huntington's disease, Amyotrophic Lateral Sclerosis, Alzheimer's disease, Pick's disease, Creutzfeldt-Jakob disease, pain, migraines, diabetes, obesity and eating disorders, sleep disorders including narcolepsy, and anxiety or affective disorders, including generalized anxiety disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, and related disorders, cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, stroke, HIV disease, Parkinson's disease, Huntington's disease and other general medical conditions or substance abuse), delirium, amnestic disorders, age-related cognitive decline, schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, cancer and inflammation (including MS). Of the disorders above, the treatment of Parkinson's disease, movement disorders, cognitive disorders, neurodegenerative diseases, obesity and pain are of particular importance.

[0192] In one aspect, the disclosed compounds can be used to treat, or can be a component of a pharmaceutical composition used to treat movement disorders. As such, disclosed herein in a method for treating a movement disorder, comprising the step of administering to a mammal in need of treatment at least one compound in a dosage and amount effective to treat the disorder in the mammal, wherein the disorder is selected from Parkinson's disease, Huntington's disease, dystonia, Wilson's disease, chorea, ataxia, ballism, akathesia, athetosis, bradykinesia, ridigity, postural instability, inherited ataxias such as Friedreich's ataxia, Machado-Joseph disease, spinocerebellar ataxias, Tourette syndrome and other tic disorders, essential tremor, cerebral palsy, stroke, encephalopathies, and intoxication.

[0193] In a further aspect, the disclosed compounds can be used to treat, or can be a component of a pharmaceutical composition used to treat cognitive disorders. As such, disclosed herein in a method for treating a cognitive disorder, comprising the step of administering to a mammal in need of treatment at least one compound in a dosage and amount effective to treat the disorder in the mammal, wherein the disorder is selected from dementia (associated with Alzheimer's disease, ischemia, trauma, stroke, HIV disease, Parkinson's disease, Huntington's disease and other general medical conditions or

substance abuse), delirium, amnestic disorders and age-related cognitive decline. The fourth edition (Revised) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool for cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, stroke, HIV disease, Parkinson's disease, Huntington's disease and other general medical conditions or substance abuse), delirium, amnestic disorders and age-related cognitive decline.

[0194] In a further aspect, the disclosed compounds can be used to treat, or can be a component of a pharmaceutical composition used to neurodegenerative disorders. As such, disclosed herein in a method for treating a neurodegenerative disorder, comprising the step of administering to a mammal in need of treatment at least one compound in a dosage and amount effective to treat a neurodegenerative disorder in the mammal.

[0195] In a still further aspect, the disclosed compounds provide a method for treating schizophrenia or psychosis. As such, disclosed herein in a method for treating a disorder related to schizophrenia or psychosis, comprising the step of administering to a mammal in need of treatment at least one compound in a dosage and amount effective to treat the disorder in the mammal, wherein the disorder related to schizophrenia or psychosis is selected from paranoid, disorganized, catatonic or undifferentiated, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-induced psychotic disorder. The fourth edition (Revised) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool for c include paranoid, disorganized, catatonic or undifferentiated, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-induced psychotic disorder.

[0196] The subject compounds are further useful in the prevention, treatment, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents, including an mGluR agonist.

2. Coadministration methods

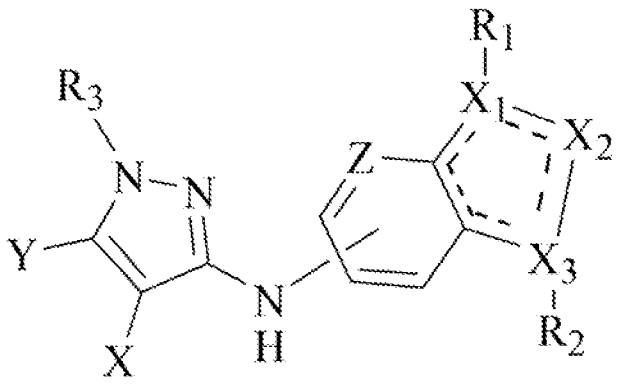
[0197] The disclosed compounds may be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which compounds of formula I or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) may be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the compound is preferred. However, the combination therapy can also be

administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent.

[0198] In one aspect, the compounds can be coadministered with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, muscarinic agonists, muscarinic potentiators HMG-CoA reductase inhibitors, NSAIDs and anti-amyloid antibodies. In a further aspect, the compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), 5-HT2 antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbitol, and salts thereof and combinations thereof.

[0199] In a further aspect, the subject compound may be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor), anitcholinergics such as biperiden, COMT inhibitors such as entacapone, A2a adenosine antagonists, cholinergic agonists, NMDA receptor antagonists and dopamine agonists.

[0200] In one aspect, the invention relates to methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

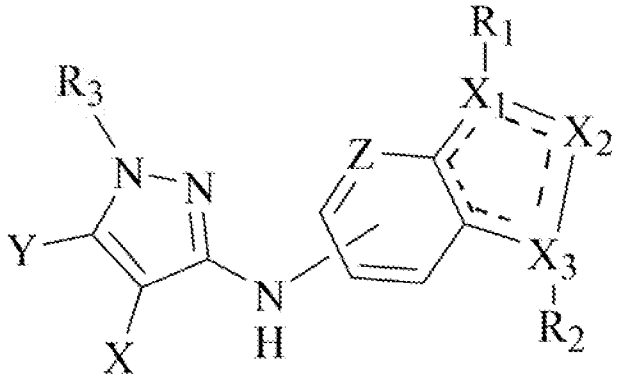
provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; with a drug having a known side-effect of increasing metabotropic glutamate receptor activity.

[0201] In one aspect, the invention relates to methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

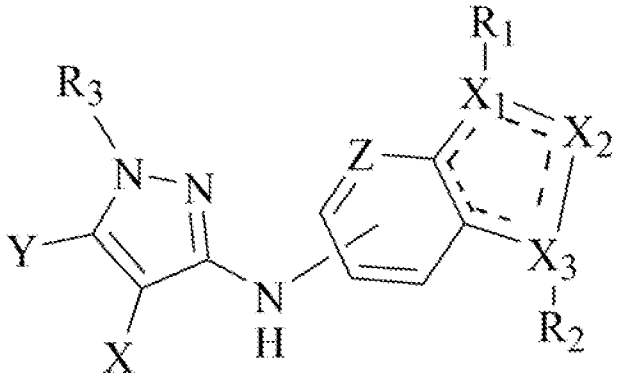
R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; with a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity.

[0202] In one aspect, the invention relates to methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; with a drug known to treat the neurotransmission dysfunction and other disease states.

M. Metabotropic glutamate receptor activity

[0203] The disclosed compounds and compositions can be evaluated for their ability to act as a potentiator of metabotropic glutamate receptor activity, in particular mGluR4 activity, by any suitable known methodology known in the art. For example, Chinese Hamster Ovary (CHO) cells transfected with human mGluR4 or HEK cells co-transfected with rat mGluR4 and the G-protein regulated Inwardly Rectifying Potassium channel (GIRK) were plated in clear bottom assay plates for assay in a Hamamatsu FDSS Fluorometric Plate Reader. The cells were loaded with either a Ca2+-sensitive fluorescent dye or the thallium responsive dye and the plates were washed and placed into a suitable kinetic plate reader. For human mGluR4 assays, a fluorescence baseline was established for 3-5 seconds, the disclosed compounds were then added to the cells, and the response in cells was measured. Approximately two and a half minutes later, a concentration of mGluR4 orthosteric agonist (e.g.

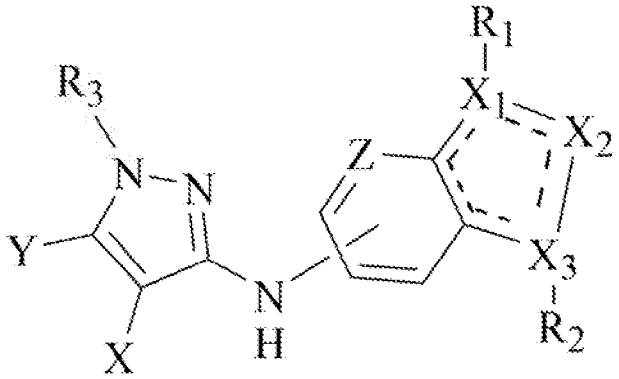
glutamate or L-AP4) eliciting approximately 20% (EC20) of the maximal agonist response was added to the cells, and the response was measured. Two minutes later, a concentration of mGluR4 agonist (e.g. glutamate or L-AP4) eliciting 80% (EC80) of the maximal agonist response was added to the cells, and the response was measured. For rat mGluR4/GIRK experiments, a baseline was established for approximately five seconds, disclosed compounds were added, and either an EC20 or EC80 concentration of agonist was added approximately two and one half minutes later. Potentiation of the agonist response of mGluR4 by the disclosed compounds was observed as an increase in response to the EC20 concentration of agonist in the presence of compound compared to the response to agonist in the absence of compound. Similarly, antagonism of the agonist response of mGluR4 by the disclosed compounds was observed as a decrease in response to the EC80 concentration of agonist in the presence of compound compared to the response to agonist in the absence of compound.

[0204] The above described assay operated in two modes. In the first mode, a range of concentrations of the disclosed compounds are added to cells, followed by a single fixed concentration of agonist. If the compound acts as a potentiator, an EC_{50} value for potentiation and a maximum extent of potentiation by the compound at this concentration of agonist is determined by non-linear curve fitting. If the compound acts as a noncompetitive antagonist, an IC_{50} value is determined by non-linear curve fitting. In the second mode, several fixed concentrations of the disclosed compounds are added to various wells on a plate, followed by a range in concentrations of agonist for each concentration of disclosed compound. The EC_{50} values for the agonist at each concentration of compound are determined by non-linear curve fitting. A decrease in the EC_{50} value of the agonist with increasing concentrations of the sample compound (a leftward shift of the agonist concentration-response curve) is an indication of the degree of mGluR4 potentiation at a given concentration of the sample compound. A decrease in the maximal response of the agonist with increasing concentrations of the sample compounds, with or without a rightward shift in agonist potency, is an indication of the degree of noncompetitive antagonism at mGluR4. The second mode also indicates whether the sample compounds also affect the maximum response to mGluR4 to agonists.

[0205] In particular, the compounds of the following examples were found to have activity in potentiating the mGluR4 receptor in the aforementioned assays, generally with an EC_{50} for potentiation of less than about 10 □M. One aspect of the disclosed compounds have activity in potentiating rat and human mGluR4 receptors with an EC_{50} for potentiation of less than about 500 nM. These compounds further caused a leftward shift of the agonist EC_{50} by greater than 3-fold. These compounds are positive allosteric modulators (potentiators) of human and rat mGluR4 and were selective for mGluR4 compared to the other seven subtypes of metabotropic glutamate receptors.

N. Manufacture of a medicament

[0206] In one aspect, the invention relates to methods for the manufacture of a medicament for potentiating mGluR4 receptor activity in a mammal comprising combining a compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl,

alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

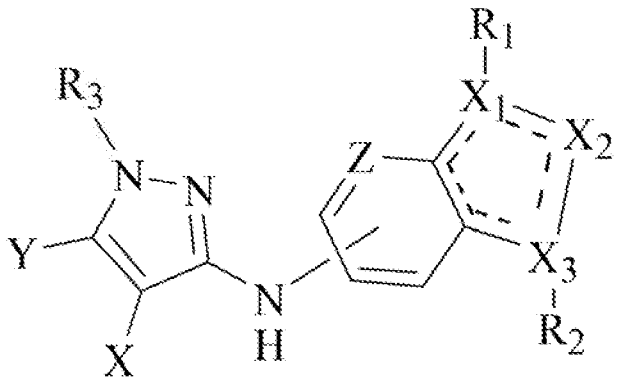
R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier.

[0207] Thus, the disclosed compounds and compositions can be further directed to a method for the manufacture of a medicament for potentiating glutamate receptor activity (*e.g.*, treatment of one or more neurological and/or psychiatric disorder and other disease states associated with glutamate dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or compositions with a pharmaceutically acceptable carrier or diluent.

O. Uses of compounds

[0208] In one aspect, the invention relates to uses of a compound for potentiating mGluR4 receptor activity in a mammal, wherein the compound has a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

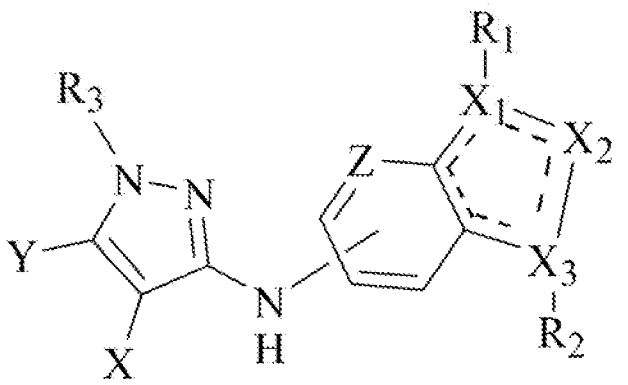
R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0209] The disclosed uses for potentiating mGluR4 receptor activity in a mammal can further be directed for use in treating one or more disorders, for example neurological and psychiatric disorders

and other disease states associated with glutamate dysfunction (e.g., Parkinson's disease) in a subject, for example a mammal or a human.

P. Kits

[0210] In one aspect, the invention relates to kits comprising a compound having a structure represented by formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl,

methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, and one or more of a drug having a known side-effect of increasing metabotropic glutamate receptor activity, a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or a drug known to treat the neurotransmission dysfunction and other disease states.

[0211] In various aspects, the kits can comprise disclosed compounds, compositions, and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, or a pharmacist can provide a kit comprising a disclosed oral dosage forms and another component for delivery to a patient.

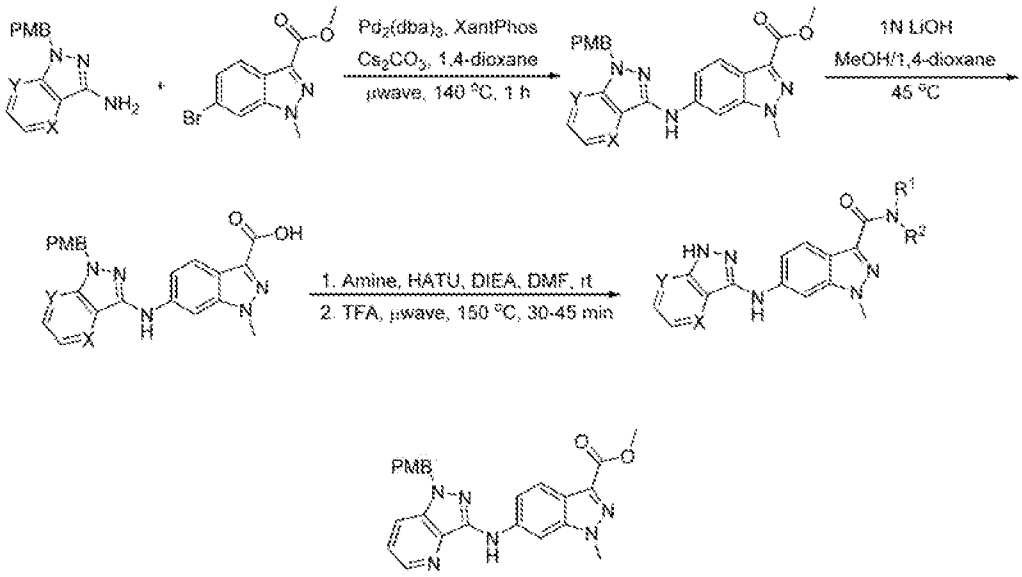
[0212] In further aspects, the kits can comprise one or more other components (e.g., one or more of a drug having a known side-effect of increasing metabotropic glutamate receptor activity, a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or a drug known to treat the neurotransmission dysfunction and other disease states) and instructions for coadminstration to a patient with one or more disclosed compounds, compositions, and/or products. For example, a drug manufacturer, a drug reseller, a physician, or a pharmacist can provide a kit comprising one or more other components (e.g., one or more of a drug having a known side-effect of increasing metabotropic glutamate receptor activity, a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or a drug known to treat the neurotransmission dysfunction and other disease states) and instructions for coadminstration to a patient with one or more disclosed compounds, compositions, and/or products.

Q. Experimental

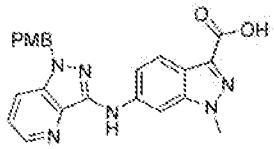
[0213] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[0214] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein. All NMR spectra were recorded on either a Varian Inova 400 (400 MHz) or Varian Inova 500 (500 MHz) spectrophotometer. ^{1}H chemical shifts are reported in δ values in ppm downfield from Me_4Si as the internal standard in $CDCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). ^{13}C chemical shifts are reported in δ values in ppm with the $CDCl_3$ carbon peak set to 77.23 ppm. Low resolution mass spectra were obtained on an HP1100 MSD with electrospray ionization. High resolution mass spectra were recorded on a Bruker Daltonics 3T Fourier transform ion cyclotron resonance mass spectrometer (FT/ICR) with electrospray ionization. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Analytical HPLC was performed on an HP1100 with UV detection at 214 and 254 nm along with ELSD detection, LC/MS (J-Sphere80-C18, 3.0 x 50 mm, 4.1 min gradient, 5%[0.05%TFA/CH_3CN]:95%[0.05%TFA/H_2O] to 100% [0.05%TFA/CH_3CN]. Preparative purification was performed on a custom HP1100 purification system (reference 16) with collection triggered by mass detection. Solvents for extraction, washing and chromatography were HPLC grade. N-Boc-p-phenylenediamine was purchased from Fluka and 1,2-benzenedisulfonyl dichloride was purchased from TCI America. All other reagents were purchased from Aldrich Chemical Co. and were used without purification.

General Scheme I:

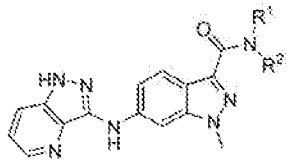


methyl 6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazole-3-carboxylate: Tris(dibenzylideneacetone)dipalladium(0) (69.86 mg, 0.07 mmol, 0.05 eq.), XantPhos (39.08 mg, 0.07 mmol, 0.05 eq.), methyl 6-bromo-1-methyl-1H-indazole-3-carboxylate (454.09 mg, 1.69 mmol, 1.25 eq.),1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-amine (343.29 mg, 1.35mmol, 1.0 eq.) and cesium carbonate (1.32g, 4.05mmol, 3.0 eq.) were charged in a microwave vial. The vial was evacuated and purged with nitrogen (3X) and 1,4-Dioxane (7.5mL) was added. The reaction mixture was subjected to microwave reactor for 140 °C. After 1h, the reaction mixture was cooled and filtered through a pad of Celite which was washed with EtOAc. Solvents were removed under reduced pressure. The crude mixture was purified using reverse phase (Gilson HPLC, acidic method (ACN/water/0.1% TFA), gradient: 47-76%) Gilson fractions were neutralized with sat. soln. $NaHCO_3$ and extracted with EtOAc (3X). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the title compound as a yellow solid (276 mg, 46% yield). ES-MS $[M+1]^+$: 443.2;



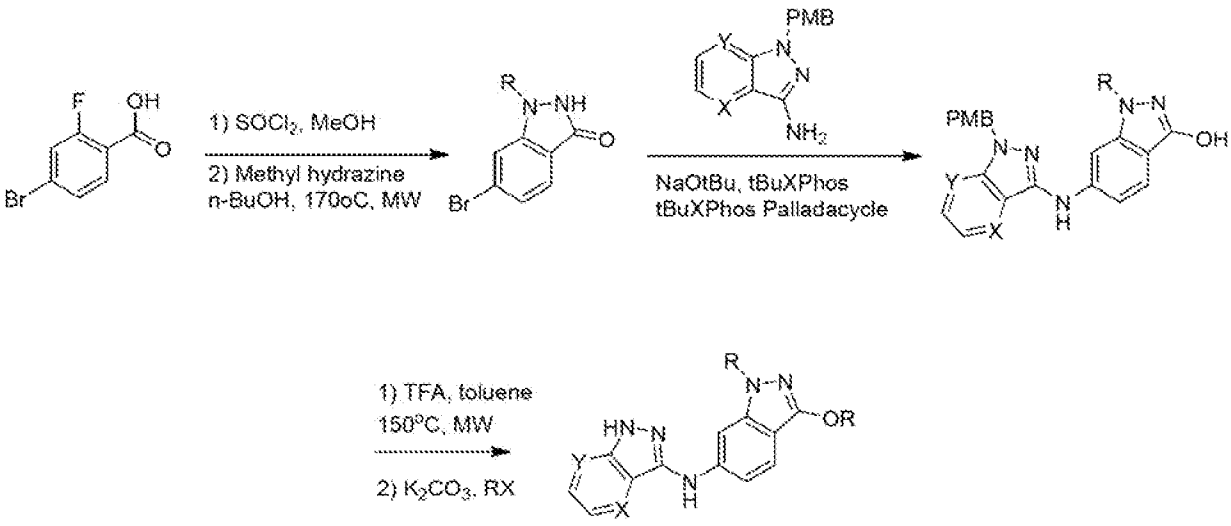
6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazole-3-carboxylic acid: To a solution of methyl 6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazole-3-carboxylate (275 mg, 0.62 mmol, 1.0 eq) in 1,4-Dioxane (5.0 mL) and methanol (1.0 mL) was added a solution of 1N LiOH (6.22mL, 6.22 mmol, 10.0 eq.). The reaction mixture was stirred at 50 °C for 45 min. Solvents were removed under reduced pressure. The aqueous layer was adjusted to pH 3-4 with 1M HCl solution. The resulting mixture was extracted with

$CHCl_3$/iPA (3:1, v/v, 3X). The combined extracts were concentrated under reduced pressure. The yellow solid was dried in the vacuum oven at 45 °C for 3 h to provide the title compound as a yellow solid (230mg, 86.4% yield). ES-MS $[M+1]^+$: 429.0;

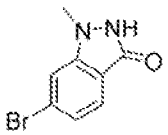


General Procedure for amide formation: A mixture of (**6**) (14.86mg, 0.035 mmol, 1.0 eq.), amine (0.07 mmol. 2.0 eq.) and HATU (19.96mg, 0.050mmol, 1.5 eq.) in DMF (1.0 mL) was stirred for 5 min at rt and DIEA (9.55 uL, 0.07 mmol, 2.0 eq.) was added. The reaction mixture was continued to stir at rt for 45 min. Upon completion by LCMS, the reaction mixture was purified using reverse phase Gilson HPLC system with acidic method (ACN/water/0.1% TFA). The Gilson fractions were concentrated. The resulting residue was dissolved in TFA (0.1 M) and heated in a microwave reactor for 30 min at 150 °C. Solvent was removed under reduced pressure. The crude product was purified using reverse phase Gilson HPLC system with acidic method (ACN/water/0.1% TFA). The sample was concentrated and submitted as a TFA salt.

General Scheme II:



General Procedures:

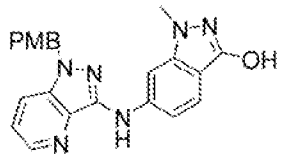


To a white suspension of 4-BROMO-2-FLUOROBENZOIC ACID-(112704-79-7) (1eq) in DCM (0.3M) was added OXALYL CHLORIDE-(79-37-8) (1.05eq) and DMF (2-3 drops). The rxn was

stirred until a solution formed and no further gas evolution was evident. Methanol (12eq) was added. After 30 min at rt, the volatiles were removed under reduced pressure and the residue was partitioned between water and DCM. The Organics were washed with saturated $NaHCO_3$ (aq) and passed through a hydrophobic frit. The solution was concentrated to afford methyl 4-bromo-2-fluoro-benzoate.

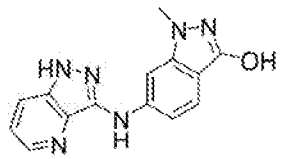
To methyl 4-bromo-2-fluoro-benzoate (1eq) in 1-Butanol (0.35M) was added METHYLHYDRAZINE-(60-34-4) (3.7eq) at rt. The rxn was heated to 170°C for 40 min in the microwave. The rxn was added to EtOAc:water (1:1) and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated. The residue was recrystallized from EtOAc/hexanes to yield 6-bromo-1-methyl-2H-indazol-3-one (66% yield over 2 steps).

LCMS (90 second method): R_T = 0.772 min, >98% @ 215 and 254 nM, *m/z* = 227.0[M + H]$^+$.



To a RBF, was added 6-bromo-1-methyl-2H-indazol-3-one (1eq), 1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-amine (1eq), SODIUM TERT-BUTOXIDE-(865-48-5) (2.1eq), tBuXPhos (0.01eq), Pd-tBuXPhos (0.01). The rxn was evacuated and purged with Nitrogen (3x), followed by the addition of tert-butanol (0.1M). The heterogeneous rxn was heated to 90°C and monitored by LCMS. After 24hrs, the rxn was added to EtOAc:NH_4Cl (aq)(1:1). The organic layer was separated and washed with water (2x), brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. The crude residue was purified by normal phase chromatography (solid loading with Celite, Biotage, 1-10%MeOH/DCM) to afford 6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazol-3-ol (69% yield) .

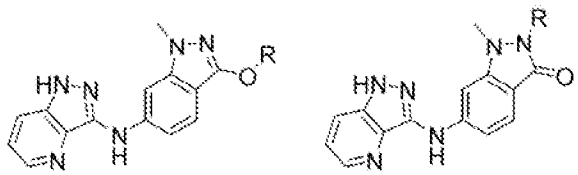
LCMS (90 second method): R_T = 0.855 min, >98% @ 215 and 254 nM, *m/z* = 401.0[M + H]$^+$.



The 6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazol-3-ol (1eq) was dissolved in TRIFLUOROACETIC ACID-(76-05-1) and Toluene (2:1; 0.2M) in a microwave vial and heated to 150°C for 30 min in a microwave. LCMS confirms product formation. After the solvent was removed under reduced pressure, the residue was dissolved in DMSO, syringe filtered and purified

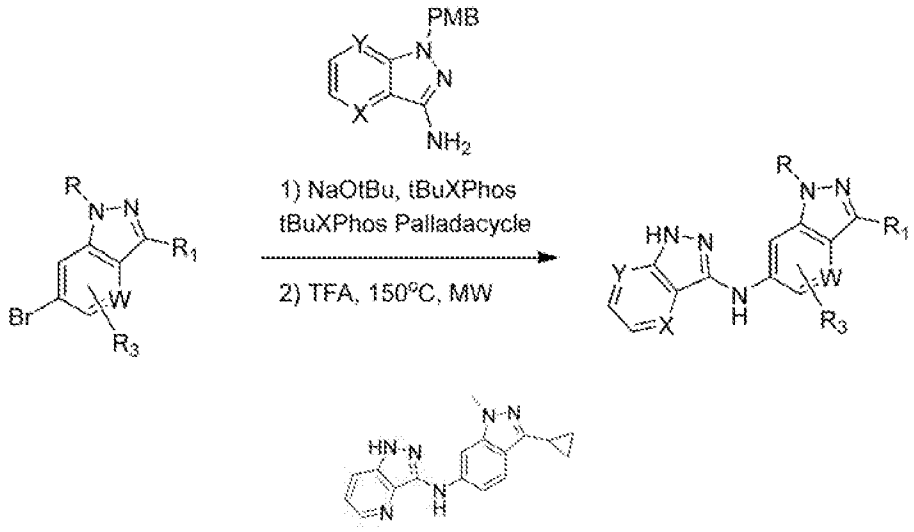
by reverse phase chromatography (Gilson, acidic method 5-45% acetonitrile in 0.1% aq. TFA) to afford 1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)-2H-indazol-3-one; 2,2,2-trifluoroacetic acid (81% yield).

LCMS (90 second method): R_T = 0.575 min, >98% @ 215 and 254 nM, *m/z* = 281.1[M + H]$^+$.



In a microwave vial, to a solution of 1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-ol; 2,2,2-trifluoroacetic acid (1eq) in DMF (0.1M) was added POTASSIUM CARBONATE-(584-08-7) (3eq), followed by alkyl halide (1eq). After 15 min at 120°C in the microwave, LCMS confirms product. The rxn was filtered through a syringe filter and purified with Gilson HPLC (5-95% acetonitrile:water with 0.05%NH_4OH) to afford after concentration the desired O-alkylated product (3-38% yield) and N-alkylated product (0-15%).

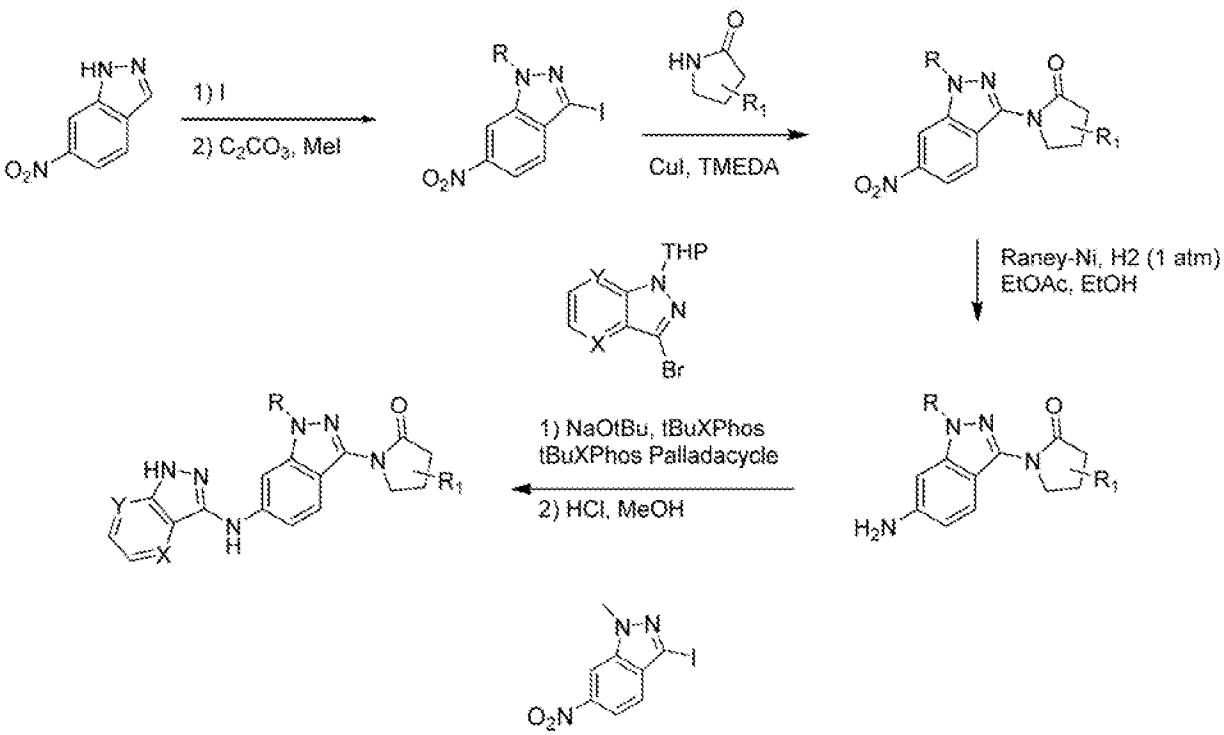
General Scheme III:



(6) In a microwave vial, was added 1-(4-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-amine (1eq), 6-bromo-3-cyclopropyl-1-methyl-1H-indazole (1eq), NaO^{t}Bu (2.1 eq), ^{t}BuXPhos (1 mol %) and ^{t}BuXPhos Palladacycle (1mol%). The vial was sealed and evacuated and purged with Argon (3x). ^{t}BuOH (0.06M) was added and the rxn was heated to 60°C. After 4h, the rxn was added to EtOAc:NH_4Cl (aq) (1:1). The organic layer was separated and washed with water (2x), brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. The crude residue was redissolved in TFA (0.1M) and subjected to microwave irradiation at 150°C for 20 min. The solvent was removed and the crude residue was purified by reverse phase chromatography (Gilson, 25-90%

acetonitrile:water w/0.1% TFA) to afford N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine.

Scheme IV:

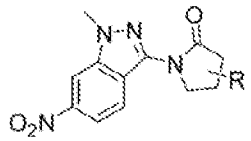


A mixture of 6-nitro-1H-indazole (1.0eq) in 1,4-dioxane (0.3M) and NaOH (2M) was stirred for 1h at rt. Iodine crystals (1.25eq) were added. After 12h at rt, to the rxn was added 10% citric acid aqueous solution and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with NaHCO3 (10% aqueous), brine, dried (MgSO4), filtered and concentrated. The material was purified by normal phase chromatography (10-60% EtOAc/hexanes) to afford 3-Iodo-6-nitro-1H-indazole.

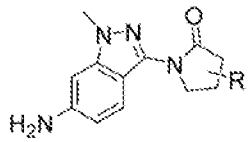
LCMS (90 second method): RT = 0.893 min, >98% @ 215 and 254 nM, m/z = 290.0 [M + H]+.

In a vial, 3-Iodo-6-nitro-1H-indazole (1eq), Cs2CO3 (1.5eq) and DMF were added at rt. After 5 min, MeI (1.2eq) was added. After an additional 24h at rt, rxn was added to EtOAc:water (1:1). Organic layer was separated, washed with water (2x), brine, dried (MgSO4), filtered and concentrated. The residue was purified by normal phase chromatography (Biotage, 0-15% hexanes/EtOAc) to afford 3-iodo-1-methyl-6-nitro-1H-indazole (46% over 2 steps).

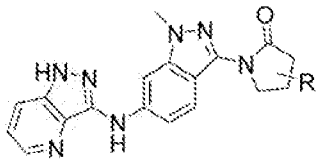
LCMS (90 second method): RT = 1.003 min, >98% @ 215 and 254 nM, m/z = 304.0 [M + H]+.



In a microwave vial, to a suspension of 2 (1.5eq), lactam (1eq), TMEDA (5.5eq) and K2CO3 (2eq) in toluene (0.12M) was added copper (I) iodide (2eq). The rxn mixture was heated to 120°C for 16 h. Upon completion, the mixture was cooled and filtered through a syringe filter. The solvents were removed and the crude product was dissolved in DCM. The solution was purified by normal phase chromatography (Biotage, 3-45% EtOAc/hexanes) to afford the compound.

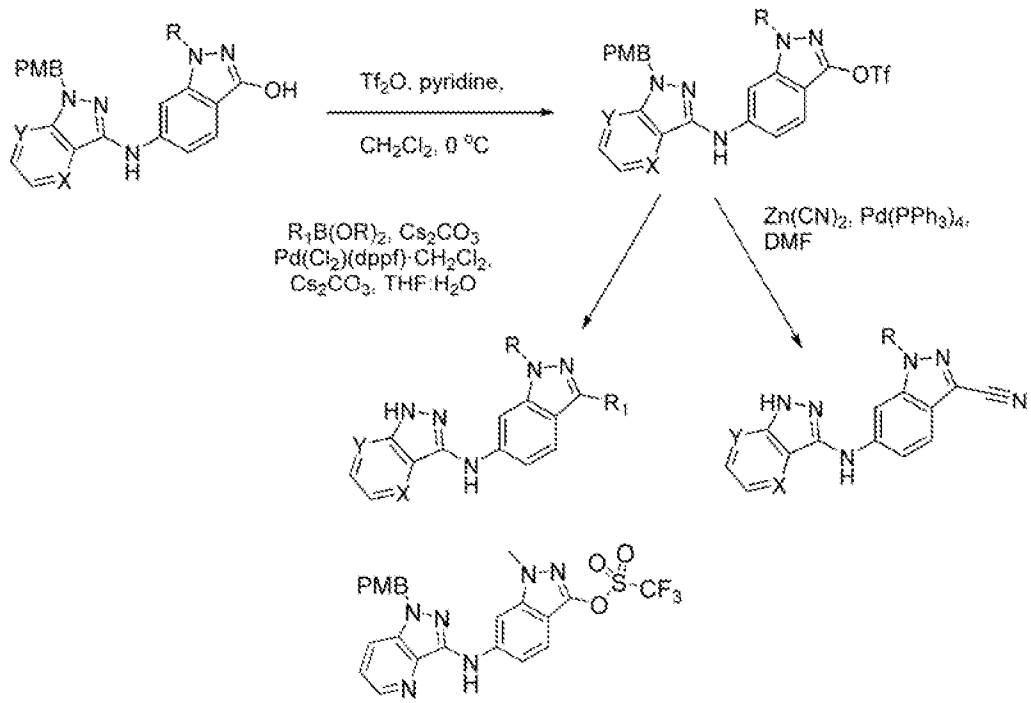


To a solution of the nitro comopund (1eq) in EtOH/EtOAc (1:1; 0.2M) was evacuated and purged with Nitrogen (3x). To the rxn was added Raney-Nickel (~50 mg) and the atmosphere was evacuated and purged with Nitrogen (3x), followed by evacuation and purging with Hydrogen (3x, 1atm). After 12h at rt, the rxn was filtered through a plug of Celite and rinsed thoroughly with MeOH (3x). After the solvent was removed, the material was taken through without further purification.



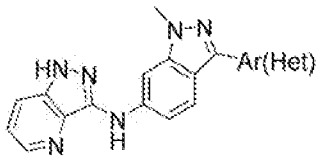
In a 5 mL microwave vial, was added 3-bromo-1-tetrahydropyran-2-yl-pyrazolo[4,3-b]pyridine (1eq), SODIUM TERT-BUTOXIDE-(865-48-5) (2.1eq), tBuXPhos (0.01eq), Pd-tBuXPhos (0.01eq). The rxn was evacuated and purged with Argon (3x), followed by the addition of a solution of amine 4 (1eq) in tert-butanol (0.05M). The heterogenous rxn was heated to 60oC. After 12 h, the rxn was added to EtOAc:NH4Cl (aq) (1:1). The organic layer was separated and washed with water (2x), brine and dried (MgSO4). After filtration, the solvent was removed under reduced pressure. LCMS shows the ring opened lactam as a major product. To the crude residue was added MeOH (0.1M) and HCl in dioxane (3eq, 4M) at rt and the rxn was heated to 65°C. After 12 h, desired product was evident via LCMS. Solvent was removed. The crude residue was dissolved in DMSO and purified by reversed-phase HPLC (20-90% acetonitrile:water w/ 0.1%TFA gradient). After the fractions were collected, the material was neutralized with NaHCO3 (aq):EtOAc. The organic layer was washed with water, brine and dried (MgSO4). Filtered and concentrated to afford desired 5.

Scheme V:



To a RBF was added 6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazol-3-ol (1eq), PYRIDINE-(110-86-1) (3eq) and DCM (0.2M). At 0°C, was added TRIFLUOROMETHANESULFONIC ANHYDRIDE-(358-23-6) in DCM (1.0M, 1.5eq) dropwise. After 2h at 0°C, TLC shows product (R_f=0.9, 100% EtOAc), so DCM:water (1:1) were added to the rxn. Organic layer was separated through a phase separator and the solvent was removed. The crude residue was purified by normal phase chromatography (Biotage, 20-75% EtOAc/hexanes) to afford [6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazol-3-yl] trifluoromethanesulfonate (88% yield) .

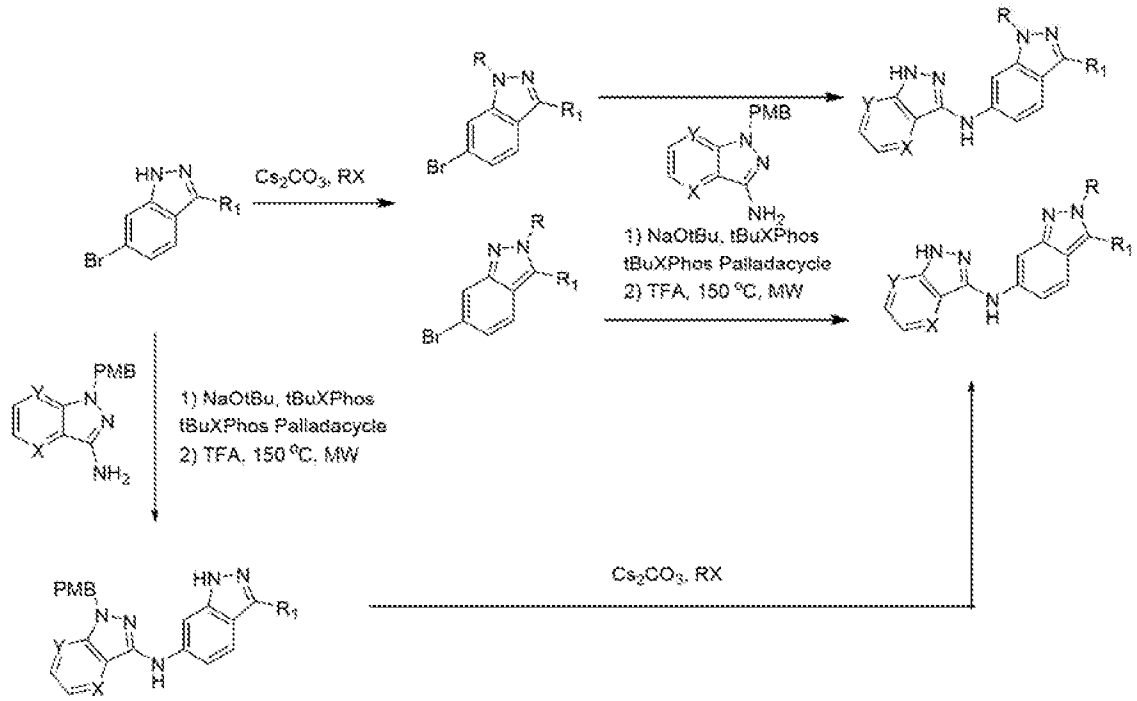
LCMS (90 second method): R_T = 1.288 min, >98% @ 215 and 254 nM, *m/z* = 533.0[M + H]$^+$.



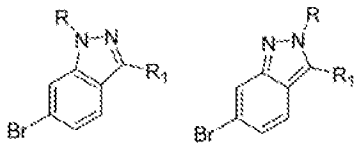
In a microwave vial, was added boronic acid (1.1eq), [6-[[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-yl]amino]-1-methyl-indazol-3-yl] trifluoromethanesulfonate (1eq), $Pd(dppf)Cl_2$ (0.1eq). The rxn was evacuated and purged with Nitrogen (3x). To the vial was added a solution Cs_2CO_3 (3eq) in THF:water (2:1; 0.1M). The reaction was heated to 120°C for 20 min in the microwave. The rxn was added to EtOAc:water (1:1) and the organic layer was separated, washed with water, brine and concentrated. The crude residue was dissolved in TFA (0.1M) and the solution was heated to 150°C for 30 min in the microwave. LCMS confirms product. After the solvent was removed under reduced

pressure, the residue was dissolved in DMSO, syringe filtered and purified by reverse phase chromatography (Gilson, acidic method 5-75% acetonitrile in 0.1% aq. TFA) to afford the desired compound (13-78% yield).

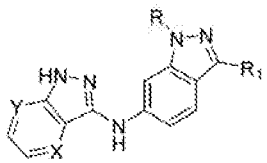
Scheme VI:



General Procedures:

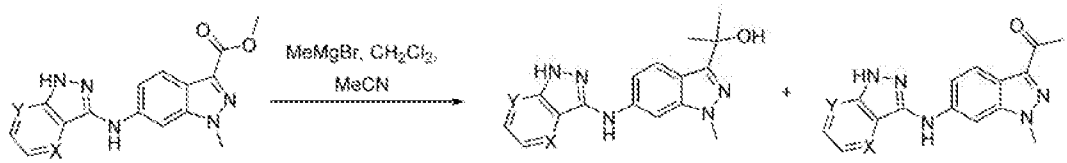


In a 5 mL microwave vial, was added 6-bromo-3-methyl-1H-indazole (1eq), CESIUM CARBONATE-(534-17-8) (2eq), DMF (0.2M) and alkyl halide (1.5eq). The rxn was heated to 150°C in the microwave for 25 min. The rxn was added to EtOAc:water (1:1). The organic layer was separated and washed with water (2x), brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. Purification on normal phase chromatography (Biotage; 5-30% EtOAc/hexanes) to provide 6-bromo-3-methyl-1-alkyl-indazole (64% yield) and 6-bromo-3-methyl-2-alkyl-indazole (23% yield).



In a microwave vial, was added 1-(4-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-amine (1eq), 6-bromo-3-methyl-1-alkyl-indazole (1eq), NaO^{t}Bu (2.1 eq), ^{t}BuXPhos (1 mol %) and ^{t}BuXPhos Palladacycle (1mol%). The vial was sealed and evacuated and purged with Argon (3x). ^{t}BuOH (0.06M) was added and the rxn was heated to 60°C. After 4h, the rxn was added to EtOAc:NH_4Cl (aq) (1:1). The organic layer was separated and washed with water (2x), brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. The crude residue was redissolved in TFA (0.1M) and subjected to microwave irradiation at 150°C for 20 min. The solvent was removed and the crude residue was purified by reverse phase chromatography (Gilson, 25-90% acetonitrile:water w/0.1% TFA) to afford the desired product.

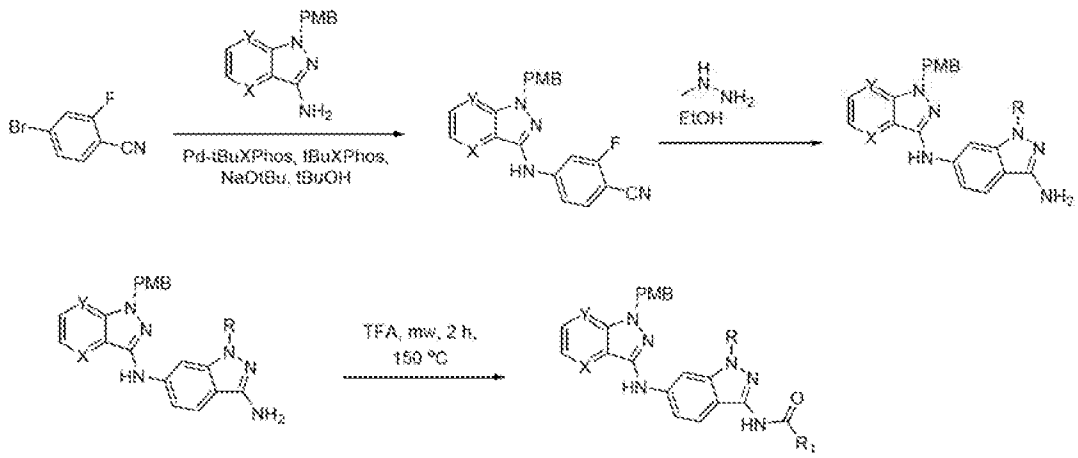
Scheme VII:

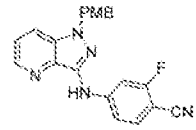


To a solution of ester (1eq) in DCM:acetonitrile (9:1; 0.1M) at 0°C was added MeMgBr (3eq), dropwise. After 5 min, the ice bath was removed. After an additional 30 min at rt, NH_4Cl (aq) was added and the rxn was stirred for 15 min. The organic layer was separated and concentrated. The crude residue was dissolved in DMSO and purified by reversed-phase HPLC (15-75% acetonitrile:water w/ 0.1%TFA gradient). After the fractions were collected, the material was neutralized with $NaHCO_3$ (aq):EtOAc. The organic layer was washed with water, brine and dried (MgSO4). Filtered and concentrated to afford the desired compound.

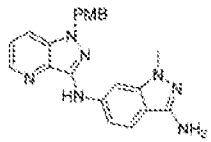
LCMS (90 second method): R_T = 0.764 min, >98% @ 215 and 254 nM, *m/z* = 323.1 $[M + H]^+$.

Scheme VIII:

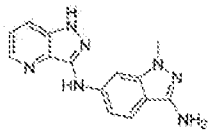




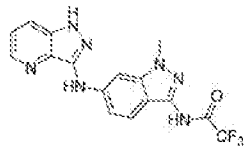
2-fluoro-4-((1-(4-methoxybenzyl)-1H-pyrazolo[4,3-*b*]pyridin-3-yl)amino)benzonitrile. A vial was charged with 1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-*b*]pyridin-3-amine (509 mg, 2 mmol), 4-bromo-2-fluorobenzonitrile (400 mg, 2 mmol), Pd-^{t}BuXPhos (13 mg, 0.02 mmol), ^{t}BuXPhos (9 mg, 0.02 mmol), and sodium tert-butoxide (202 mg, 2.1 mmol). The vial was purged with argon for 2 minutes. Tert-butanol (10 mL) was added. The reaction mixture was stirred at rt for 15 minutes then at 50 °C overnight. The reaction mixture was allowed to reach rt, then filtered over a pad of silica gel. The solids were washed with 50% methanol:ethyl acetate. The filtrate was concentrated, then purified on silica gel with 50% hexanes:ethyl acetate to provide the title compound as a white solid (493 mg, 66% yield). LCMS: RT = 1.147 min; M+H = 374.1.



***N*6-[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-*b*]pyridin-3-yl]-1-methyl-indazole-3,6-diamine.** A microwave vial was charged with 2-fluoro-4-((1-(4-methoxybenzyl)-1H-pyrazolo[4,3-*b*]pyridin-3-yl)amino)benzonitrile (50 mg, 0.13 mmol), methylhydrazine (62 mg, 1.3 mmol), and ethanol (2 mL). The reaction mixture was heated under microwave irradiation for 1 h at 150 °C. The volatiles were removed then the residue was purified by reverse-phase HPLC to provide the title compound as a white solid (45 mg, 84% yield). LCMS: RT = 0.834 min; M+H = 400.2.

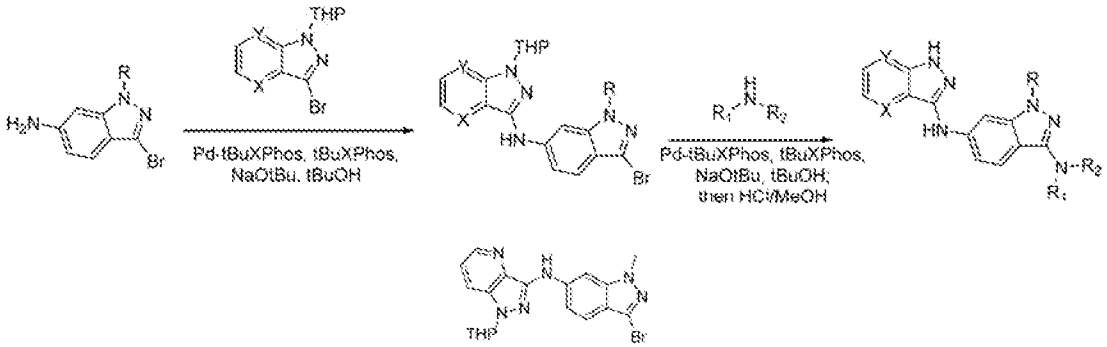


1-methyl-*N*6-(1H-pyrazolo[4,3-b]pyridin-3-yl)indazole-3,6-diamine. A microwave vial was charged with *N*6-[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-*b*]pyridin-3-yl]-1-methyl-indazole-3,6-diamine (25 mg, 0.06 mmol) and TFA (2 mL). The reaction mixture was heated under microwave irradiation for 2 h at 150 °C. The volatiles were removed and the residue was purified by reverse-phase HPLC to provide the title compound as a yellow solid (4 mg, 23% yield). LCMS: RT = 0.856 min; M+H = 280.0.

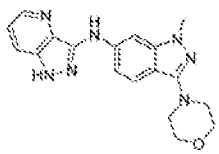


2,2,2-trifluoro-*N*-[1-methyl-6-(1H-pyrazolo[4,3-*b*]pyridin-3-ylamino)indazol-3-yl]acetamide. A microwave vial was charged with *N*6-[1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-*b*]pyridin-3-yl]-1-methyl-indazole-3,6-diamine (25 mg, 0.06 mmol) and TFA (2 mL). The reaction mixture was heated under microwave irradiation for 2 h at 150 °C. The volatiles were removed and the residue was purified by reverse-phase HPLC to provide the title compound as a yellow solid (8 mg, 36% yield). LCMS: RT = 1.126 min; M+H = 375.8.

Scheme IX:



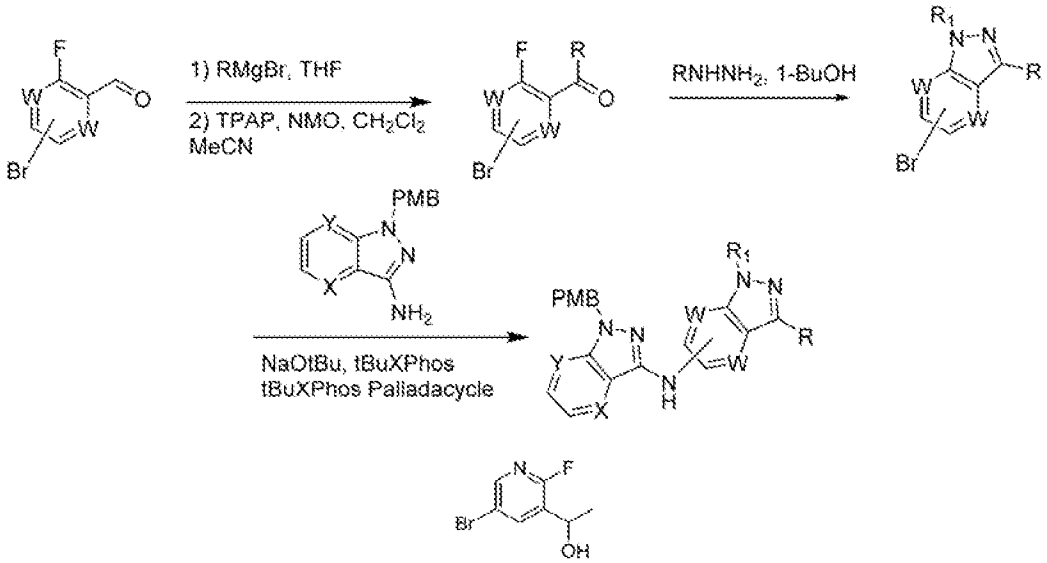
***N*-(3-bromo-1-methyl-1*H*-indazol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*b*]pyridin-3-amine.** A vial was charged with 3-bromo-1-methyl-1*H*-indazol-6-amine (452 mg, 2.0 mmol), 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*b*]pyridine (564 mg, 2.0 mmol), Pd-^{t}BuXPhos (27 mg, 0.04 mmol), ^{t}BuXPhos (17 mg, 0.04 mmol), and sodium tert-butoxide (403 mg, 4.2 mmol). The vial was purged with argon for 2 minutes. Tert-butanol (10 mL) was added. The reaction mixture was stirred at rt for 15 minutes then at 50 °C overnight. The reaction mixture was allowed to reach rt, then filtered over a pad of silica gel. The filtrate was concentrated and the residue purified on silica gel to provide the title compound (226 mg, 26% yield). LCMS: RT = 1.139 min; M+H = 427.0.



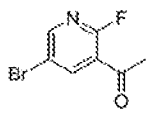
***N*-(1-methyl-3-morpholino-1*H*-indazol-6-yl)-1*H*-pyrazolo[4,3-*b*]pyridin-3-amine.** A vial was charged with *N*-(3-bromo-1-methyl-1*H*-indazol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*b*]pyridin-3-amine (60 mg, 0.14 mmol), morpholine (49 mg, 0.56 mmol), Pd-^{t}BuXPhos (2 mg, 0.002 mmol), ^{t}BuXPhos (1 mg, 0.002 mmol), and sodium tert-butoxide (28 mg, 0.3 mmol). The vial was

purged with argon for 2 minutes. Tert-butanol (10 mL) was added. The reaction mixture was stirred at rt for 15 minutes then at 50 °C overnight. The reaction mixture was concentrated then the residue was purified by RP-HPLC to provide an intermediate THP-protected pyrazolopyridine. This intermediate was dissolved in MeOH (1 mL) and conc. HCl (10 drops) was added. The reaction mixture was stirred at 50 °C for 2 h then concentrated. The residue was purified by RP-HPLC to provide the title compound. LCMS: RT = 0.734 min; M+H = 350.1.

Scheme X:

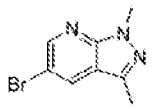


1-(5-bromo-2-fluoro-3-pyridyl)ethanol: To a solution of 5-bromo-2-fluoro-pyridine-3-carbaldehyde (4.08 g, 20.0 mmol, 1.0 eq.) in THF (91mL) at -78 °C was added dropwise a solution of methylmagnesium bromide (3M in diethyl ether, 10.0 mL, 30 mmol, 1.5 eq.). The reaction mixture was allowed to warm to rt and stirred overnight. A saturated solution of NH_4Cl (130.0 mL) was added. The mixture was extracted with EtOAc (3X). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified flash column chromatography (0-50% EtOAc/hexanes) to afford the title compound as a pale yellow oil (3.89 g, 88.4% yield). ES-MS $[M+1]^+$: 220.0; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 3.7 Hz, 1H), 8.10 (ddd, J = 0.6, 2.5, 8.3 Hz, 1H), 5.12 (q, J = 6.4 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H).

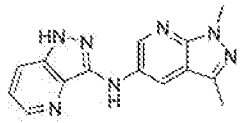


1-(5-bromo-2-fluoro-3-pyridyl)ethanone: To a solution of the above compound (3.15 g, 14.32 mmol, 1.0 eq.) in DCM (95.5 mL) and MeCN (9.5 mL) was added 4-methylmorpholine N-oxide (6.71 g, 57.26 mmol, 4.0 eq.) followed by tetrapropylammonium perruthenate (251.54 mg, 0.72 mmol, 0.5 eq.). The reaction mixture was stirred at rt until completion by TLC. The mixture was filtered through a pad

of Celite which was washed with DCM. Solvents were removed under reduced pressure. The crude residue was purified using flash chromatography (0-30% EtOAc/hexanes) to provide the title compound **(2)** as a white crystalline solid (2.19 g, 70.2% yield). TLC (25% EtOAc/hexanes): Rf = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.43 (m, 2H), 2.70 (d, J = 4.7 Hz, 3H).



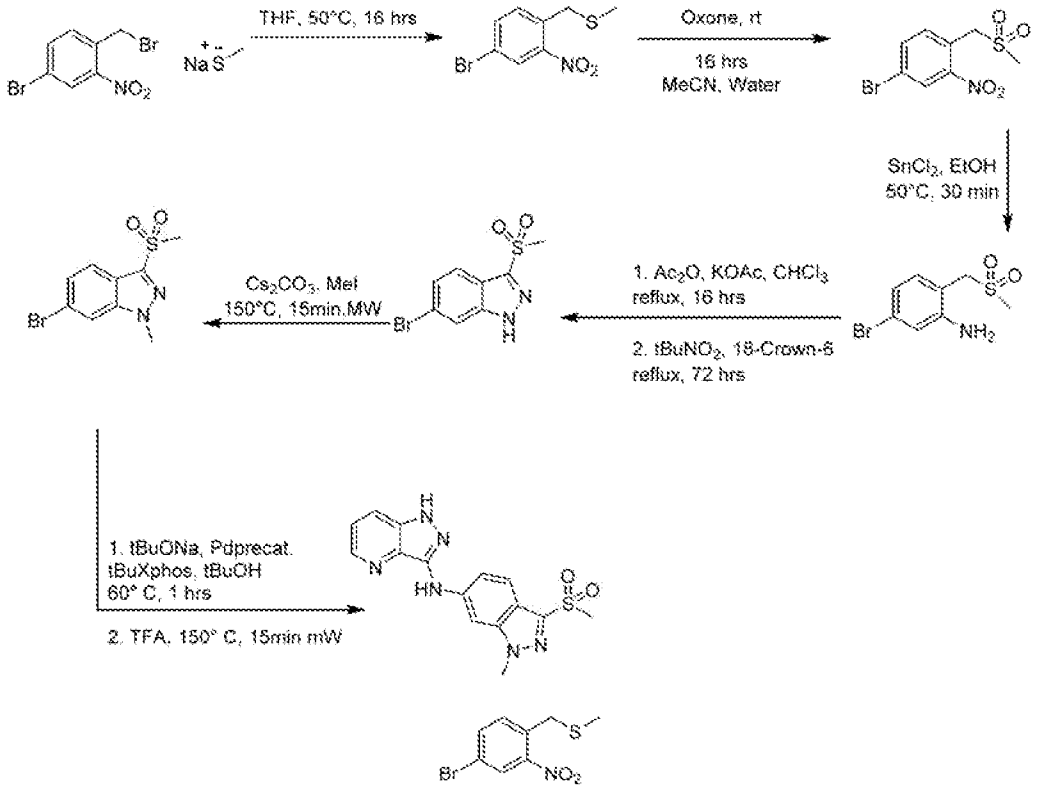
5-bromo-1,3-dimethyl-pyrazolo[3,4-b]pyridine: A solution of the above compound (160.0 mg, 0.73 mmol, 1.0 eq.) and methylhydrazine (193.2 uL, 3.67 mmol, 3.0 eq.) in 1-butanol (2.5 mL) was heated to 150 °C in a microwave reactor for 45 min. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified using flash chromatography (0-40% EtOAc/hexanes) to provide the title compound (3) as a pale yellow solid (150 mg, 90.4% yield). ES-MS $[M+1]^+$: 228.2.



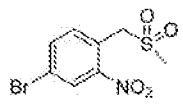
N-(1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine: 1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridin-3-amine (12.71 mg, 0.05 mmol, 1.0 eq.), (3) (33.91 mg, 0.15 mmol, 1.5 eq.), ^{t}BuXPhos (1 mol %), ^{t}BuXPhos Palladacycle (1mol%), NaO^{t}Bu (14.42 mg, 0.15 mmol, 1.5 eq), were charged into a microwave vial which was evacuated and back-filled with Argon (3X) then purged with a stream of Argon for 10 min. The reaction mixture was heated to 90 °C. After 45 min, the reaction was cooled to rt and partitioned between NH4Cl and EtOAc (1:1 v/v). The organic layer was separated. The aqueous layer was extracted with EtOAc (3X). The combined extracts were washed with water (2X), brine and dried (Na_2SO_4), filtered and concentrated under reduced pressure.

The crude residue was redissolved in TFA (0.1M) and subjected to microwave reactor at 150°C for 30 min. The solvent was removed and the crude residue was purified by reverse phase chromatography (Gilson HPLC, 11-43% acetonitrile:water w/0.1% TFA). Gilson fractions were neutralized with sat. soln $NaHCO_3$ and extracted with EtOAc (3X). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the title compound as a pale yellow solid (14.6 mg, 52% yield). ES-MS $[M+1]^+$: 280.2;

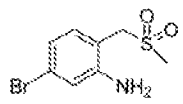
Scheme XI:



Sodium thiomethoxide (285 mg, 4.07 mmol) was added to a solution of 4-bromo-2-nitrobenzylbromide (1g, 3.39 mmol) in THF (20 mL). The rxn was heated to 50 °C for 16 h and concentrated under reduced pressure. The residue was suspended in $CHCl_3$ (50 mL) and filtered. The filtrate was concentrated to afford (4-bromo-2-nitrobenzyl)(methyl)sulfane.

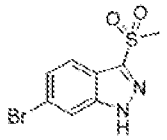


A solution of (4-bromo-2-nitrobenzyl)(methyl)sulfane (0.89g, 3.39 mmol) in MeCN (40 mL) was slowly added to a mixture of OXONE (14 g, 22.77 mmol) in water (32 mL). After 16 h at room temperature, the rxn was partitioned between EtOAc:water (1:1, 200 mL). The aqueous waste was extracted with EtOAc (2 x 200 mL). The organic layer was washed with water (2 x 100 mL) and brine (50 mL). Solvent was removed under reduced pressure to yield 4-bromo-1-(methylsulfonylmethyl)-2-nitro-benzene.

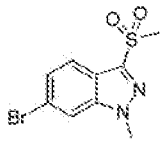


Stannous chloride (2.89 g, 15.26 mmol) was added to a solution of 4-bromo-1-(methylsulfonylmethyl)-2-nitro-benzene in ethanol (30 mL). In a nitrogen environment, the rxn was heated to 50 °C for 30 min. The solution changed from a cloudy suspension to a clear homogeneous solution. Solvent was removed

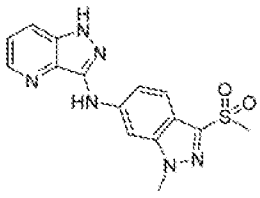
under reduced pressure. The resulting residue was suspended in DCM (400 mL) and 2M NaOH solution (60 mL). The solution was shaken vigorously, and DCM solution was collected as filtrate through a hydrophobic filter. The solvent was removed under reduced pressure to yield 5-bromo-2-(methylsulfonylmethyl)aniline (377.5 mg, 1.43mmol, 56.2%yield).



To a mixture of 5-bromo-2-(methylsulfonylmethyl)aniline (260 mg, 1.12 mmol) in $CHCl_3$ (8 mL) was added potassium acetate (110 mg, 1.12 mmol) and acetic anhydride (0.2 mL, 2.06 mmol). The rxn was refluxed under a nitrogen environment for 16h. To the rxn was added 18-crown-6 (260 mg, 0.980 mmol) and ^{t}butyl nitrite (0.35 mL, 2.94 mmol). After being refluxed for 72 h, the solvent was removed under reduced pressure. Fractions were separated via automated silica column chromatography (Biotage Isolera One) in a gradient of EtOAc (20-60%) in hexanes. Fractions were concentrated in an air concentrator to yield 6-bromo-3-(methylsulfonyl)-1H-indazole (111 mg, 0.400 mmol, 41.0%yield).

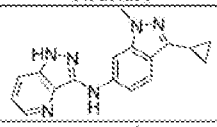
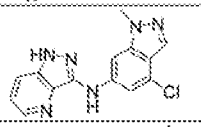
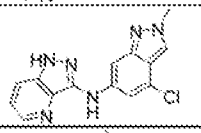
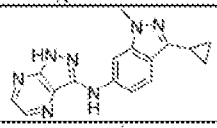
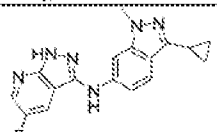
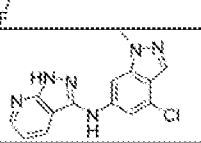
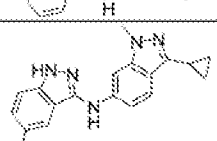
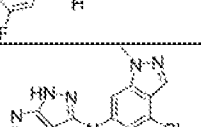


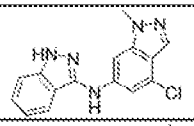
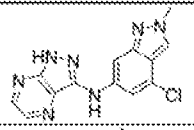
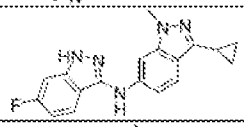
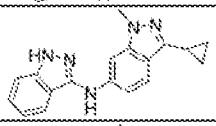
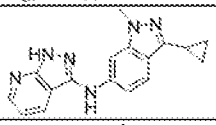
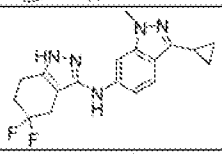
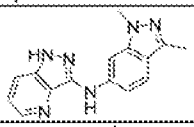
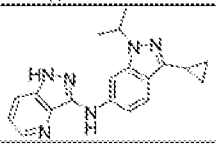
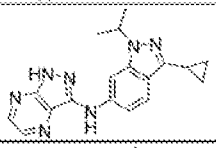
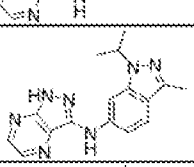
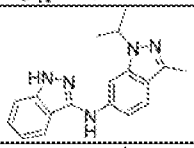
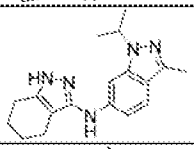
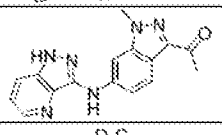
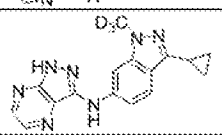
To a solution of 6-bromo-3-(methylsulfonyl)-1H-indazole (111 mg, 0.403 mmol) and cesium carbonate (293 mg, 0.810 mmol) in DMF (3 mL) was added iodomethane (0.04 mL, 0.610 mmol). After 30 min at 100°C, the rxn was cooled to rt and added to a mixture of water:EtOAc (3:1, 20 mL) and saturated NH_4Cl(aq) (3 mL). The organic layer was washed with water (15 mL). The aqueous layer was extracted with EtOAc (5 x 25 mL). Organic extractions were combined, and solvent was removed under reduced pressure to yield 6-bromo-1-methyl-3-methylsulfonyl-indazole (116 mg, 0.400 mmol, 99.4%yield).

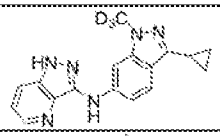
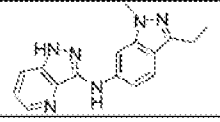
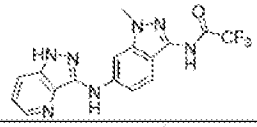
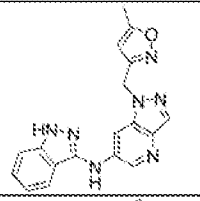
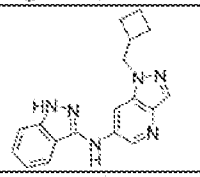
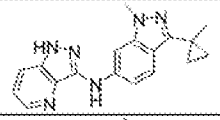
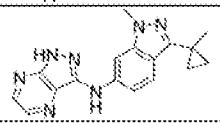
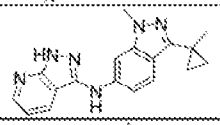
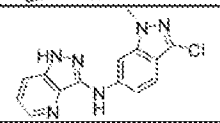
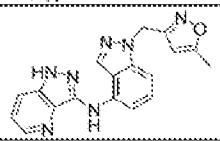
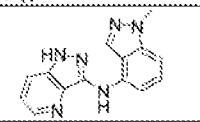
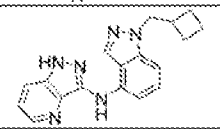
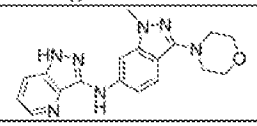


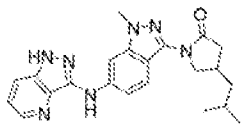
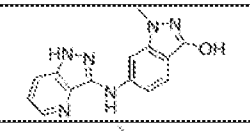
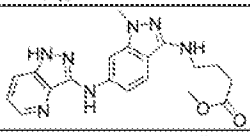
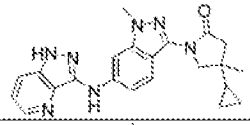
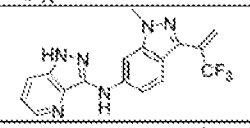
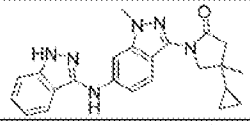
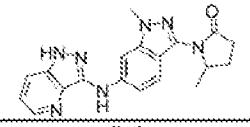
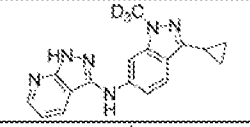
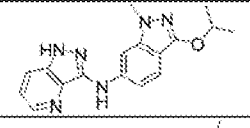
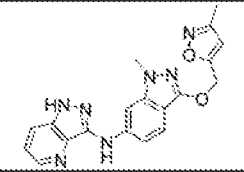
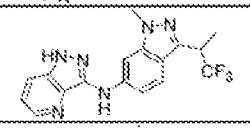
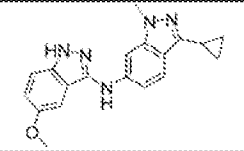
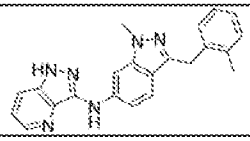
To a rxn vial was added 6-bromo-1-methyl-3-methylsulfonyl-indazole (30 mg, 0.100 mmol), $_t$BuONa (24 mg, 0.250 mmol), 1-[(4-methoxyphenyl)methyl]pyrazolo[4,3-b]pyridine-3-amine (29 mg, 0.114 mmol), $_t$butylXPhos (0.44 mg, 0.001 mmol), and $_t$butylXPhos-palladacycle (0.71 mg, 0.001 mmol). The rxn vial was purged and backfilled with nitrogen 3X. To the rxn was added $_t$BuOH (1 mL). After 30 min at 60°C, the rxn was added to a mixture of water:EtOAc (1:1, 20 mL). The aqueous layer was

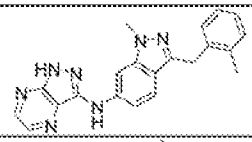
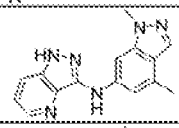
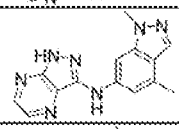
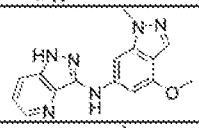
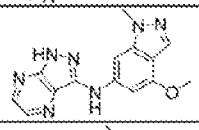
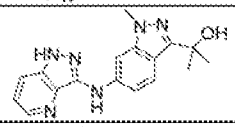
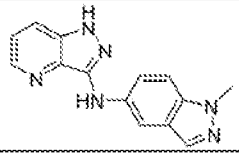
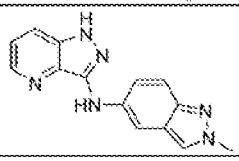
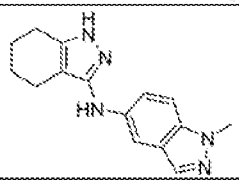
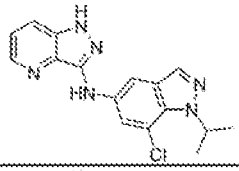
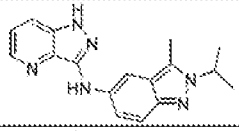
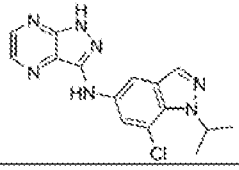
extracted with EtOAc (5 x 50 mL). Organic layers were washed with water (2 x 20 mL) and concentrated under reduced pressure. The residue was dissolved in TFA (2 mL) and transferred to a microwave vial, and the solution was heated to 150°C for 15 min in MW. Solvent was removed under reduced pressure, and residue was dissolved in DMSO. Fractions were separated by reverse phase HPLC in a gradient of MeCN (20-60%) in water (0.1%TFA). Fractions were combined and added to a mixture of water:EtOAc (1:1, 20 mL) and saturated $NaHCO_3$(aq) (1 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the organic layers were washed with water (1 x 10 mL). Organic layers were combined, and solvent was removed under reduced pressure. The residue was dissolved in DCM:MeOH (5:1, 2.5 mL) and filtered through a hydrophobic filter. Filtrate was collected and concentrated in an air concentrator to yield N-(1-methyl-3-(methylsulfonyl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine (11.3 mg, 0.030 mmol, 31.8%yield) as a yellow-green solid.

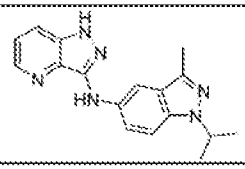
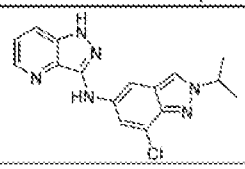
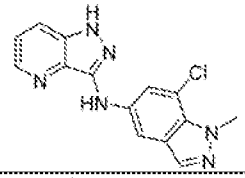
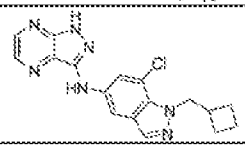
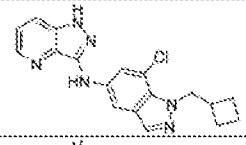
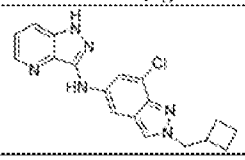
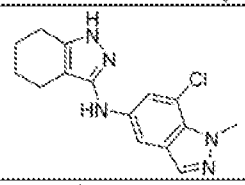
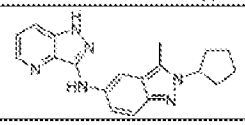
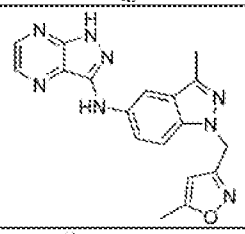
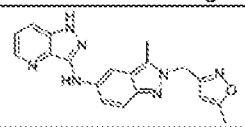
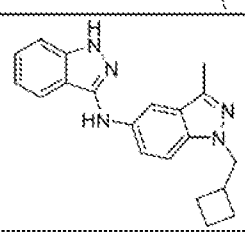
Example	Structure	Name	LCMS	Scheme
1		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.786 min, M+H=305.2; >98% @ 215 and 254 nm";1H NMR (d-DMSO): >95%	III
2		N-(4-chloro-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.821 mm, M+H=299.1; >98% @ 215 and 254 nm	VI
3		N-(4-chloro-2-methyl-2H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.739 min, M+H=299.1; >98% @ 215 and 254 nm	VI
4		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.851 min, M+H=306.1; >98% @ 215 and 254 nm";1H NMR (d-DMSO): >95%	III
5		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.911 min, M+H=323.1; >98% @ 215 and 254 nm	III
6		N-(4-chloro-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.838 min, M+H=299.1; >98% @ 215 and 254 nm	VI
7		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-5-fluoro-1H-indazol-3-amine	Rt=0.972 min, M+H=322.2; >98% @ 215 and 254 nm	III
8		N-(4-chloro-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.874 min, M+H=300.1; >98% @ 215 and 254 nm	VI

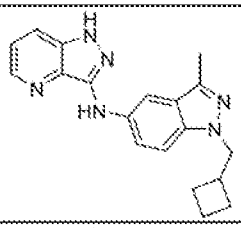
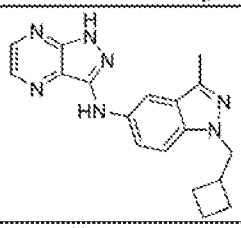
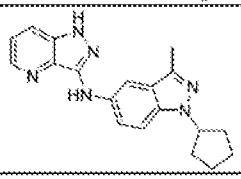
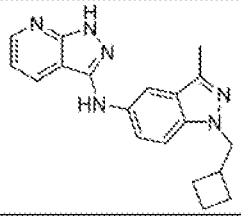
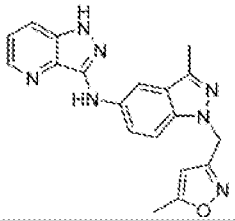
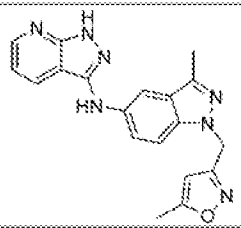
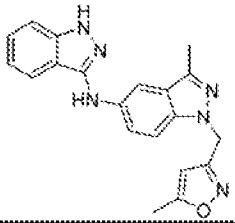
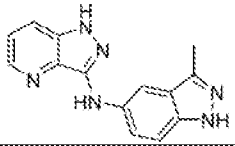
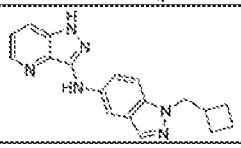
9		N-(4-chloro-1-methyl-1H-indazol-6-yl)-1H-indazol-3-amine	Rt=0.985 min, M+H=298.1; >98% @ 215 and 254 nm	VI
10		N-(4-chloro-2-methyl-2H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.793 min, M+H=300.1; >98% @ 215 and 254 nm	VI
11		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-6-fluoro-1H-indazol-3-amine	Rt=0.974 min, M+H=322.1; >92% @ 215 and >96% @ 254 nm	III
12		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-1H-indazol-3-amine	Rt=0.944 min, M+H=304.1; >98% @ 215 and 254 nm	III
13		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.818 min, M+H=305.2; >98% @ 215 and 254 nm";1H NMR (d-DMSO): >95%	III
14		3-cyclopropyl-N-(5,5-difluoro-4,5,6,7-tetrahydro-1H-indazol-3-yl)-1-methyl-1H-indazol-6-amine	254 nm: 100%;RT: 0.882,M+H: 344.2	III
15		N-(1,3-dimethyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.652 min, M+H=279.1; >98% @ 215 and 254 nm	III
16		N-(3-cyclopropyl-1-isopropyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.889 min, M+H=333.2; >98% @ 215 and 254 nm	X
17		N-(3-cyclopropyl-1-isopropyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.934 min, M+H=334.2; >98% @ 215 and 254 nm	X
18		N-(1-isopropyl-3-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.830 min, M+H=308.2; >98% @ 215 and 254 nm	X
19		N-(1-isopropyl-3-methyl-1H-indazol-6-yl)-1H-indazol-3-amine	Rt=0.920 min, M+H=306.2; >98% @ 215 and 254 nm	X
20		1-isopropyl-3-methyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-indazol-6-amine	Rt=0.863 min, M+H=310.2; >98% @ 215 and 254 nm	X
21		1-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)ethan-1-one	Rt=0.770 min, M+H=307.1; >98% @ 254 nm	X
22		N-(3-cyclopropyl-1-(methyl-d3)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.854 min, M+H=309.2; >98% @ 215 and 254 nm	VI

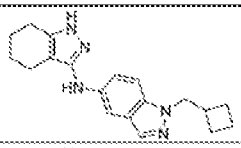
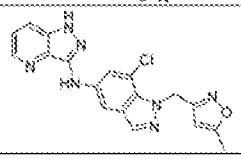
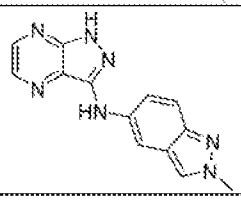
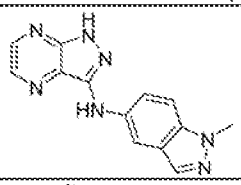
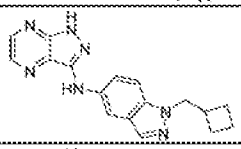
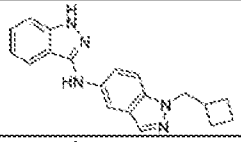
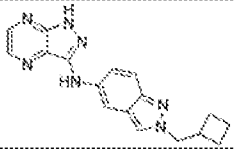
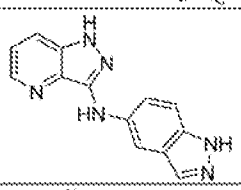
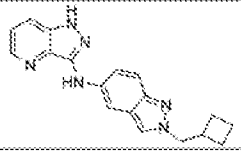
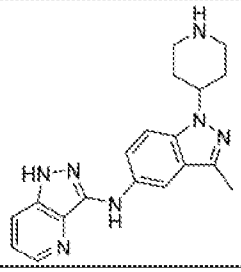
23		N-(3-cyclopropyl-1-(methyl-d3)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.812 min, M+H=308.2; >98% @ 215 and 254 nm	VI
24		N-(3-ethyl-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.745 min, M+H=293.1; >98% @ 215 and 254 nm	VI
25		N-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoroacetamide	254 nm: >95%;R.T: 0.765;M+H: 376.1	VIII
26		N-(1H-indazol-3-yl)-1-((5-methylisoxazol-3-yl)methyl)-1H-pyrazolo[4,3-b]pyridin-6-amine	Rt=0.806min, m+H=346.1, >98%@215and 254nm	VI
27		1-(cyclobutylmethyl)-N-(1H-indazol-3-yl)-1H-pyrazolo[4,3-b]pyridin-6-amine	Rt=0.886min, m+H=319.2, >98%@215 and 254nm	VI
28		N-(1-methyl-3-(1-methylcyclopropyl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.882 min, M+H=319.1; >98% @ 215 and 254 nm	X
29		N-(1-methyl-3-(1-methylcyclopropyl)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.918 min, M+H=320.2; >98% @ 215 and 254 nm	X
30		N-(1-methyl-3-(1-methylcyclopropyl)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.881 min, M+H=319.2; >98% @ 215 and 254 nm	X
31		N-(3-chloro-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.844min, m+H=299.1, >98%@215 and 254nm	VI
32		N-(1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-4-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.785 min, m+H=346.1, >95%@215 and 254nm	VI
33		N-(1-methyl-1H-indazol-4-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.700min, m+H=265.1, >98%@216 and 254nm	VI
34		N-(1-(cyclobutylmethyl)-1H-indazol-4-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.940min, m+H=319.2, >98%@215 and 254nm;1H NMR: (d-DMSO) >90%	VI
35		N-(1-methyl-3-morpholino-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	254 nm: >95%;R.T: 0.734;M+H: 350.1	IX

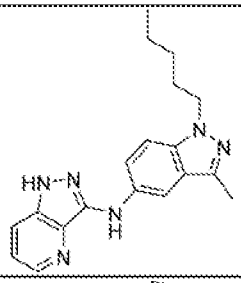
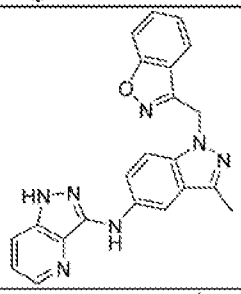
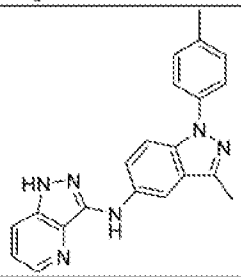
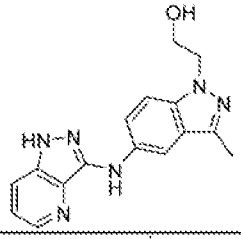
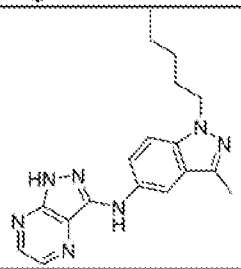
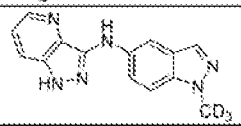
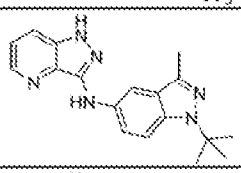
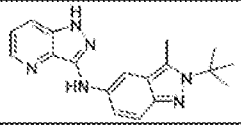
36		1-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)-4-isobutylpyrrolidin-2-one	Rt=0.996 min, M+H=404.2; >98% @ 215 and 254 nm	IV
37		6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-ol	Rt=0.179min, M+H=281.1; >98% @ 215 and 254 nm	II
38		methyl 4-((6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)amino)butanoate	Rt=0.739 min, M+H=380.1; >98% @ 215 and 254 nm	IV
39		1-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)-4-cyclopropyl-4-methylpyrrolidin-2-one	Rt=0.923 min, M+H=402.1; >98% @ 215 and 254 nm	IV
40		N-(1-methyl-3-(3,3,3-trifluoroprop-1-en-2-yl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	254 nm: >95%;RT: 1.004;M+H: 358.8	V
41		1-(6-((1H-indazol-3-yl)amino)-1-methyl-1H-indazol-3-yl)-4-cyclopropyl-4-methylpyrrolidin-2-one	Rt=1.048 min, M+H=401.1; >98% @ 215 and 254 nm	IV
42		1-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)-5-methylpyrrolidin-2-one	Rt=0.710 min, M+H=362.2; >95% @ 215 and 254 nm	IV
43		N-(3-cyclopropyl-1-(methyl-d3)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.832min, m+H=308.2, >98%@215 and 254 nm (low absorbance at 215nm)	X
44		N-(3-isopropoxy-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.926 min, M+H=323.1; >98% @ 215 and 254 nm	II
45		N-(1-methyl-3-((3-methylisoxazol-5-yl)methoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.872 min, M+H=376.1; >98% @ 215 and 254 nm	II
46		N-(1-methyl-3-(1,1,1-trifluoropropan-2-yl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	254 nm. >95%;RT: 0.929;M+H: 361.1	V
47		N-(3-cyclopropyl-1-methyl-1H-indazol-6-yl)-5-methoxy-1H-indazol-3-amine	Rt=0.957 min, m+H=334.2, >98%@215 and 254nm	III
48		N-(1-methyl-3-(2-methylbenzyl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.959 min, M+H=369.2; >98% @ 215 and 254 nm	III

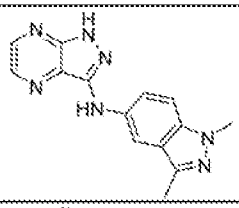
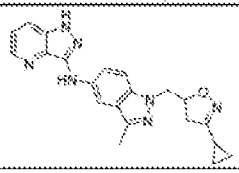
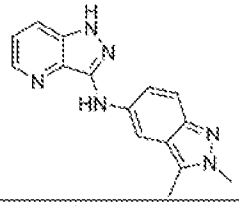
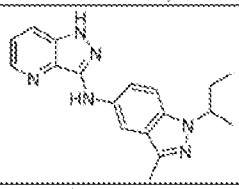
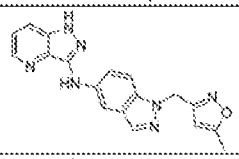
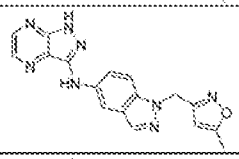
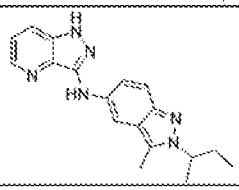
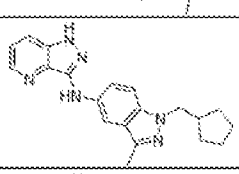
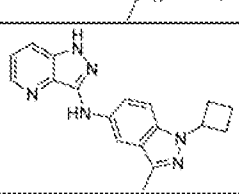
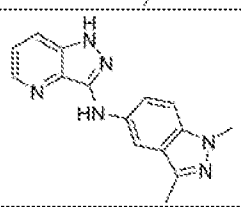
49		N-(1-methyl-3-(2-methylbenzyl)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=1.018 min, M+H=370.1; >98% @ 215 and 254 nm";1H NMR (CD3OD): >95%	III
50		N-(1,4-dimethyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.751 min, m+H=279.1, >98%@215 and 254nm	III
51		N-(1,4-dimethyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS:Rt=0.761min, m+H=280.1, >98%@215 and 254nm	III
52		N-(4-methoxy-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.792min, m+H=295.1, >98%@215 and 254nm,1H NMR: (d-DMSO) >95%	III
53		N-(4-methoxy-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.754min, m+H=296.1, >98%@215 and 254nm	III
54		2-(6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)propan-2-ol	Rt=0.764 min, M+H=323.1; >98% @ 215 and 254 nm	VII
55		N-(1-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.543min, m+H=265.1, >98%@215 and 254nm	VI
56		N-(2-methyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.156 min, M+H=265.1; >98% @ 215 and 254 nm	VI
57		1-methyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-indazol-5-amine	Rt=0.730 min, M+H=268.2; >98% @ 215 and 254 nm	VI
58		N-(7-chloro-1-isopropyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.968 min, M+H=327.1; >98% @ 215 and 254 nm	VI
59		N-(2-isopropyl-3-methyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.724 min, M+H=307.0; >98% @ 215 and 254 nm	VI
60		N-(7-chloro-1-isopropyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=1.009 min, M+H=328.1; >98% @ 215 and 254 nm	VI

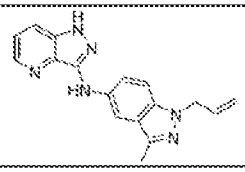
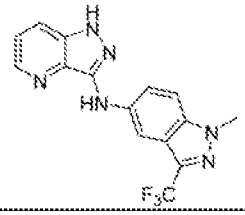
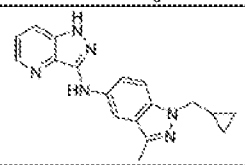
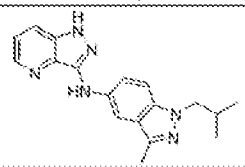
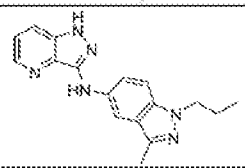
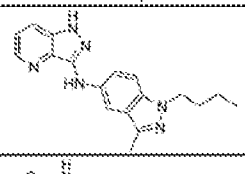
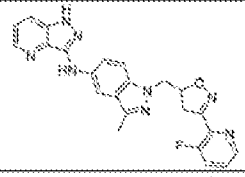
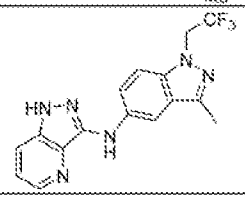
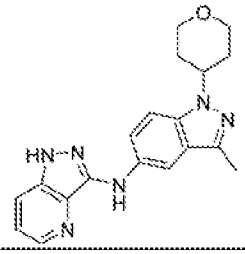
61		N-(1-isopropyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.782 min, M+H=307.1; >98% @ 215 and 254 nm	VI
62		N-(7-chloro-2-isopropyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.823 min, M+H=327.1; >98% @ 215 and 254 nm	VI
63		N-(7-chloro-1-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.811min, m+H=299.1, >97%@215 and 254nm	VI
64		N-(7-chloro-1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=1.095min, m+H=354.1, >98%@215 and 254nm	VI
65		N-(7-chloro-1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=1.051min, m+H=353.1, >97%@215 and 254nm	VI
66		N-(7-chloro-2-(cyclobutylmethyl)-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.930min, m+H=353.1, >98%@215 and 254nm	VI
67		7-chloro-1-methyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-indazol-5-amine	Rt=0.839min, m+H=302.1, >98%@215 and 254nm	VI
68		N-(2-cyclopentyl-3-methyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.759 min, M+H=333.2; >98% @ 215 and 254 nm	VI
69		N-(3-methyl-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.841 min, M+H=361.1; >98% @ 215 and 254 nm	VI
70		N-(3-methyl-2-((5-methylisoxazol-3-yl)methyl)-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.727 min, M+H=360.1; >98% @ 215 and 254 nm	VI
71		N-(1-(cyclobutylmethyl)-3-methyl-1H-indazol-5-yl)-1H-indazol-3-amine	Rt=1.039 min, M+H=332.2; >92% @ 215 and >98% @ 254 nm	VI

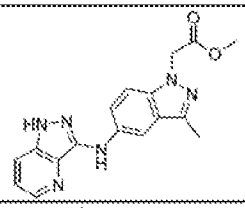
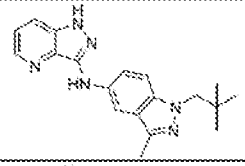
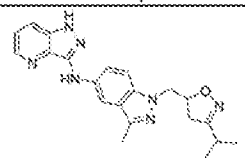
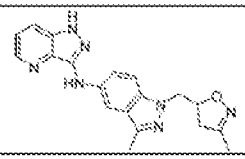
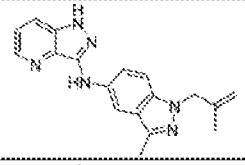
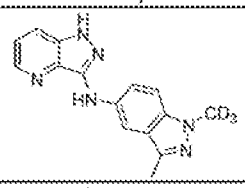
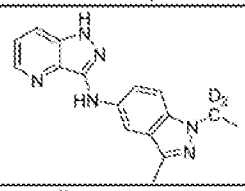
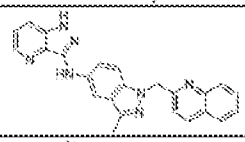
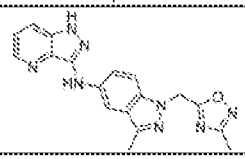
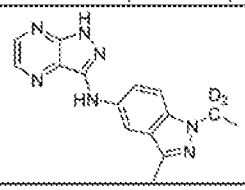
72		N-(1-(cyclobutylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.912 min, M+H=333.2; >98% @ 215 and 254 nm	VI
73		N-(1-(cyclobutylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.966 min, M+H=334.2; >98% @ 215 and 254 nm	VI
74		N-(1-cyclopentyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.934 min, M+H=333.2; >91% @ 215 and >94% @ 254 nm	VI
75		N-(1-(cyclobutylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.909 min, M+H=333.2; >97% @ 215 and 254 nm	VI
76		N-(3-methyl-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.780 min, M+H=360.1; >98% @ 215 and 254 nm	VI
77		N-(3-methyl-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.775 min, M+H=360.1; >98% @ 215 and 254 nm	VI
78		N-(3-methyl-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-indazol-3-amine	Rt=0.933 min, M+H=359.1; >98% @ 215 and 254 nm	VI
79		N-(3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.434 min, M+H=265.1; >98% @ 215 and 254 nm	VI
80		N-(1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.903min, m+H=319.2, >98%@215 and 254nm	VI

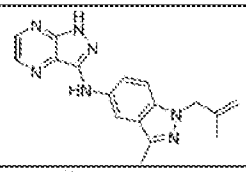
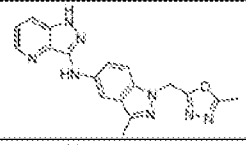
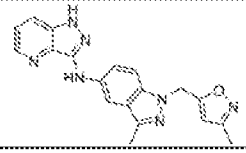
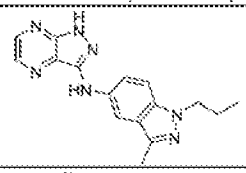
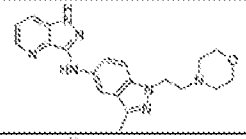
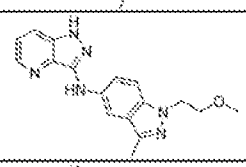
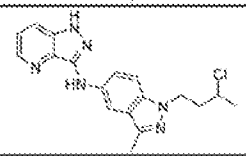
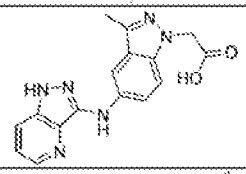
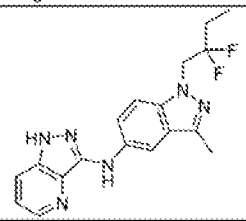
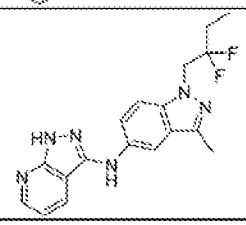
81		1-(cyclobutylmethyl)-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-indazol-5-amine	Rt=0.908min, m+H=322.2, >98%@215 and 254nm	VI
82		N-(7-chloro-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.871min, m+H=380.1, >98%@215 and 254nm	VI
83		N-(2-methyl-2H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.587min, m+H=266.2, >92%@215 and 254nm	VI
84		N-(1-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.718min, m+H=266.1, >98%@254nm	VI
85		N-(1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.956min, m+H=320.2, >95%@254nm	VI
86		N-(1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-indazol-3-amine	Rt=1.028min, m+H=318.2, >97%@215 and 254nm	VI
87		N-(2-(cyclobutylmethyl)-2H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.852min, m+H=320.2, >90%@215 and 254nm	VI
88		N-(1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.517min, m+H=251.1, >95%@215 and 254nm	VI
89		N-(3-(cyclobutylmethyl)-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.796min, m+H=319.2, >98%@215 and 254nm	VI
90		N-(3-methyl-1-(piperidin-4-yl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.617 min, M+H=348.2; >97% @ 215 and >98% @ 254 nm	VI

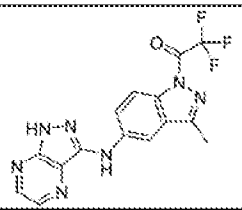
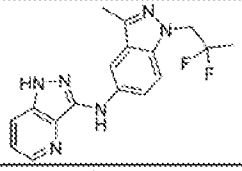
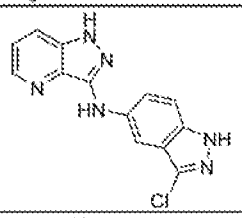
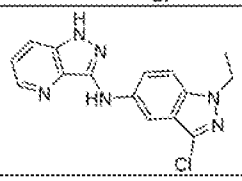
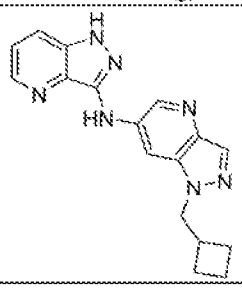
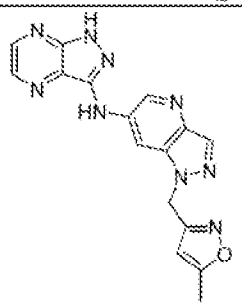
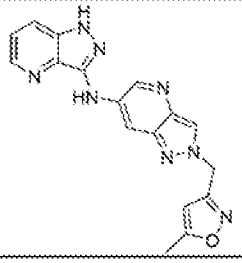
91		N-(3-methyl-1-pentyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.963 min. M+H=335.2; >98% @ 215 and 254 nm	VI
92		N-(1-(benzo[d]isoxazol-3-ylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.912 min. M+H=396.1; >98% @ 215 and 254 nm	VI
93		N-(3-methyl-1-(p-tolyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=1.015, M+H=355.1; >98% @ 215 and 254 nm	VI
94		2-(5-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-3-methyl-1H-indazol-1-yl)ethan-1-ol	Rt=0.630 min, M+H=309.2; >93% @ 215 and >92% @ 254 nm	VI
95		N-(3-methyl-1-pentyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=1.018 min. M+H=336.2; >98% @ 215 and 254 nm	VI
96		N-(1-(methyl-d3)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.651mm. m+H=268.2, >98%@215 and 254 nm	VI
97		N-(1-(tert-butyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.900 min, M+H=321.2; >98% @ 215 and 254 nm	VI
98		N-(2-(tert-butyl)-3-methyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.722 min. M+H=321.2; >98% @ 215 and 254 nm	VI

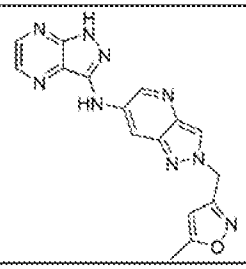
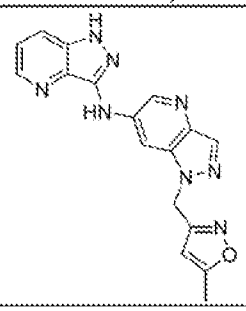
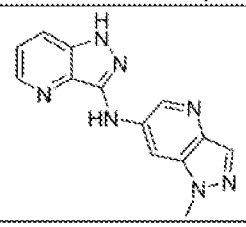
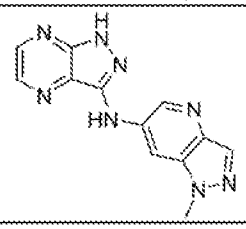
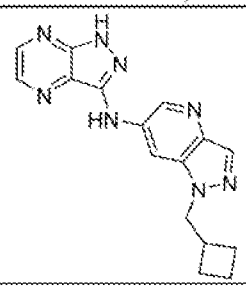
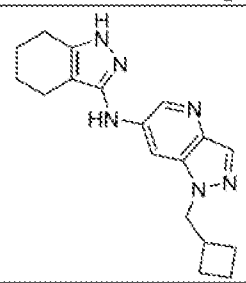
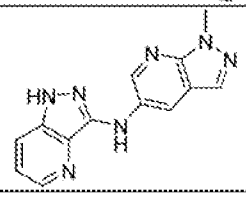
99		N-(1,3-dimethyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.752min, m+H=280.2, >98%@215 and 254nm	VI
100		N-(1-((3-cyclopropyl-4,5-dihydroisoxazol-5-yl)methyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.771min, m+H=388.1, >95%@215 and 254nm	VI
101		N-(2,3-dimethyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.114min, m+H=279.1, >98%@215 and 254nm	VI
102		N-(1-(sec-butyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.867min, m+H=321.2, >98%@215 and 254nm	VI
103		N-(1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.774 min, m+H=346.1, >98%@215 and 254nm	VI
104		N-(1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.808min, m+H=347.1, >98%@215 and 254nm	VI
105		N-(2-(sec-butyl)-3-methyl-2H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.735min, m+H=321.2, >95%@215 and 254nm	VI
106		N-(1-(cyclopentylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.969min, m+H=347.2, >98%@215 and 254nm	VI
107		N-(1-cyclobutyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.874min, m+H=319.2, >98%@215 and 254nm	VI
108		N-(1,3-dimethyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.582min, m+H=279.2, >98%@215 and 254 nm	VI

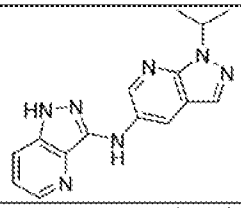
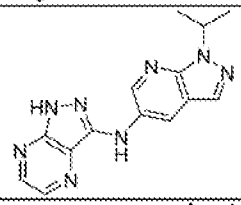
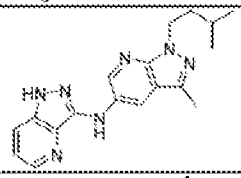
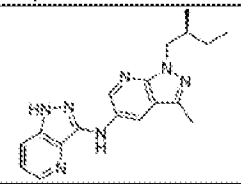
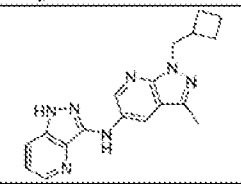
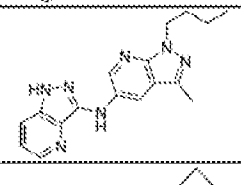
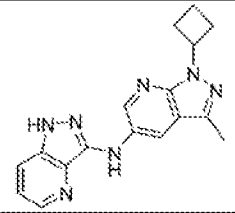
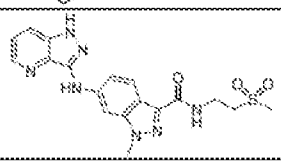
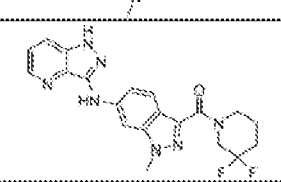
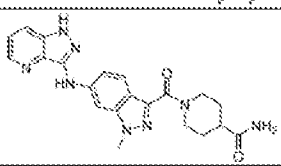
109		N-(1-allyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.794min, m+H=305.1, >95%@215 and 254nm	VI
110		N-(1-methyl-3-(trifluoromethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.886min, m+H=333.1, >98%@215 and 254 nm	VI
111		N-(1-(cyclopropylmethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.827min, m+H=319.2, >98%@215 and 254nm	VI
112		N-(1-isobutyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.884min, m+H=321.2, >95%@215 and 254 nm	VI
113		N-(3-methyl-1-propyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.812 min, m+H=307.1, >98%@215 and 254nm	VI
114		N-(1-butyl-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.891 min, m+H=321.2, >98%@215 and 254nm	VI
115		N-(1-((3-(3-fluoropyridin-2-yl)-4,5-dihydroisoxazol-5-yl)methyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.808min, m+H=443.1, 90%@215 and 254nm	VI
116		N-(3-methyl-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.782 min, M+H=347.2; >98% @ 215 and 254 nm	VI
117		N-(3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.713 min, M+H=349.1; >98% @ 215 and 254 nm	VI

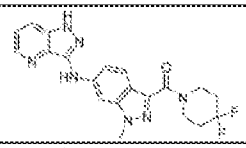
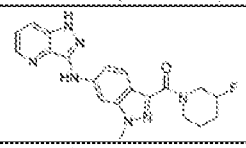
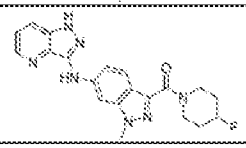
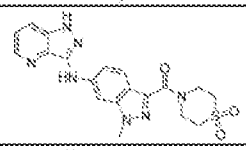
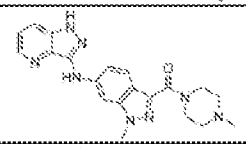
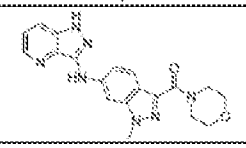
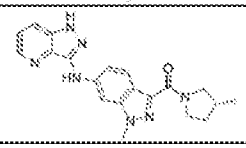
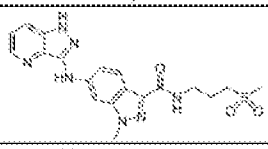
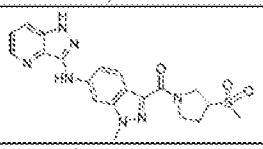
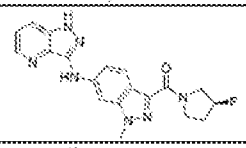
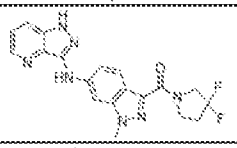
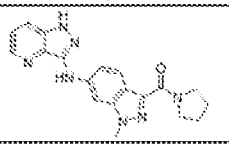
118		methyl 2-(5-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-3-methyl-1H-indazol-1-yl)acetate	Rt=0.685 mm, M+H=337.1; >98% @ 215 and 254 nm	VI
119		N-(3-methyl-1-neopentyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.949min, m+H=335.3, >98%@215 and 254nm	VI
120		N-(1-((3-isopropyl-4,5-dihydroisoxazol-5-yl)methyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.816min, m+H=390.2, >95%@215 and 254nm	VI
121		N-(3-methyl-1-((3-methyl-4,5-dihydroisoxazol-5-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.713min, m+H=362.1, >98%@215 and 254nm	VI
122		N-(3-methyl-1-(2-methylallyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.858min, m+H=319.1, >98%@215 and 254nm;1H NMR: (CDCl3) >95%	VI
123		N-(3-methyl-1-(methyl-d3)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.657min, m+H=282.2, >98%@215 and 254	VI
124		N-(1-(ethyl-1,1-d2)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.759min, m+H=295.1, >98%@215and 254nm	VI
125		N-(3-methyl-1-(quinolin-2-ylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.796min, m+H=406.1, >98%@215 and 254nm	VI
126		N-(3-methyl-1-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.695min, m+H=361.1, >98%@215 and 254nm	VI
127		N-(1-(ethyl-1,1-d2)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.804min, m+H=296.2, >93%@215 and 254nm	VI

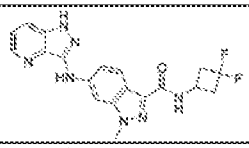
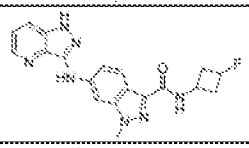
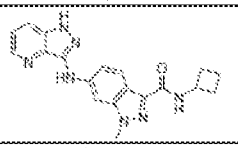
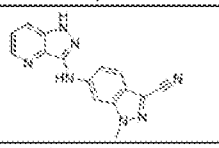
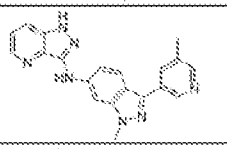
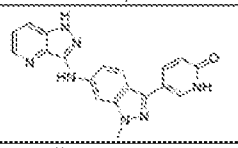
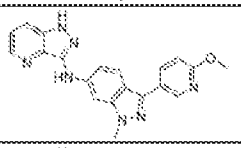
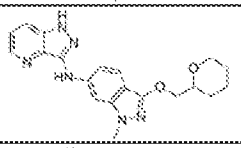
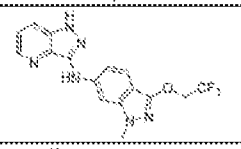
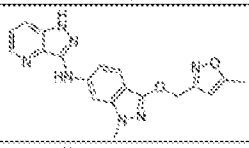
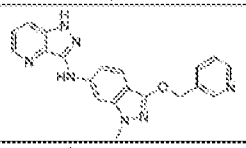
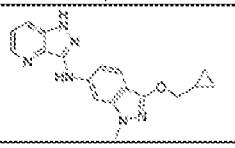
128		N-(3-methyl-1-(2-methylallyl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.898min, m+H=320.2, >94%@215 and 254nm	VI
129		N-(3-methyl-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.678min, m+H=361.1, >98%@215 and 254nm	VI
130		N-(3-methyl-1-((3-methylisoxazol-5-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.769min, m+H=360.1, >98%@215 and 254nm	VI
131		N-(3-methyl-1-propyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.869min, m+H=308.2, >98%@215 and 254nm	VI
132		N-(3-methyl-1-(2-morpholinoethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.614min, m+H=378.1, >98%@215 and 254nm	VI
133		N-(1-(2-methoxyethyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.721min, m+H=323.1, >98%@215 and 254nm	VI
134		N-(1-(3-chlorobutyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.920min, m+H=355.1, >95%@215 and 254nm	VI
135		2-(5-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-3-methyl-1H-indazol-1-yl)acetic acid	Rt=0.641 min, M+H=323.1; >98% @ 215 and 254 nm	VI
136		N-(1-(2,2-difluorobutyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.896 min, M+H=357.1; >97% @ 215 and 254 nm	VI
137		N-(1-(2,2-difluorobutyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	Rt=0.891 min, M+H=357.1; >95% @ 215 and 254 nm	VI

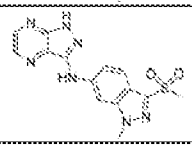
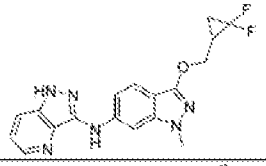
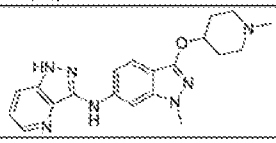
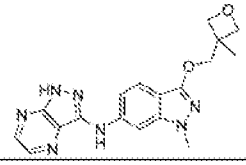
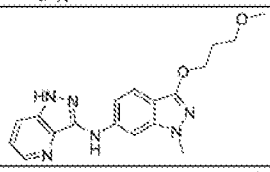
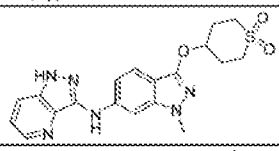
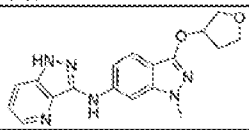
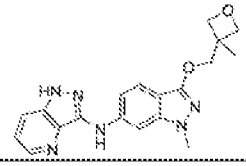
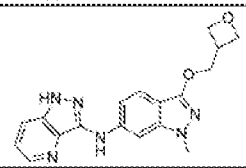
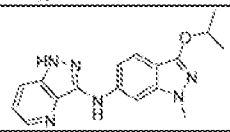
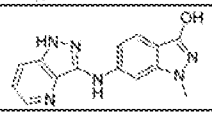
138		1-(5-((1H-pyrazolo[3,4-b]pyrazin-3-yl)amino)-3-methyl-1H-indazol-1-yl)-2,2,2-trifluoroethan-1-one	Rt=0.832 min, M+H=362.0; >98% @ 215 and 254 nm	VI
139		N-(1-(2,2-difluoropropyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.819 min, M+H=343.1; >98% @ 215 and 254 nm	VI
140		N-(3-chloro-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.706min, m+H=285.1, >98%@215 and 254nm	VI
141		N-(3-chloro-1-ethyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.856min, m+H=313.1, >98%@215 and 254nm	VI
142		N-(1-(cyclobutylmethyl)-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.735min, m+H=320.2, >98%@215 and 254nm	VI
143		N-(1-((5-methylisoxazol-3-yl)methyl)-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.121min, m+H=348.1, >98%@215 and 254nm	VI
144		N-(2-((5-methylisoxazol-3-yl)methyl)-2H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.608min, m+H=347.1, >98%@215 and 254nm	VI

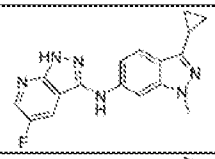
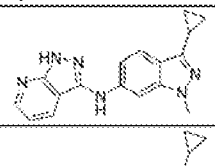
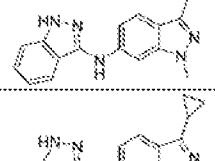
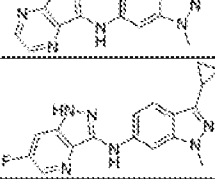
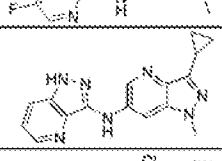
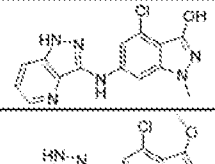
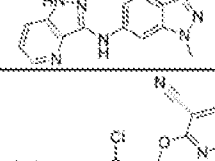
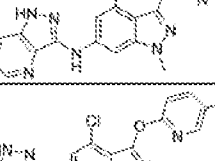
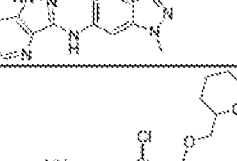
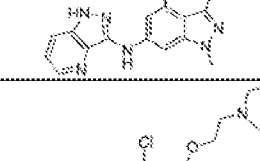
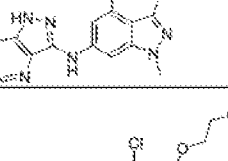
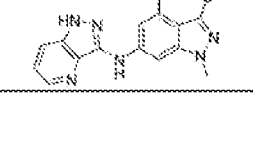
145		N-(2-((5-methylisoxazol-3-yl)methyl)-2H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.117min, m+H=348.1, >98%@215 and 254nm	VI
146		N-(1-((5-methylisoxazol-3-yl)methyl)-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.610min, m+H=347.1, >98%@215 and 254nm	VI
147		N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.476 min, m+H=266.2, >98%@215 and 254nm	VI
148		N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.102min, m+H=267.1, >98%@215 and 254nm	VI
149		N-(1-(cyclobutylmethyl)-1H-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.777min, m+H=321.1, >98%@215 and 254nm	VI
150		1-(cyclobutylmethyl)-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-pyrazolo[4,3-b]pyridin-6-amine	Rt=0.842min, m+H=323.2, >98%@215 and 254nm	VI
151		N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.577 min, M+H=266.1; >98% @ 215 and 254 nm	X

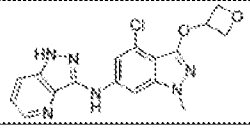
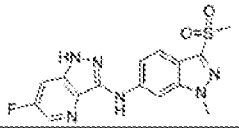
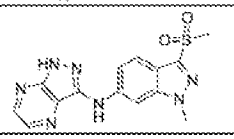
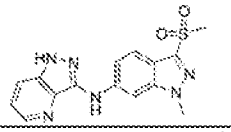
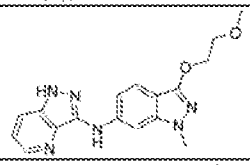
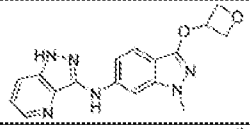
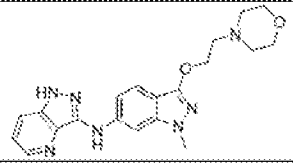
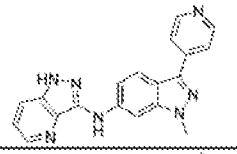
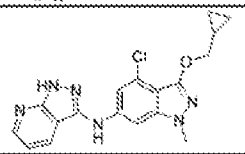
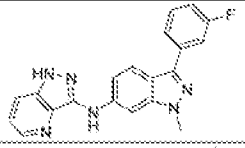
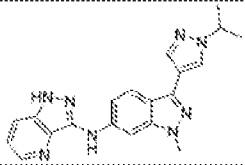
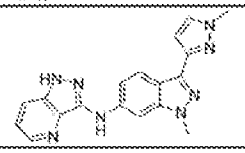
152		N-(1-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	Rt=0.752 min, M+H=294.2; >98% @ 215 and 254 nm	X
153		N-(1-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	Rt=0.805 min, M+H=295.1; >98% @ 215 and 254 nm	X
154		1-isopentyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.918 min, M+H=336.4, >98% at 215 nm and 254 nm	X
155		3-methyl-1-[(2S)-2-methylbutyl]-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.906 min, M+H=336.4, >98% at 215 nm and 254 nm	X
156		1-(cyclobutylmethyl)-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.869 min, M+H=334.4.2, >98% at 215 nm and 254 nm	X
157		1-(cyclobutylmethyl)-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.869 min, M+H=334.4.2, >98% at 215 nm and 254 nm	X
158		1-cyclobutyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS: Rt=0.817 min, M+H=320.4; >98% @ 215 and 254 nm	X
159		1-methyl-N-(2-methylsulfonylethyl)-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carboxamide	LCMS (90 second Method): RT = 0.624 min, M+H=414.2, >98% at 215 and 254 nm	1
160		(3,3-difluoro-1-piperidyl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.814 min, M+H=414.3, >98% at 215 and 254 nm	1
161		1-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carbonyl]piperidine-4-carboxamide	LCMS (90 second Method): RT = 0.586 min, M+H=419.2, >98% at 215 and 254 nm	1

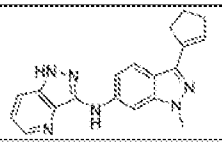
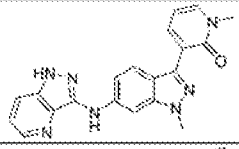
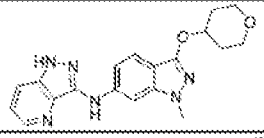
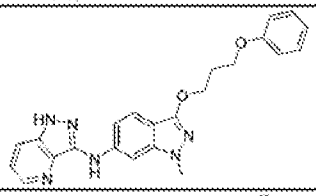
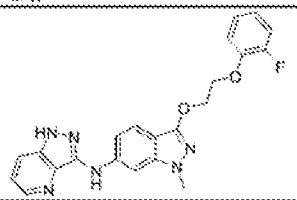
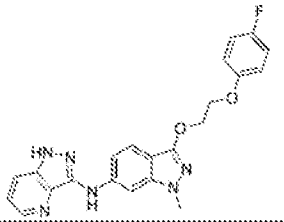
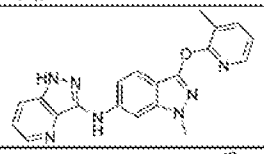
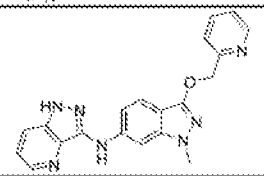
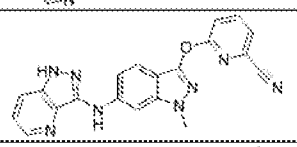
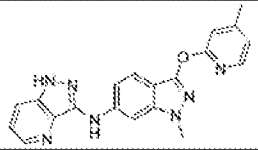
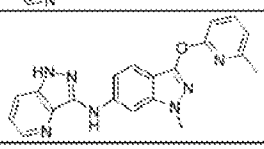
162		(4,4-difluoro-1-piperidyl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.835 min, M+H=412.3, >98% at 215 nm	1
163		(3-fluoro-1-piperidyl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.756 min, M+H=394.2, >97% at 215 and 254 nm	1
164		(4-fluoro-1-piperidyl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.766 min, M+H=394.3, >97% at 215 nm	1
165		(1,1-dioxo-1,4-thiazinan-4-yl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.652 min, M+H=426.2, >95% at 215 nm; 1H-NMR (400 MHz, DMSO-d6): verified, >95%	1
166		(4-methylpiperazin-1-yl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.531 min, M+H=391.3, >98% at 215 nm	1
167		[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]-morpholino-methanone	LCMS (90 second Method): RT = 0.666 min, M+H=378.3, >97% at 215 nm	1
168		[(3R)-3-fluoropyrrolidin-1-yl]-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.742 min, M+H=380.3, >92% at 215 and >93% at 254 nm	1
169		1-methyl-N-(3-methylsulfonylpropyl)-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carboxamide	LCMS (90 second Method): RT = 0.632 min, M+H=428.2, >98% at 215 and 254 nm	1
170		[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]-(3-methylsulfonylpyrrolidin-1-yl)methanone	LCMS (90 second Method): RT = 0.647 min, M+H=440.3, >92% at 215 nm	1
171		[(3S)-3-fluoropyrrolidin-1-yl]-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second Method): RT = 0.741 min, M+H=380.3, >92% at 215 nm	1
172		(3,3-difluoropyrrolidin-1-yl)-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]methanone	LCMS (90 second method): RT = 0.833 min, M+H=398.3.2, >92% at 215 nm ; 1H-NMR (400 MHz, DMSO-d6): verified, >92%	1
173		[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]-pyrrolidin-1-yl-methanone	LCMS: Rt=0.769 min, M+H=362.3; >96% @ 215 and >98% @ 254 nm	1

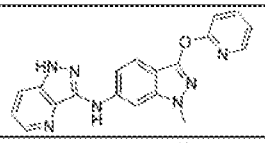
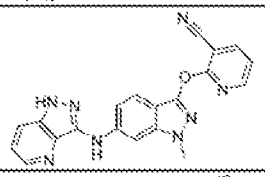
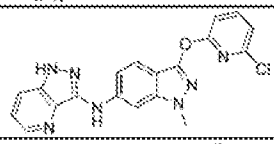
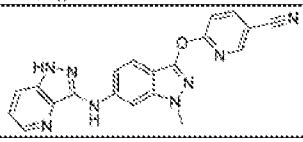
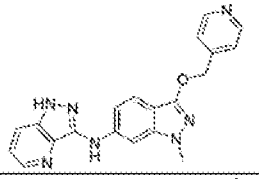
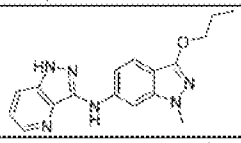
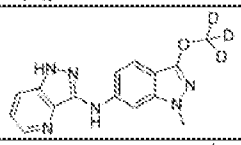
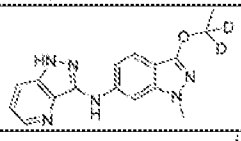
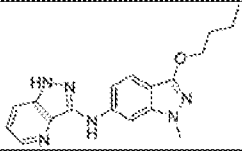
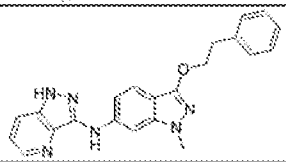
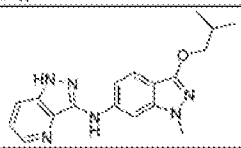
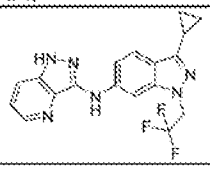
174		N-(3,3-difluorocyclobutyl)-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carboxamide	LCMS (90 second Method): RT = 0.813 min, M+H=398.2, >97% at 215	I
175		N-(3-fluorocyclobutyl)-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carboxamide	LCMS (90 second Method): RT = 0.762 min, M+H=380.3, >98% at 215 nm	I
176		N-cyclobutyl-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carboxamide	LCMS (90 second Method): RT = 0.811 min, M+H=362.3, >95% at 215 nm and 254 nm	I
177		1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazole-3-carbonitrile	LCMS: Rt=0.766 min, M+H=290.1; >98% @ 215 and 254 nm	V
177		N-(1-methyl-3-(5-methylpyridin-3-yl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.732 min, M+H=356.2	V
179		5-[1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]-1H-pyridin-2-one	LCMS: Rt=0.717 min, M+H=358.1	V
180		N-[3-(6-methoxy-3-pyridyl)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.869 min, M+H=372.1	V
181		N-(1-methyl-3-((tetrahydro-2H-pyran-2-yl)methoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.821 min, M+H=377.1; >98% @ 215 and 254 nm	II
182		N-(1-methyl-3-(2,2,2-trifluoroethoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.962 min, M+H=363.1; >98% @ 215 and 254 nm	II
183		N-(1-methyl-3-((5-methylisoxazol-3-yl)methoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.878 min, M+H=376.1; >98% @ 215 and 254 nm	II
184		N-(1-methyl-3-(pyridin-3-ylmethoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.648 min, M+H=372.1; >98% @ 215 and 254 nm	II
185		N-(3-(cyclopropylmethoxy)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.915 min, M+H=335.1; >98% @ 215 and 254 nm	II

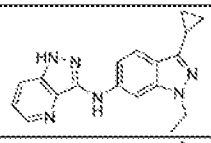
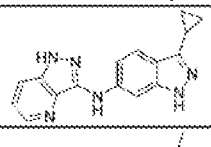
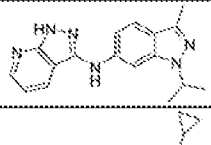
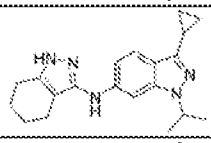
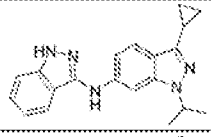
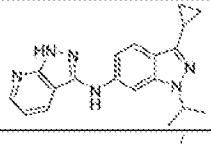
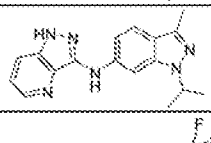
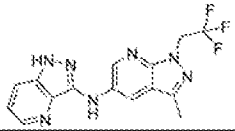
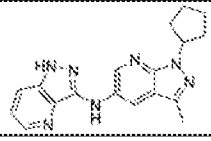
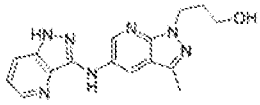
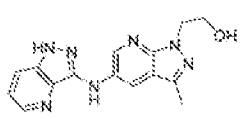
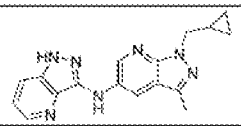
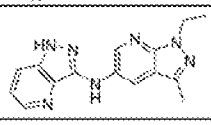
186		N-(1-methyl-3-(methylsulfonyl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.648 min, M+H=343.0; >98% @ 215 and 254 nm	XI
187		N-(1-methyl-3-(methylsulfonyl)-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS: Rt=0.686 min, M+H=344.0; >98% @ 215 and 254 nm	XI
188		N-[3-[(2,2-difluorocyclopropyl)methoxyl-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS:0.878 min, M+H=371.0; >98% @ 215 and 254 nm	II
189		N-[1-methyl-3-[(1-methyl-4-piperidyl)oxy]indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.593 min, M+H=378.0; >98% @ 215 and 254 nm	II
190		N-[1-methyl-3-[(3-methyloxetan-3-yl)methoxy]indazol-6-yl]-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS: Rt= 0.698 min, M+H= 366.0; >99% pure	II
191		N-[3-(3-methoxypropoxy)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.795 min, M+H=353.0; >98% @ 215 and 254 nm	II
192		N-[3-(1,1-dioxothian-4-yl)oxy-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.728 min, M+H=413.0; >98% @ 215 and 254 nm	II
193		N-(1-methyl-3-tetrahydrofuran-3-yloxy-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.745 min, M+H=351.0; >98% @ 215 and 254 nm	II
194		N-[1-methyl-3-[(3-methyloxetan-3-yl)methoxy]indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.787 min, M+H=365.0; >98% @ 215 and 254 nm	II
195		N-[1-methyl-3-(oxetan-3-ylmethoxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.755 min, M+H=351.0; >98% @ 215 and 254 nm	II
196		3-isopropoxy-1-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[4,3-b]pyridin-6-amine	LCMS: Rt= 0.752, M+H= 324.7; >98% at 215 and 254 nm	II
197		1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)pyrazolo[4,3-b]pyridin-3-ol	LCMS: Rt=0.582 min, M+H=282.1; >98% @ 215 and 254 nm	II

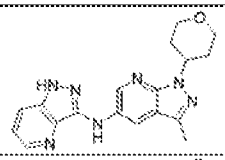
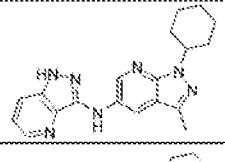
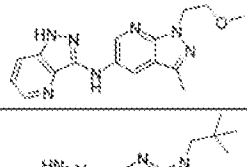
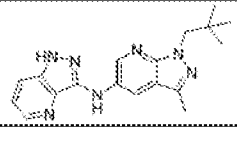
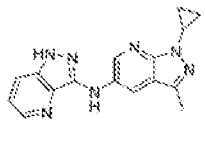
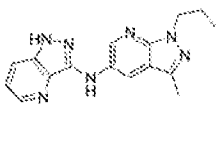
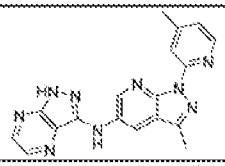
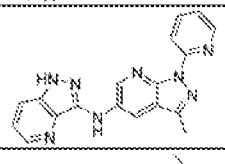
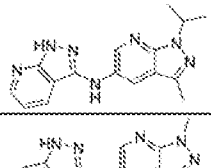
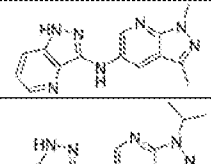
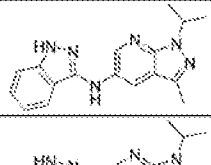
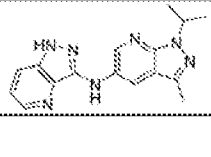
198		3-cyclopropyl-N-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-pyrazolo[4,3-b]pyridin-6-amine	LCMS:RT=0.762min, m+H=324.4, >98%@215 and 254nm	VI
199		3-cyclopropyl-1-methyl-N-(1H-pyrazolo[3,4-b]pyridin-3-yl)pyrazolo[4,3-b]pyridin-6-amine	LCMS:RT=0.667min, m+H=306.1, >98%@215 and 254nm	VI
200		3-cyclopropyl-N-(1H-indazol-3-yl)-1-methyl-pyrazolo[4,3-b]pyridin-6-amine	LCMS:RT=0.775min, m+H=305.2, >98%@215 and 254nm	VI
201		N-(3-cyclopropyl-1-methyl-pyrazolo[4,3-b]pyridin-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS:RT=0.691min, m+H=307.4, >98%@215 and 254nm	VI
202		3-cyclopropyl-N-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-3-yl)-1-methyl-pyrazolo[4,3-b]pyridin-6-amine	LCMS:RT=0.781min, m+H=324.0, >98%@215 and 254nm	VI
203		3-cyclopropyl-1-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[4,3-b]pyridin-6-amine	LCMS:RT=0.726 min, m+H=306.1, >98%@215 and 254nm	VI
204		4-chloro-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-ol	LCMS at 215 nm RT = 0.630, M+1=315.2	II
205		N-(4-chloro-3-methoxy-1-methyl-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nm RT = 0.874 min, M+1=329.0	II
206		2-[4-chloro-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]oxypyridine-3-carbonitrile	LCMS at 215 nm RT = 0.883, M+1=416.9	II
207		6-[4-chloro-1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl]oxypyridine-3-carbonitrile	LCMS at 215 nm RT = 0.919 min, M+1=416.9	II
208		N-[4-chloro-1-methyl-3-(tetrahydropyran-2-ylmethoxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nm RT = 0.999 min, M+1=413.0	II
209		N-[4-chloro-1-methyl-3-(2-morpholinoethoxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nm RT = 0.661 min, M+1=428.0	II
210		N-[4-chloro-3-(2-methoxyethoxy)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nm RT = 0.870 min, M+1=373.0	II

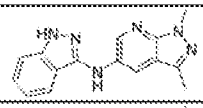
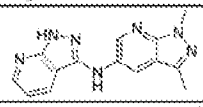
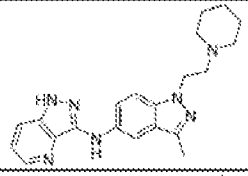
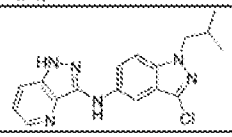
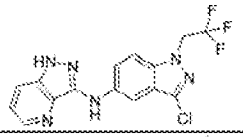
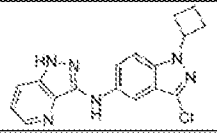
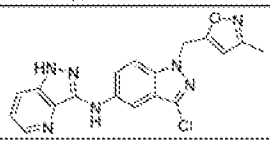
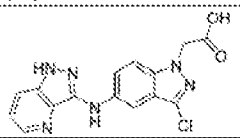
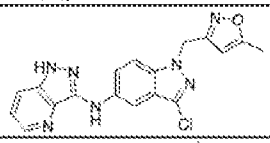
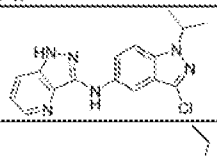
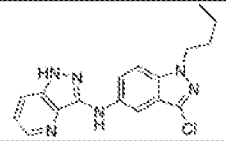
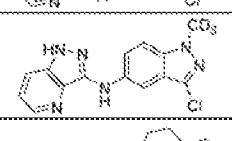
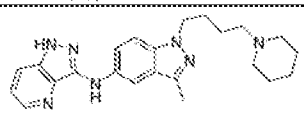
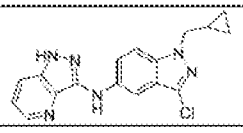
211		N-[4-chloro-1-methyl-3-(oxetan-3-yloxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nM RT = 0.863 min, M+1=371.0	II
212		6-fluoro-N-(1-methyl-3-methylsulfonyl-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS at 215 nM RT = 0.752 min, M+1=361.0	XI
213		N-(1-methyl-3-methylsulfonyl-indazol-6-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS (90 second method): RT= 0.686 min, M+H= 344.0, >98%@215 and 254nm	XI
214		N-(1-methyl-3-methylsulfonyl-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.647 min, M+H= 343.0, >98%@215 and 254nm	XI
215		N-[3-(2-methoxyethoxy)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.730 min, M+H=339.0; >98% @ 215 and 254 nm	II
216		N-[1-methyl-3-(oxetan-3-yloxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.732 min, M+H=337.0; >98% @ 215 and 254 nm	II
217		N-[1-methyl-3-(2-morpholinoethoxy)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: RT=0.569 min, M+H=394.0; >91% @ 215 and >92% @ 254 nm	II
218		N-[1-methyl-3-(4-pyridyl)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.664 min, M+H=342.1	V
219		N-[4-chloro-3-(cyclopropylmethoxy)-1-methyl-indazol-6-yl]-1H-pyrazolo[3,4-b]pyridin-3-amine	M+1=368.8	II
220		N-[3-(3-fluorophenyl)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.00 min, M+H=359.1	V
221		N-[3-(1-isopropylpyrazol-4-yl)-1-methyl-indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.850 min, M+H=373.2	V
222		N-[1-methyl-3-(1-methylpyrazol-3-yl)indazol-6-yl]-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.810 min, M+344.1	V

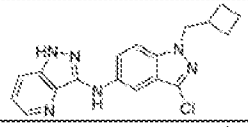
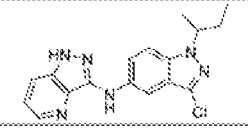
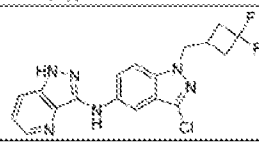
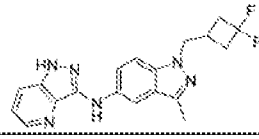
223		N-(3-(cyclopenten-1-yl)-1-methyl-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.937 min, M+H=331.2	V
224		1-methyl-3-(1-methyl-6-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)indazol-3-yl)pyridin-2-one	LCMS: Rt=0.723 min, M+H=372.1	V
225		N-(1-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.827 min, M+H=365.1; >98% @ 215 and 254 nm	II
226		N-(1-methyl-3-(3-phenoxypropoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.058, M+H=415.1; >98% @ 215 and 254 nm	II
227		N-(3-(2-(2-fluorophenoxy)ethoxy)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.014 min, M+H=419.1; >98% @ 215 and 254 nm	II
228		N-(3-(2-(4-fluorophenoxy)ethoxy)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.025 min, M+H=419.1; >98% @ 215 and 254 nm	II
229		N-(1-methyl-3-((3-methylpyridin-2-yl)oxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.907 min, M+H=372.2; >98% @ 215 and 254 nm	II
230		N-(1-methyl-3-(pyridin-2-ylmethoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.697 min, M+H=372.1; >98% @ 215 and 254 nm	II
231		6-((6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)oxy)picolinonitrile	LCMS: Rt=0.858 min, M+H=383.1; >98% @ 215 and 254 nm	II
232		N-(1-methyl-3-((4-methylpyridin-2-yl)oxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.013 min, M+H=372.1; >98% @ 215 and 254 nm	II
233		N-(1-methyl-3-((6-methylpyridin-2-yl)oxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.034 min, M+H=372.1; >98% @ 215 and 254 nm	II

234		N-(1-methyl-3-(pyridin-2-yloxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.973 min, M+H=358.1; >98% @ 215 and 254 nm	II
235		2-((6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)oxy)nicotinonitrile	LCMS: Rt=0.829 min, M+H=383.1; >98% @ 215 and 254 nm	II
236		N-(3-((6-chloropyridin-2-yl)oxy)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.094 min, M+H=392.0; >98% @ 215 and 254 nm	II
237		6-((6-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-1-methyl-1H-indazol-3-yl)oxy)nicotinonitrile	LCMS: Rt=0.842 min, M+H=383.1; >98% @ 215 and 254 nm	II
238		N-(1-methyl-3-(pyridin-4-ylmethoxy)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.688 min, M+H=372.2; >98% @ 215 and 254 nm	II
239		N-(1-methyl-3-propoxy-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.915 min, M+H=323.1; >98% @ 215 and 254 nm	II
240		N-(3-(methoxy-d3)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.774 min, M+H=298.1; >98% @ 215 and 254 nm	II
241		N-(3-(ethoxy-1,1-d2)-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.821 min, M+H=311.1; >98% @ 215 and 254 nm	II
242		N-(3-butoxy-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.990 min, M+H=337.1; >98% @ 215 and 254 nm	II
243		N-(1-methyl-3-phenethoxy-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=1.036 min, M+H=385.1; >98% @ 215 and 254 nm	II
244		N-(3-isobutoxy-1-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.988 min, M+H=337.1; >98% @ 215 and 254 nm	II
245		N-(3-cyclopropyl-1-(2,2,2-trifluoroethyl)-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.932 min, M+H=373.1; >98% @ 215 and 254 nm	VI

246		N-(3-cyclopropyl-1-ethyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.835 min, M+H=319.2; >98% @ 215 and 254 nm	VI
247		N-(3-cyclopropyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.660 min, M+H=291.2; >98% @ 215 and 254 nm	VI
248		N-(1-isopropyl-3-methyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	LCMS: Rt=0.803 min, M+H=307.1; >98% @ 215 and 254 nm	VI
249		3-cyclopropyl-1-isopropyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-1H-indazol-6-amine	LCMS: Rt=0.956 min, M+H=336.2; >98% @ 215 and 254 nm	VI
250		N-(3-cyclopropyl-1-isopropyl-1H-indazol-6-yl)-1H-indazol-3-amine	LCMS: Rt=1.031 min, M+H=332.2; >98% @ 215 and 254 nm	VI
251		N-(3-cyclopropyl-1-isopropyl-1H-indazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	LCMS: Rt=0.907 min, M+H=333.2; >98% @ 215 and 254 nm	VI
252		N-(1-isopropyl-3-methyl-1H-indazol-6-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.779 min, M+H=307.2; >98% @ 215 and 254 nm	VI
253		3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)-1-(2,2,2-trifluoroethyl)pyrazolo[3,4-b]pyridin-5-amine	LCMS: Rt=0.773 min, M+H=348.2; >98% @ 215 and 254 nm	X
254		1-cyclopentyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS: Rt=0.873 min, M+H=334.4; >98% @ 215 and 254 nm	X
255		3-[3-methyl-5-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)pyrazolo[3,4-b]pyridin-1-yl]propan-1-ol	LCMS: Rt=0.460 min, M+H=306.2; >98% @ 215 and 254 nm	X
256		2-[3-methyl-5-(1H-pyrazolo[4,3-b]pyridin-3-ylamino)pyrazolo[3,4-b]pyridin-1-yl]ethanol	LCMS (90 second method): RT = 0.585 min, M+H=310.4, >98% at 254 nm 1H-NMR (400 MHz, DMSO-d6): verified, >95%	X
257		1-(cyclopropylmethyl)-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.519 min, M+H=320.4, >98% at 220 nm and 254 nm	X
258		1-ethyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.668 min, M+H=294.4, >98% at 220 nm and 254 nm	X

259		3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)-1-tetrahydropyran-4-yl-pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.695 min, M+H=350.3, >98% at 220 nm and 254 nm	X
260		1-cyclohexyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.920 min, M+H=348.3, >98% at 220 nm and 254 nm	X
261		1-(2-methoxyethyl)-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.638 min, M+H=324.4, >98% at 220 nm and 254 nm	X
262		1-(2,2-dimethylpropyl)-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.896 min, M+H=336.4, >98% at 220 nm and 254 nm	X
263		1-cyclopropyl-3-methyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.682 min, M+H=306.4, >98% at 220 nm and 254 nm; Purified using Gilson HPLC system with acidic method (ACN/water/0.1% TFA), column size: 30x50 nm, gradient:18-47%, gradient time: 4.0 min	X
264		3-methyl-1-propyl-N-(1H-pyrazolo[4,3-b]pyridin-3-yl)pyrazolo[3,4-b]pyridin-5-amine	LCMS (90 second method): RT = 0.755 min, M+H=308.4.2, >98% at 220 nm and 254 nm. Purified using reverse phase Gilson HPLC system with acidic method (ACN/water/0.1% TFA), column size: 30x50 nm, gradient:23-53%, gradient time: 4.0 min	X
265		N-(3-methyl-1-(4-methylpyridin-2-yl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	X
266		N-(3-methyl-1-(pyridin-2-yl)-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	X
267		N-(1-isopropyl-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	LCMS: Rt=0.733 min, M+H=308.2; >98% @ 215 and 254 nm	X
268		N-(1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.653 min, M+H=280.2; >98% @ 215 and 254 nm	X
269		N-(1H-indazol-3-yl)-1-isopropyl-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-amine	LCMS: Rt=0.873 min, M+H=307.2' >98% @ 215 and 254 nm	X
270		N-(1-isopropyl-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS: Rt=0.744 min, M+H=308.2; >98% @ 215 and 254 nm	X

271		N-(1H-indazol-3-yl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-5-amine	LCMS: Rt=0.761 min, M+H=279.2; >98% @ 215 and 254 nm	X
272		N-(1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine	LCMS: Rt=0.617 min, M+H=280.2; >98% @ 215 and 254 nm	X
273		N-(3-methyl-1-(2-(piperidin-1-yl)ethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method). RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
274		N-(3-chloro-1-isobutyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method). RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
275		N-(3-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method). RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
276		N-(3-chloro-1-cyclobutyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
277		N-(3-chloro-1-((3-methylisoxazol-5-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
278		2-(5-((1H-pyrazolo[4,3-b]pyridin-3-yl)amino)-3-chloro-1H-indazol-1-yl)acetic acid	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
279		N-(3-chloro-1-((5-methylisoxazol-3-yl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
280		N-(3-chloro-1-isopropyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
281		N-(1-butyl-3-chloro-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
282		N-(3-chloro-1-(methyl-d3)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
283		N-(3-methyl-1-(4-(piperidin-1-yl)butyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
284		N-(3-chloro-1-(cyclopropylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI

285		N-(3-chloro-1-(cyclobutylmethyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT = 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
286		N-(1-(sec-butyl)-3-chloro-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI
287		N-(3-chloro-1-((3,3-difluorocyclobutyl)methyl)-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT= 0.983 min, M+H=537.1, >98%@215 and 254 nm	VI
288		N-(1-((3,3-difluorocyclobutyl)methyl)-3-methyl-1H-indazol-5-yl)-1H-pyrazolo[4,3-b]pyridin-3-amine	LCMS (90 second method): RT=343.1, M+H=343.1, >98%@215 and 254nm	VI

Example	EC_{50} (μM)	Example	EC_{50} (μM)
1	0.043	122	0.049
2	0.029	123	0.218
3	0.525	124	0.309
4	0.02	125	1.53
5	0.364	126	0.264
6	0.051	127	0.154
7	1.23	128	0.049
8	0.016	129	1.3
9	0.064	130	0.063
10	0.515	131	0.107
11	4.22	132	0.330
12	0.128	133	0.379
13	0.043	134	0.077
14	>10	135	0.832
15	0.078	136	0.253
16	>10	137	0.436
17	>10	138	3.4
18	>10	139	0.310
19	>10	140	0.455
20	>10	141	0.815
21	0.764	142	>10
22	0.01	143	>10
23	0.036	144	>10
24	0.038	145	>10
25	0.313	146	>10
26	>10	147	1.26
27	>10	148	3.53
28	0.068	149	>10
29	0.025	150	>10
30	0.129	151	0.582
31	0.171	152	0.371
32	0.571	153	0.413
33	>10	154	0.17
34	4.3	155	0.16
35	0.992	156	0.11
36	0.526	157	0.11
37	3.15	158	0.2
38	0.263	159	3.94
39	0.765	160	0.888
40	0.147	161	>10
41	1.42	162	0.498
42	4.0	163	2.21
43	0.16	164	1.11

44	0.413	165	0.801
45	0.104	166	>10
46	0.215	167	1.58
47	>10	168	0.903
48	4.4	169	4.61
49	4.6	170	2.34
50	0.323	171	0.765
51	0.15	172	0.289
52	0.718	173	0.825
53	0.247	174	0.116
54	0.865	175	0.794
55	0.790	176	0.653
56	0.315	177	0.467
57	>10	178	4.18
58	2.29	179	2.72
59	>10	180	>10
60	0.790	181	0.687
61	0.133	182	0.198
62	0.914	183	0.224
63	0.085	184	0.083
64	0.067	185	0.164
65	0.076	186	1.88
66	0.117	187	2.36
67	>10	188	0.112
68	>10	192	0.185
69	0.145	194	0.146
70	0.870	195	0.0966
71	0.347	207	0.487
72	0.047	209	0.322
73	0.186	214	1.880
74	0.265	216	0.629
75	0.187	217	0.238
76	0.051	218	0.871
77	0.157	225	0.046
78	0.129	231	0.119
79	0.813	237	0.157
80	0.167	238	0.0658
81	>10	239	0.171
82	0.136	240	0.294
83	0.202	241	0.356
84	0.818	244	0.231
85	0.057	247	0.452
86	0.0514	253	0.24
87	0.749	254	>10
88	0.072	255	>30
89	>10	256	>10
90	>10	257	>10
91	0.019	258	0.48
92	0.081	259	3.7
93	>10	260	0.44
94	>10	261	2.33
95	0.035	262	0.16
96	0.863	263	0.31
97	0.575	264	0.15
98	>10	265	0.23
99	0.757	266	0.077
100	0.258	267	>10
101	>10	268	>30
102	0.367	269	2.55
103	0.125	270	>30
104	0.083	271	>10
105	>10	272	>10
106	0.145	273	4.36
107	0.374	274	3.02
108	0.345	275	2.72
109	0.059	276	>10
110	0.119	277	0.31
111	0.036	278	1.56
112	0.095	279	0.29
113	0.133	280	>10
114	0.045	281	2.43
115	0.135	282	>10
116	0.096	283	3.51
117	1.46	284	>10

118	0.867		285	1.98
119	0.295		286	>10
120	0.144		287	2.99
121	0.377		288	0.68

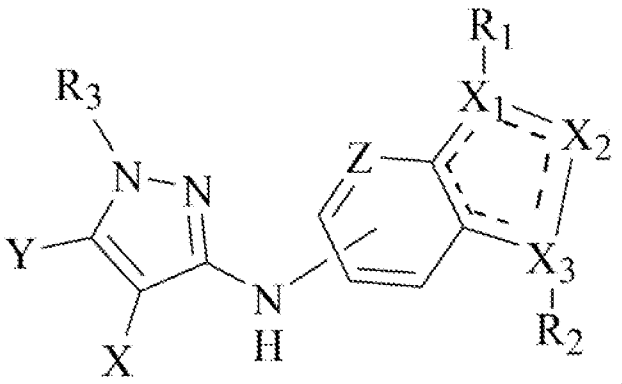
[0215] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other aspects of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0216] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used herein are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the herein are approximations that may vary depending upon the desired properties sought to be determined by the present invention.

CLAIMS

What is claimed is:

1. A compound having a structure represented by the formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl,

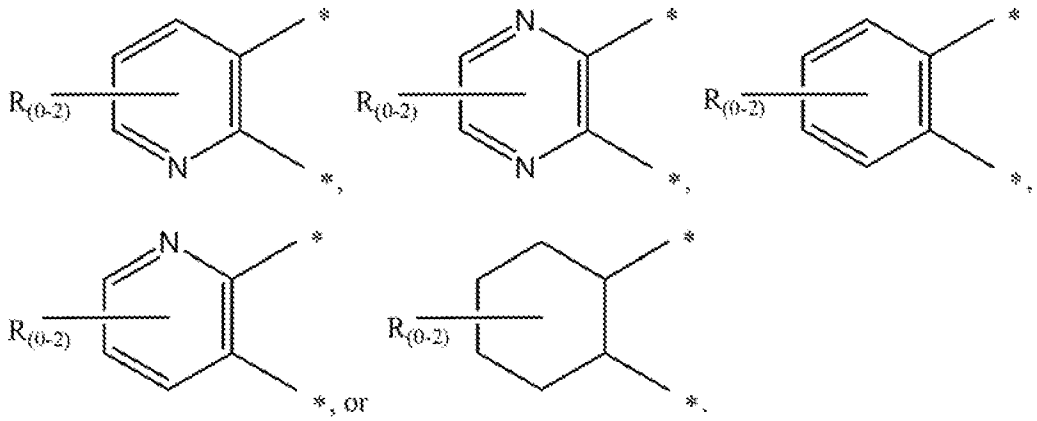
methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine;

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

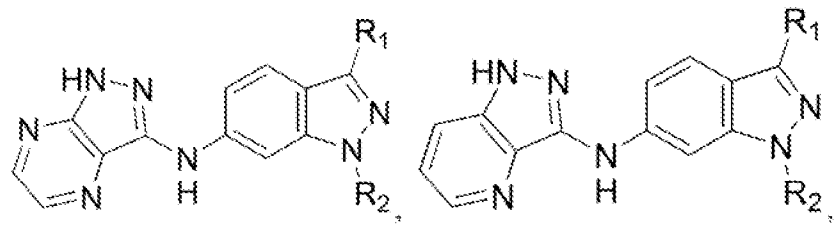
2. The compound of claim 1, wherein X and Y together form:

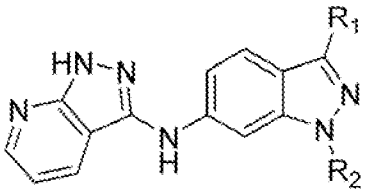


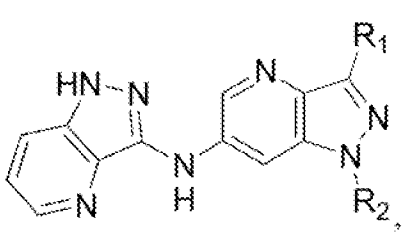
3. The compound of claim 1 or 2, wherein R, when present, is F.

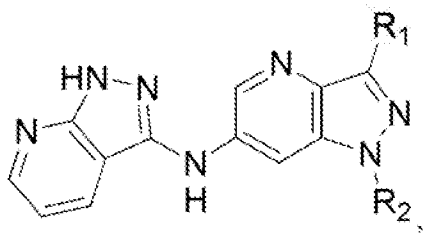
4. The compound of claims 1-3, wherein Z is N, CH, CD, or C-Cl.

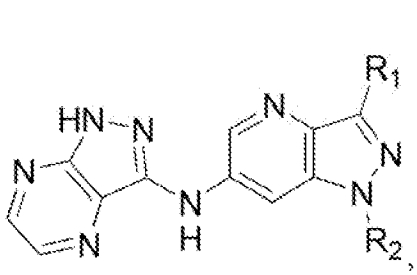
5. The compound of claim 1, of the following formula:

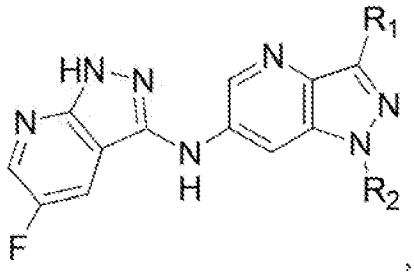


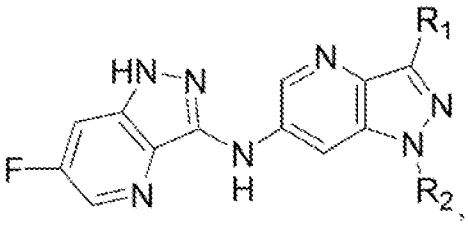


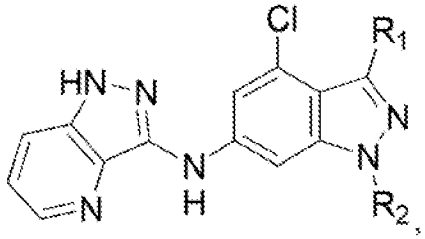


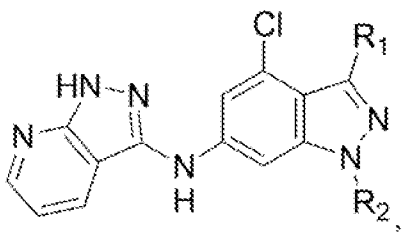


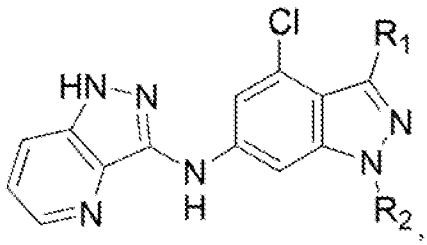


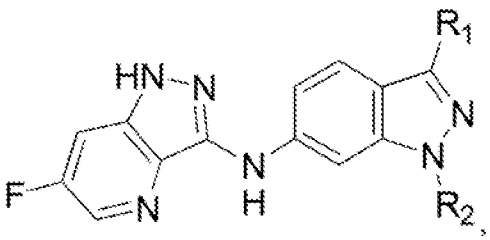


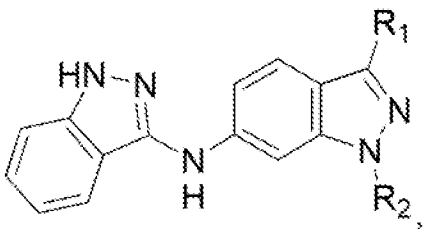


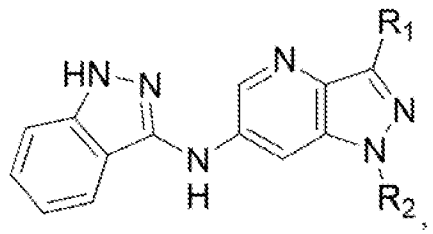
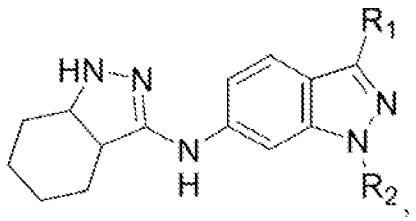
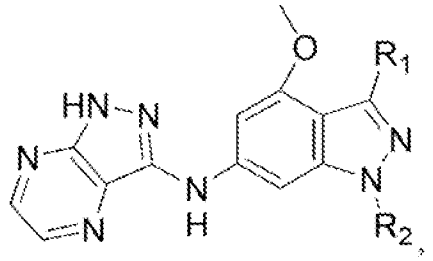
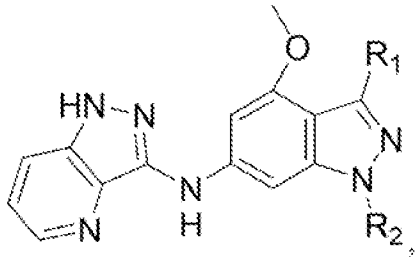
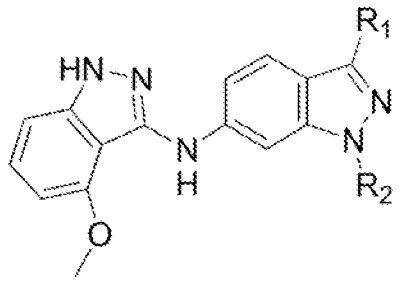
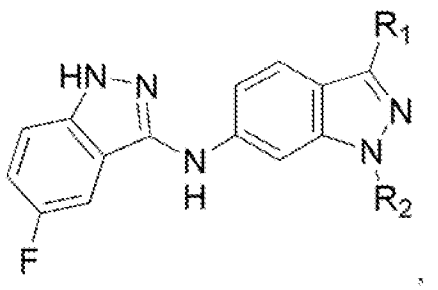
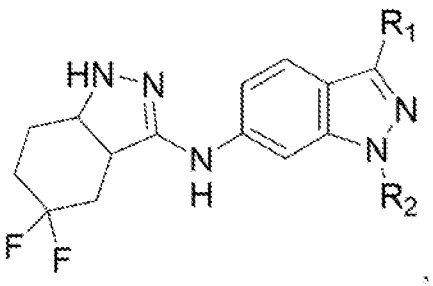
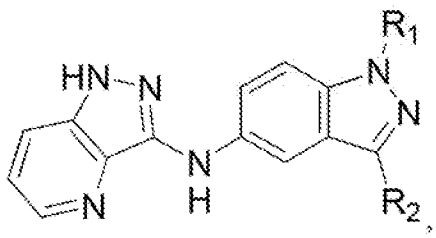
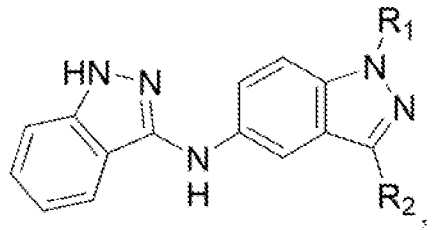
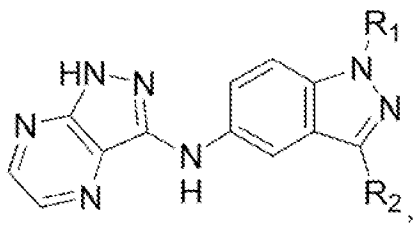
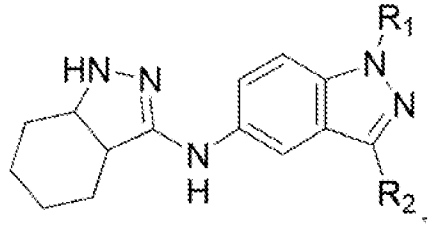
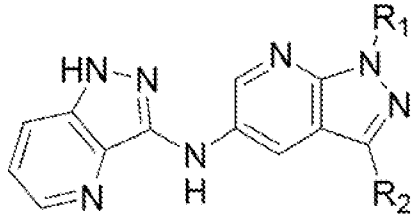


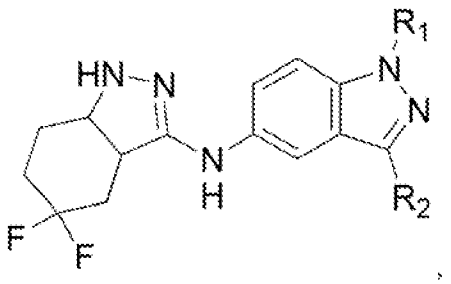






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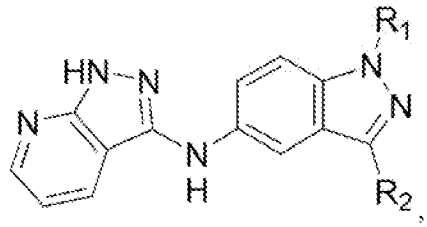
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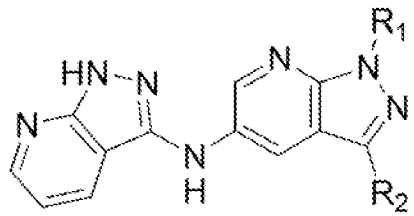
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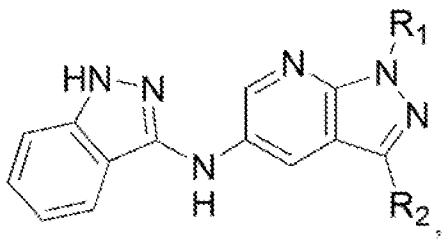
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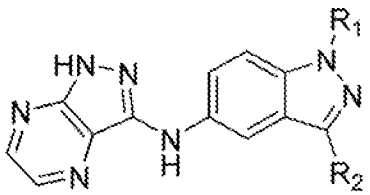
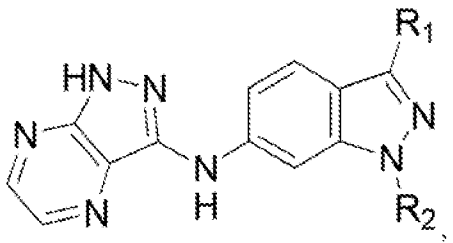


6. The compound of claim 1, of the following formula: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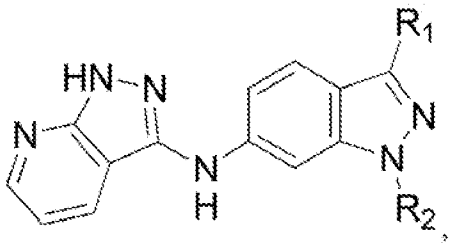
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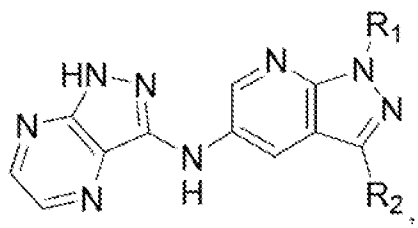
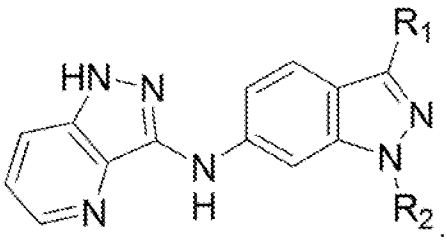
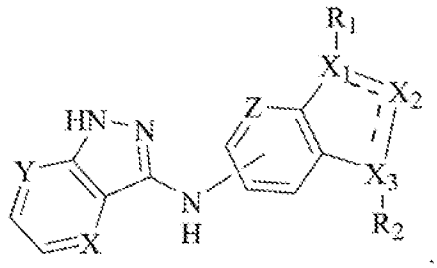
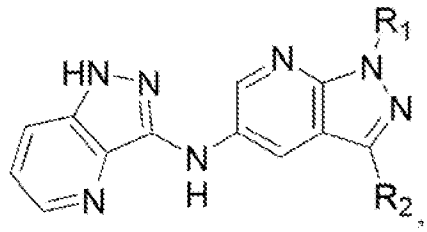

, or

.

7. The compound of claim 6, wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

8. A compound of claim 1, of the following formula:

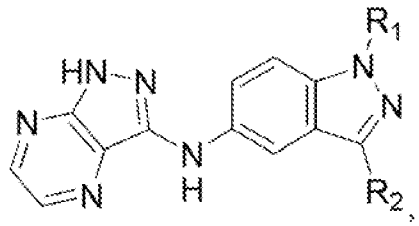


9. A compound of claim 1, of the following formula:



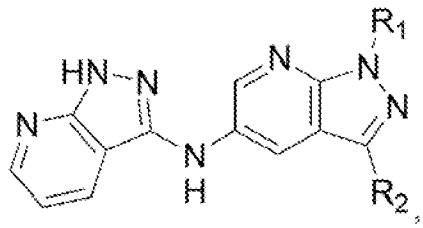
wherein R_1 is H, alkyl, cycloalkyl, heterocycloalkyl, alkyl-cycloalkyl, trifluoroalkyl, hydroxyalkyl, alkyl-alkoxy; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

10. A compound of claim 1, of the following formula:



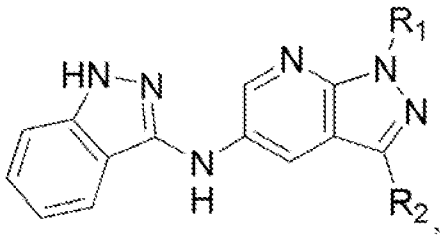
wherein R_1 is H, alkyl, cycloalkyl, heterocycloalkyl, CO-CF_3, CD_2-alkyl, alkyl-heteroaryl, alkyl-cycloalkyl, cycloalkyl, and R_2 is H, alkyl, cycloalkyl, heterocycloalkyl, alkyl-phenyl, cycloalkyl,

11. A compound of claim 1, of the following formula:



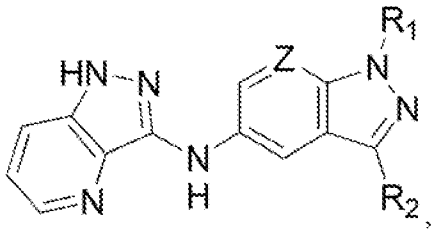
wherein R_1 is H, alkyl, cycloalkyl, heterocycloalkyl, and $R_2$is H, alkyl, cycloalkyl, heterocycloalkyl.

12. A compound of claim 1, of the following formula:



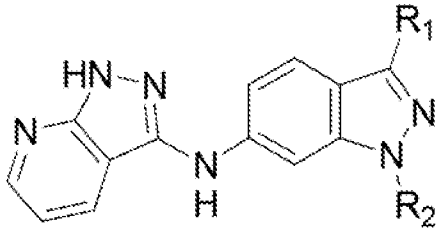
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl,

13. A compound of claim 1, of the following formula:



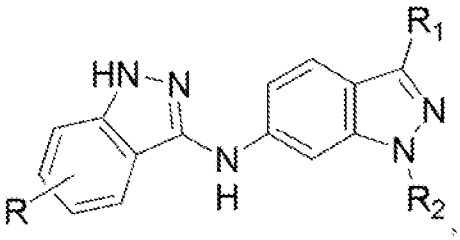
wherein R_1 is H, alkyl, alkene, alkyl-heteroalkyl, alkyl-heterocycloalkyl alkyl, heterocycloalkyl, trifluoroalkyl, alkyl-cycloalkyl, cycloalkyl, alkyl-heteroaryl, heteroaryl, alkyl-acetic acid, CD_3, alkoxy, CD_2-alkyl, alkyl-CO-alkoxy, CF_3, phenyl; fluorophenyl, alkylcarbontrichloride, alkyltricluorocarbon, and R_2 is H, alkyl, Cl, CF_3, heteroaryl, cyclopentene, alkyl-phenyl, trifluoroalkyl, cycloheteroalkyl, amino-alkyl-carboxylate ester; hydoxy, alkyl-cycloalkyl, amino, amino-CO-CF_3, cycloalkyl.

14. A compound of claim 1, of the following formula:



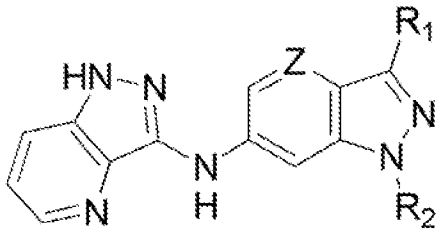
wherein R_1 is H, alkyl, cycloalkyl; and R_2 is H, alkyl, alkyl-cycloalkyl, alkyl-heteroaryl, CD_3.

15. A compound of claim 1, of the following formula:



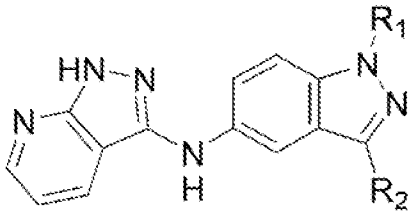
wherein R may be optionally present and when present is O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl,

16. A compound of claim 1, of the following formula:



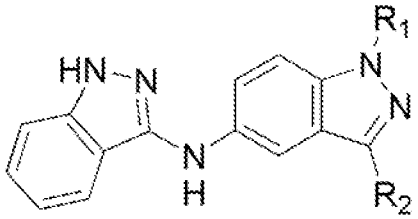
wherein Z is N, C-H, C-Me, C-O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CN, methylsulfonyl, O-alkoxy, O-cycloheteroalkyl, cycloheteroalkyl, alkoxycycloheteroalkyl, halogen, and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl, alkyl-acetic acid, heterocycloalkyl, CD_3.

17. A compound of claim 1, of the following formula:



wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene.

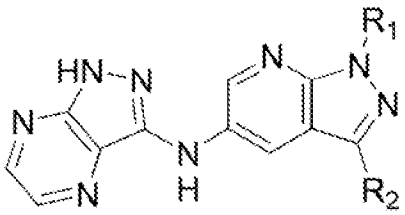
18. A compound of the following formula:



wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkoxy, alkyl-cycloalkyl,

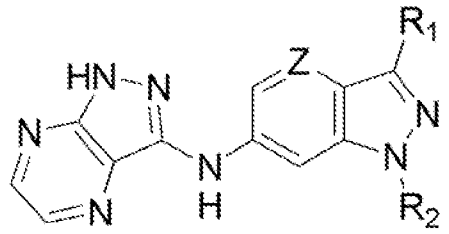
R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, cycloheteroalkyl,

19. A compound of the following formula:



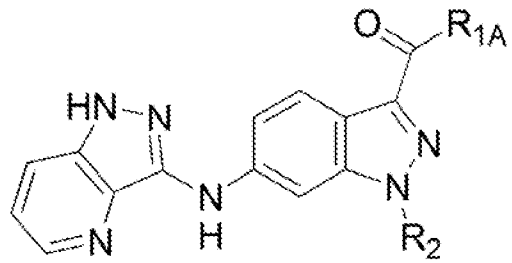
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

20. A compound of claim 1, of the following formula:



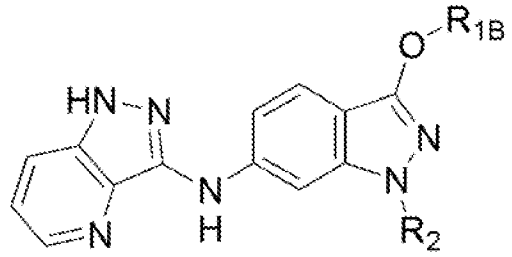
wherein Z is N, CH, CD, C;halogen, C-O-Me; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, methylsulfonyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl, CD_3.

21. A compound of claim 1, of the following formula:



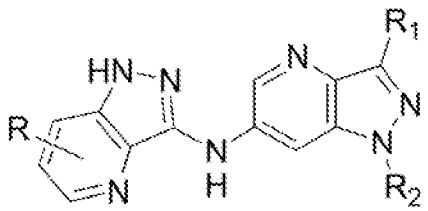
wherein R_{1A} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl-sulfonylmethyl, cycloheteroalkyl, anino-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

22. A compound of claim 1, of the following formula:



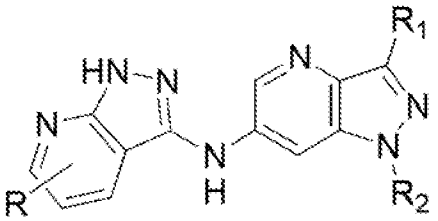
wherein R_{1B} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, cycloheteroalkyl, alkoxy, alkyl-cycloheteroalkyl, alkoxyphenyl, heteroaryl, nitrilepyridine, chloropyridine; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl,

23. A compound of claim 1, of the following formula:



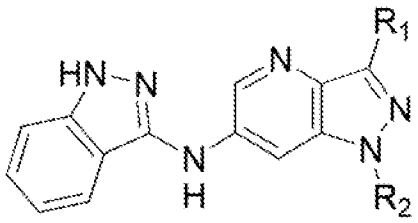
wherein R may be optionally present and when present is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkoxy, hydroxyl, cycloaklyl, methysulfonyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl.

24. A compound of claim 1, of the following formula:



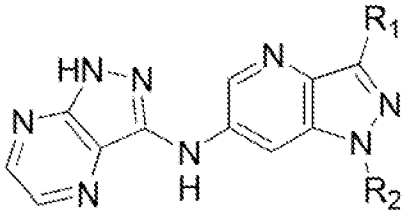
wherein R may be optionally present and when present is ; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

25. A compound of claim 1, of the following formula:



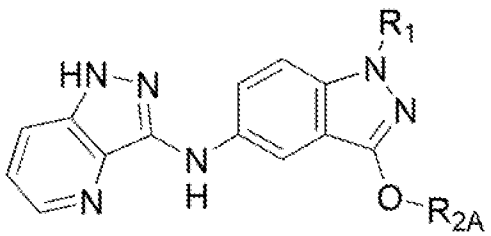
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-heteroaryl.

A compound of claim 1, of the following formula:



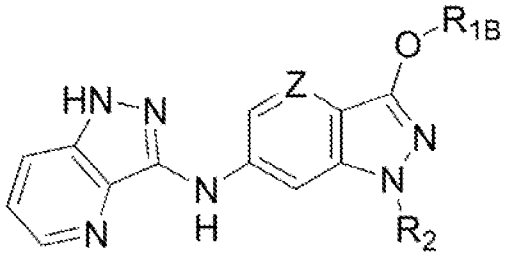
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is alkyl, alkyl-cycloalkyl, alkylheteroaryl.

26. A compound of claim 1, of the following formula:



wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, heterocycloalkyl , alkoxyphenyl, alkoxyfluorophenyl, heteroaryl, alkylheteroaryl, triflouroalkyl, alkoxyheteroaryl, alkoxy.

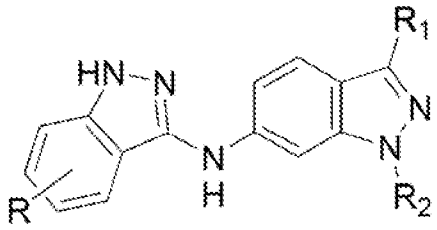
27. A compound of claim 1, of the following formula:



wherein Z is C or C-Cl; R_{1B} is H, alkyl, cycloalkyl, alkyl-cycloalkyl, heteroaryl, alkylheteroaryl, alkoxy, CD_3, CD_2alkyl, alkylcycloalkyl, alkylphenyl, alkoxy, alkyl-heterocycloalkyl;

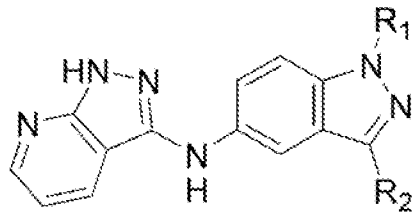
R_2 is heterocycloalkyl, H, alkyl, cycloalkyl, alkyl-cycloalkyl,

28. A compound of claim 1, of the following formula:



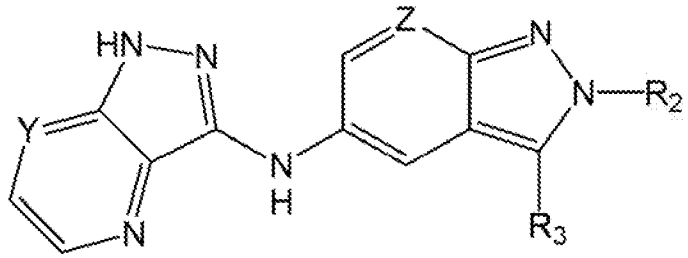
wherein R is F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CD_3.

29. A compound of claim 1, of the following formula:



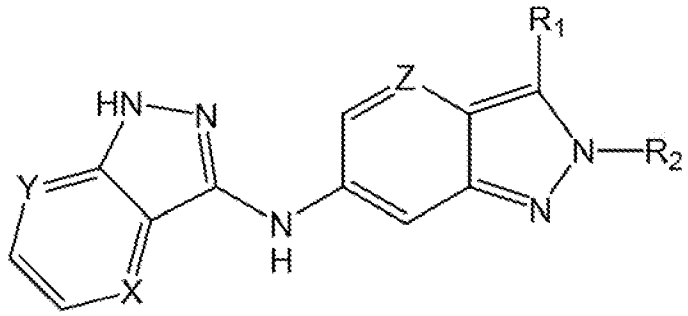
wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl

30. A compound of claim 1, of the following formula:



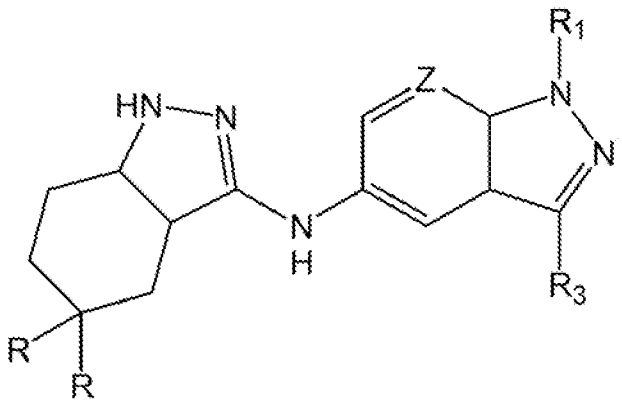
wherein Y is N or CH; Z is CH, CD, C-Cl, N; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene, CD_3, alkyl, alkyl-heteroaryl; and R_3 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

31. A compound of claim 1, of the following formula:



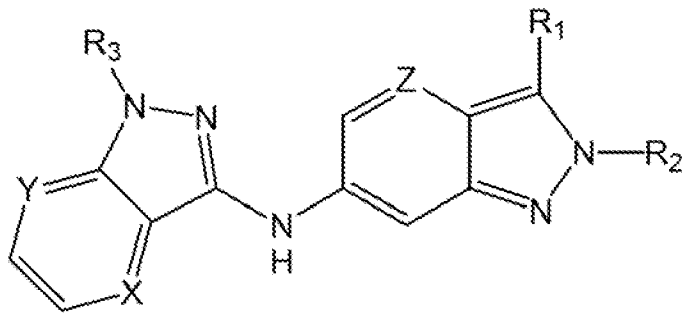
wherein Y is N or CH, CD, Z is C or N; Z is CH, CD, C-Cl, N; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, alkene, CD_3, alkyl, alkyl-heteroaryl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

32. A compound of claim 1, of the following formula:



Z is CH, CD, C-Cl, N; R is optionally and independently present, and when present is H, alkyl, F; R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_3 is H, alkyl, cycloalkyl, alkyl-cycloalkyl, CD_3,

33. A compound of claim 1, of the following formula:



R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_3 is alkoxy phenyl, pyridine, nitrilepyridine, chloropyridine.

34. A compound of claim 1, where X_1 is N and R_1 is alkyl, alkene, CH2-cycloalkyl, cycloalkyl, CH2-CF3, hydroxyalkyl, cycloheteroalkyl, alkyl-alkoxy, heteroaryl, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CD3, CO-CF3, alkyl-CO-O-alkyl,

35. A compound of claim 1, where X_1 is CH and R_1 is CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-dioxothian, hydroxyl, alkoxy, cycloalkyl, O-heteroalkyl, alkoxy-heteroalkyl, methylsulfonyl,

36. A compound of claim 9, where R_1 is cyclopentylmethyl, cyclobutylmethyl, cyclobutyl, cyclopropyl, cyclohexyl, tetrahydropyran, methoxyethyl.

37. A compound of claim 10, wherein R_1 is pyridine.

38. A compound of claim 12, wherein R_1 is pyridinepyrazole.

39. A compound of claim 13, wherein R_1 is benzisoxizole, fluoropyridine-substituted isoxazole, cyclopropyl-substituted isozazole, tetrahydropyran, methylquinolone, alkyl, piperidine, alkyl-piperadine, trifluoroethyl, cyclobutyl, methylisoxazole, methylcyclopropyl, methylcyclobutyl, methyldifluorocyclobutyl, alkylmorpholine, methyl oxadiazole, alkyl-methyl benzixoxazole,

40. A compound of claim 14, wherein R_1 is methylbenzisoxizole.

41. A compound of claim 15, wherein R_1 is methylbenzisoxizole.

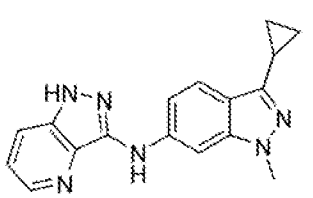
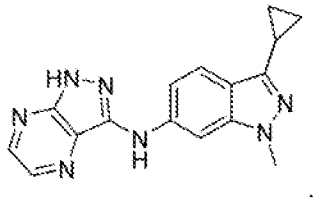
42. A compound of claim 16, wherein R_2 is piperazine.

43. A compound of claim 18, wherein R_1 is methylcyclobutyl.

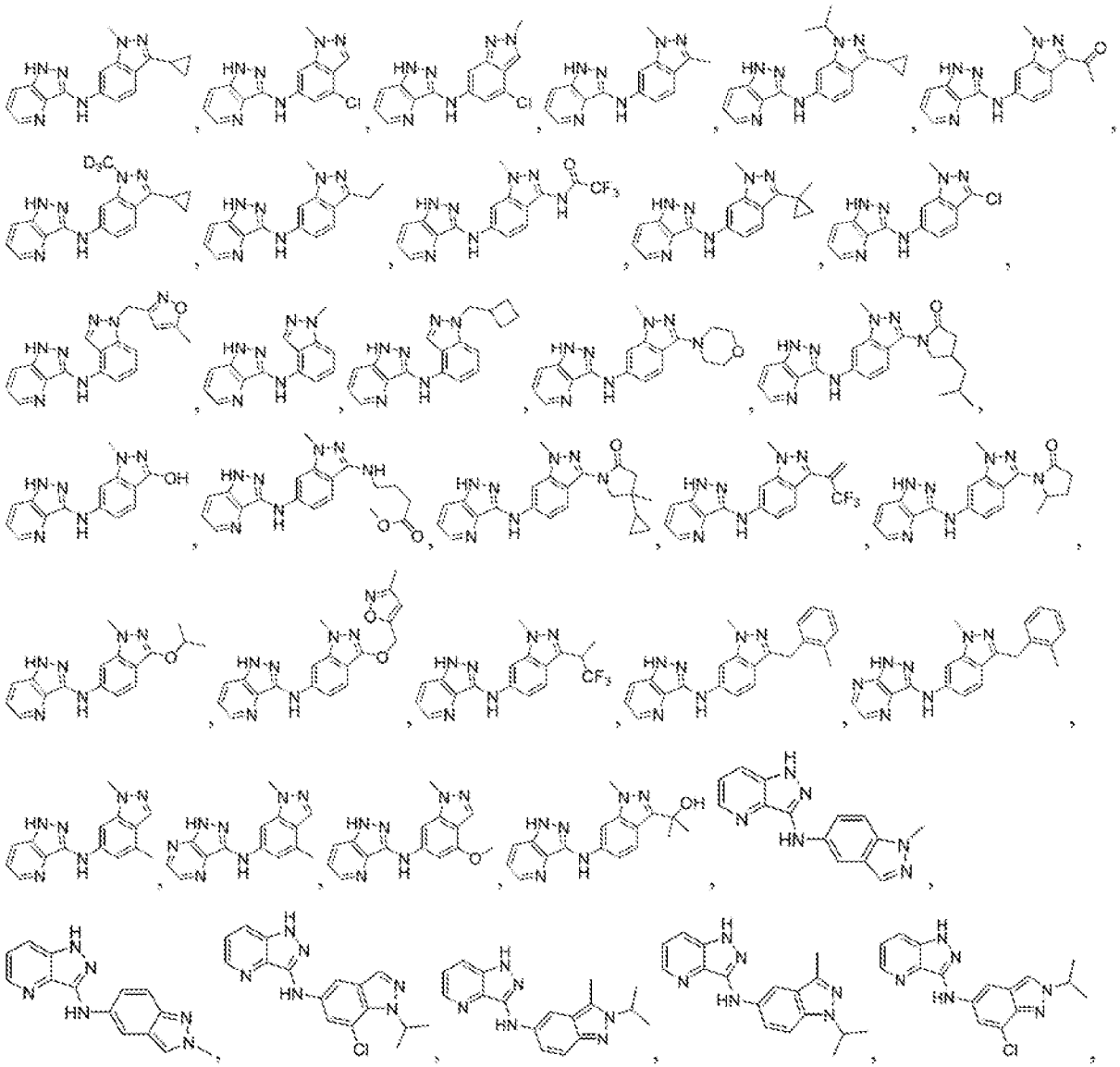
44. A compound of claim 21, wherein R_{1A} is difluoropiperidine, piperidine, piperidine-carboxamide, fluoropiperidine, thiazine, dioxothiazine, piperizine, methyl piperizine, morpholino, pyrolidine, methylsulfonylpyrrolidine, fluoropyrrolidine, difluoropyrrolidine, N-cyclobutyl, N-difluorocyclobutyl.

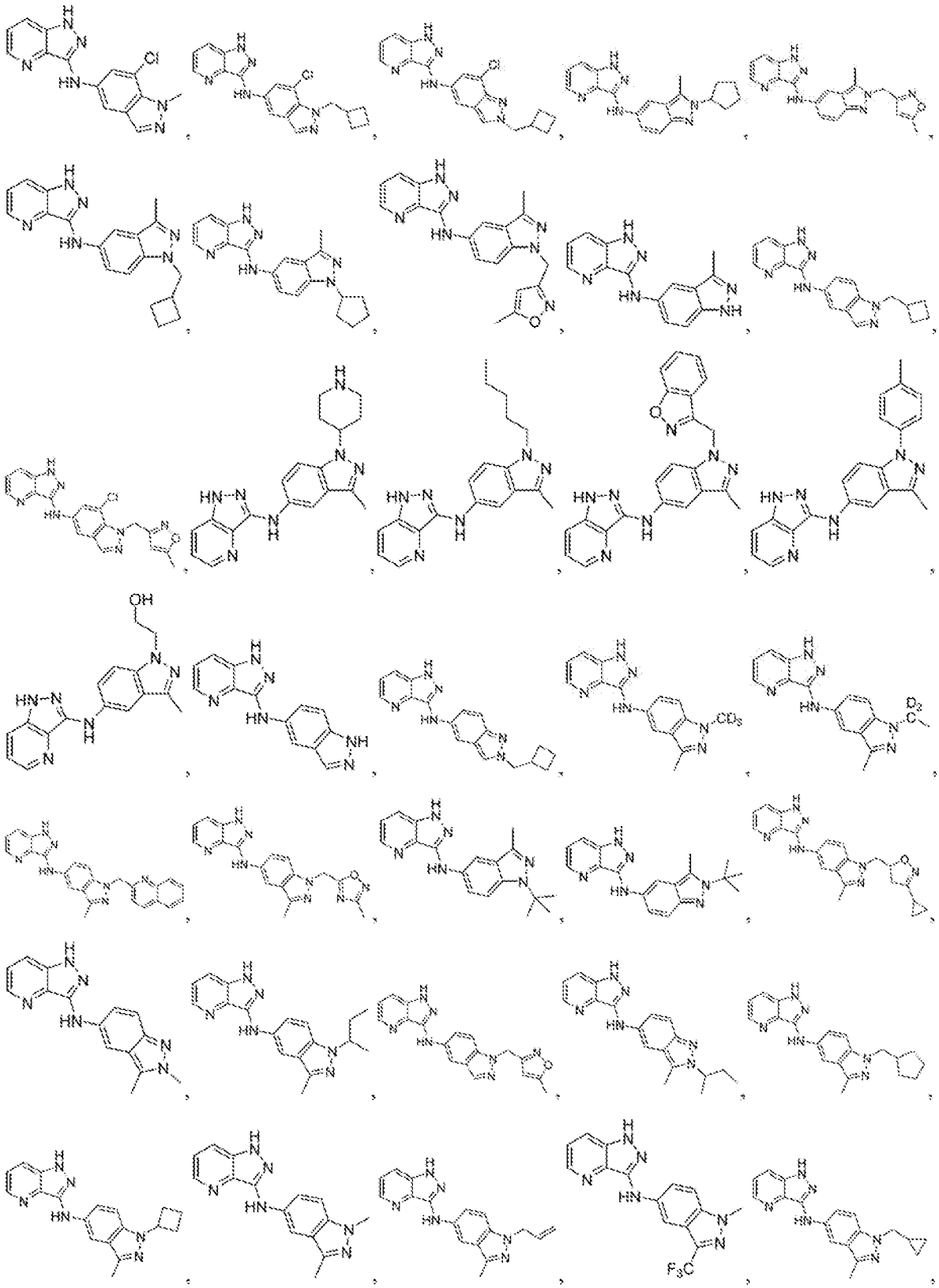
45. A compound of claim 22, wherein R_{1B} is cyclopropyl, difluorocyclopropyl, piperidine, methylpiperidine, oxetane, methyloxetame, thiane, dioxothiane, tetrahydrofuran, pyridine, carbonitrilepyridine, tetrahydropyran, morpholine, morpholinoethoxy,

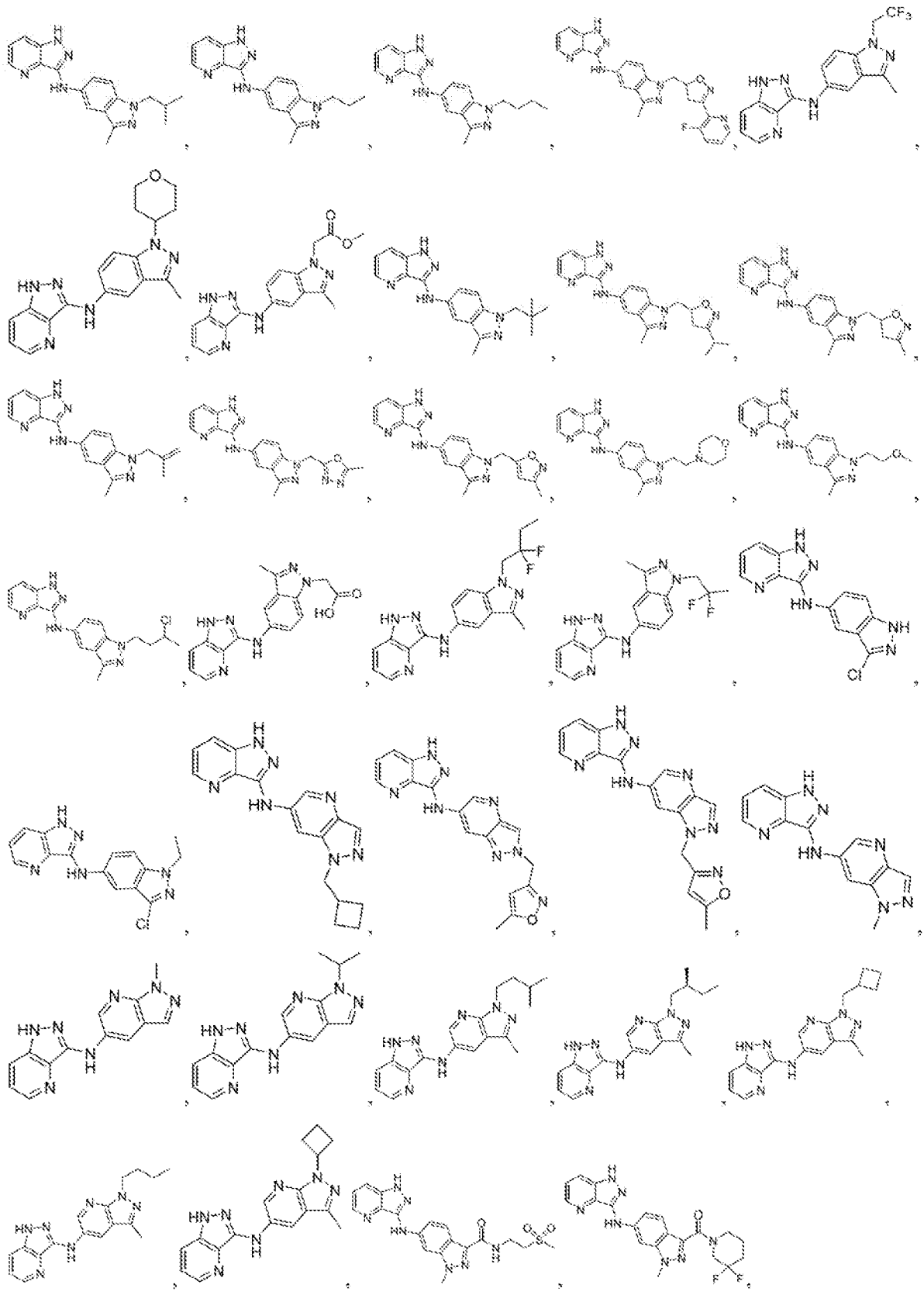
46. A compound of claim 1, of the following formula:

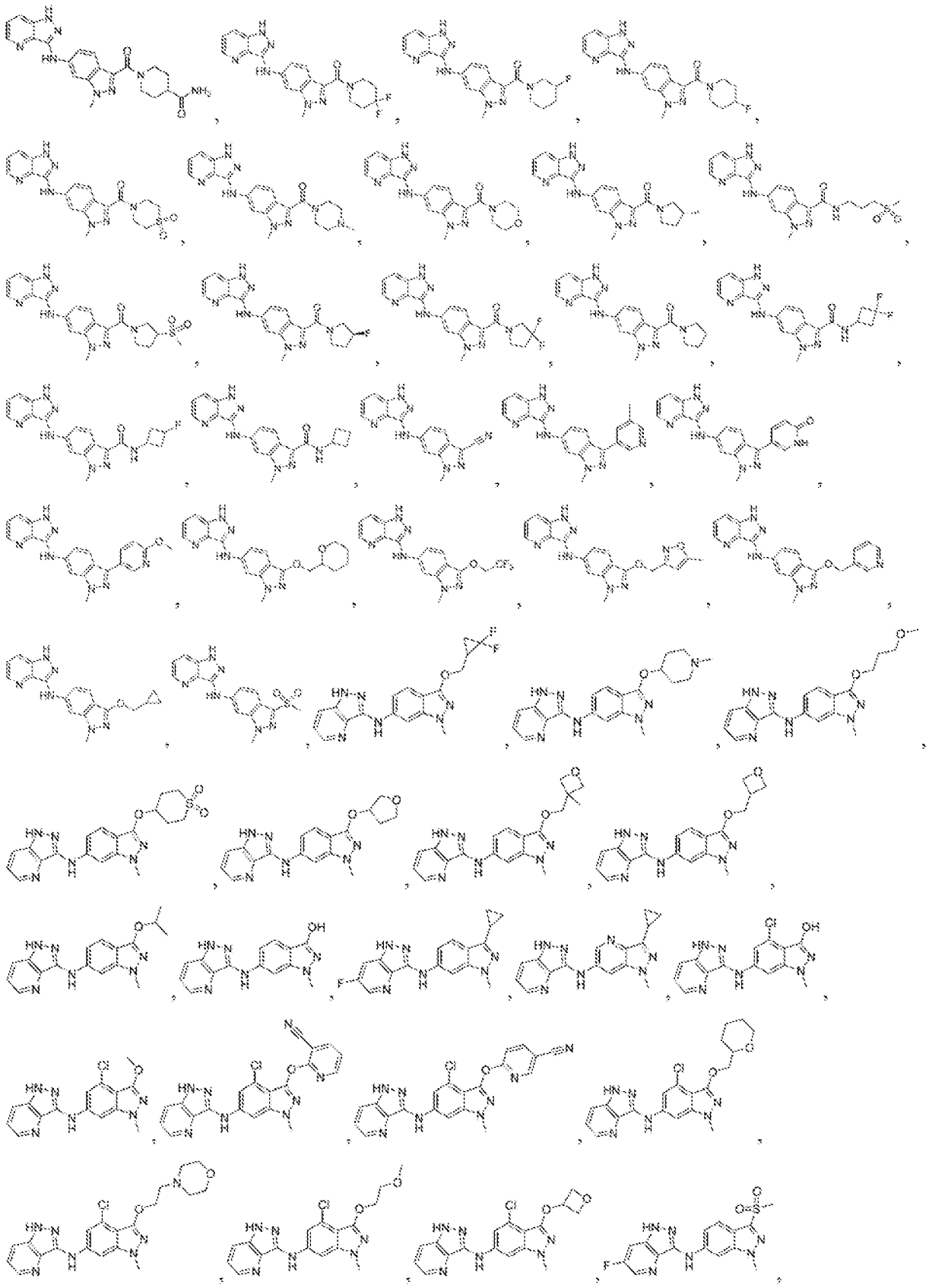



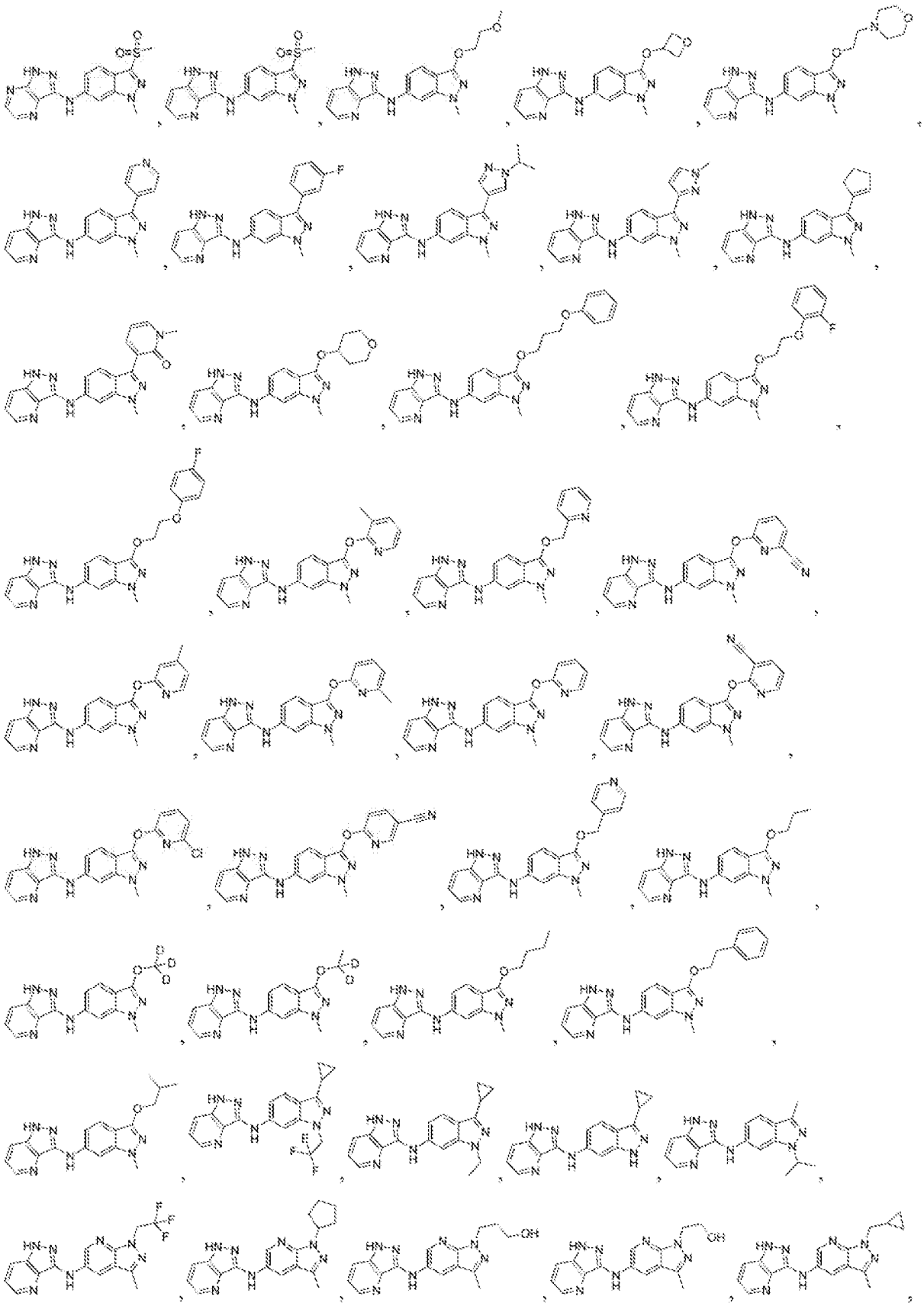
47. A compound of formula 1, of the following formula:

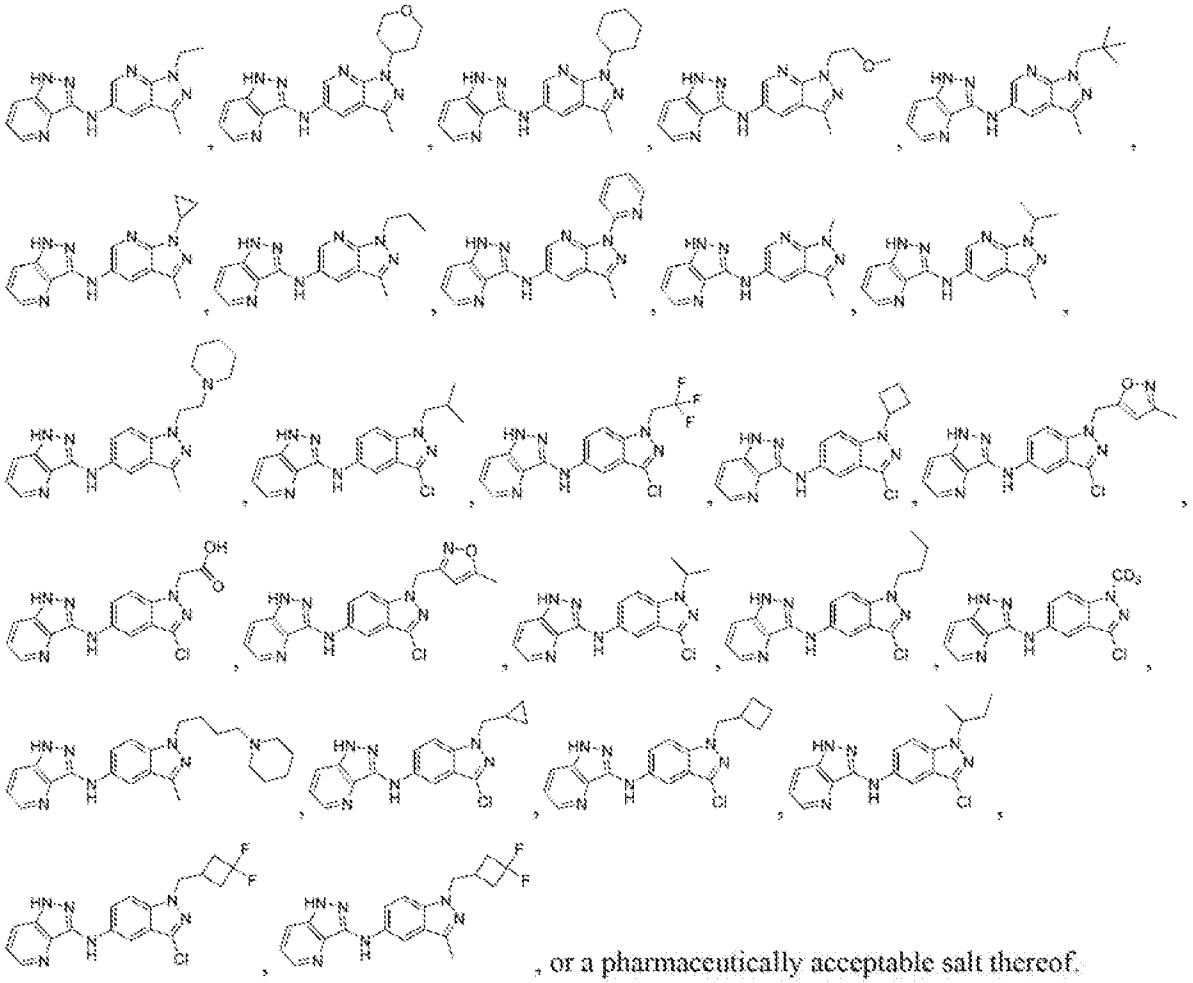






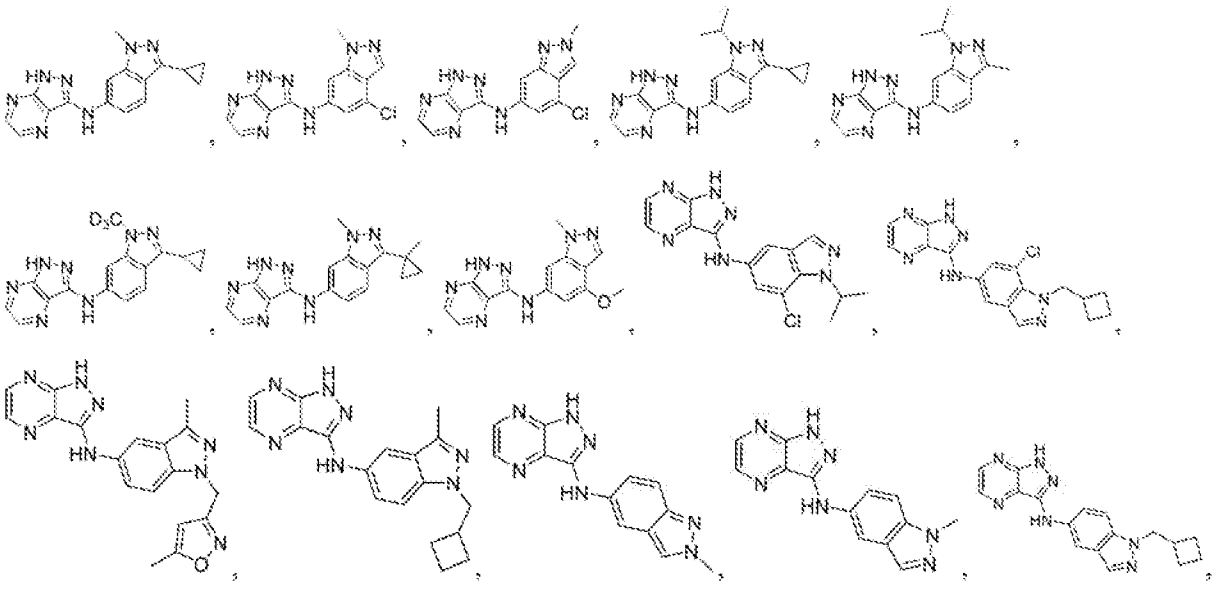


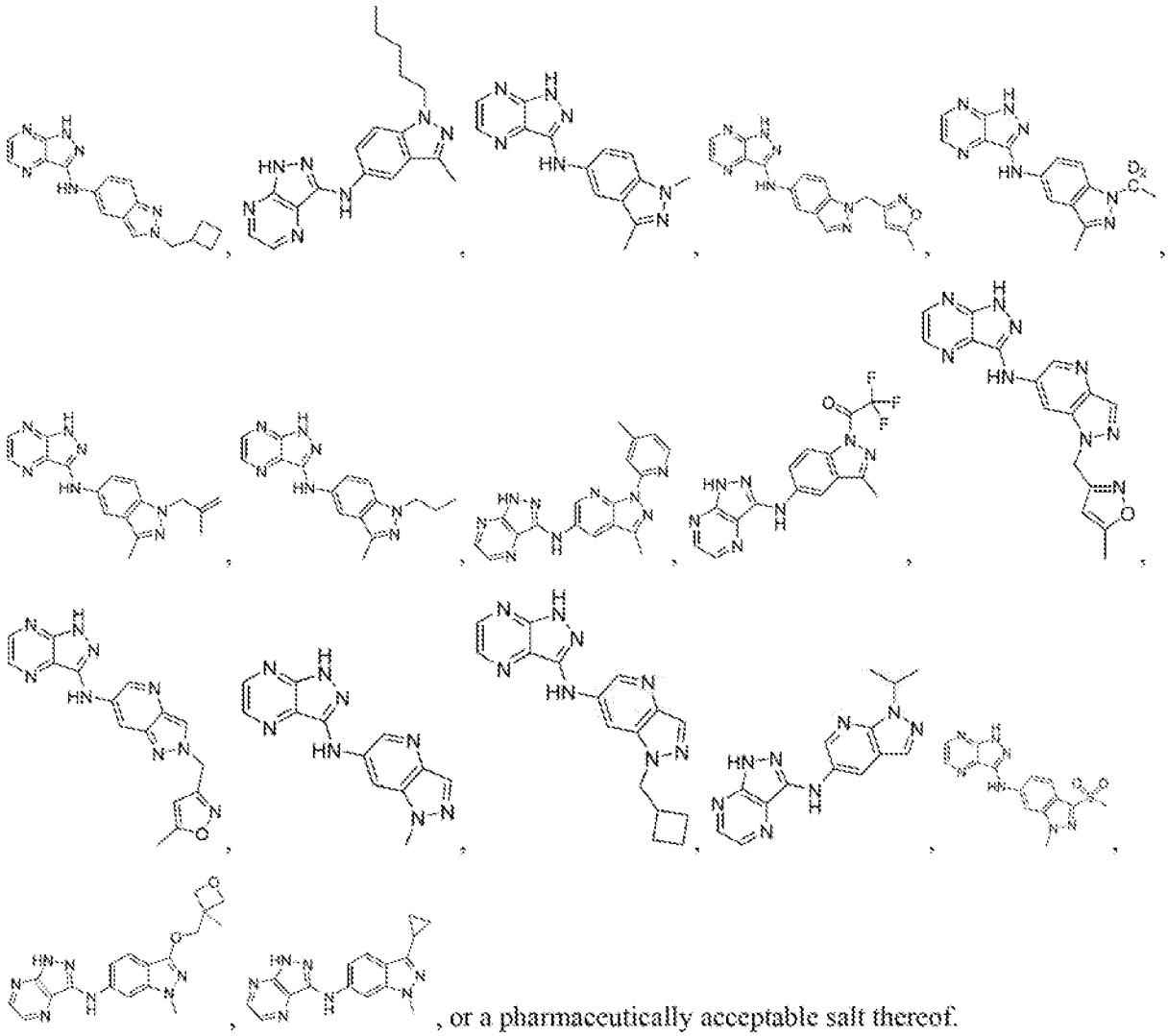




, or a pharmaceutically acceptable salt thereof.

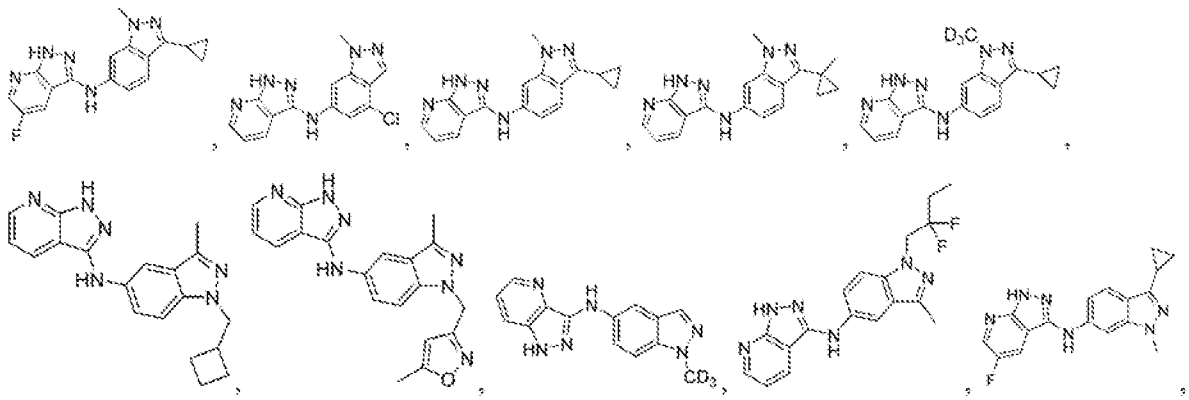
48. A compound of claim 1, of the following formula:

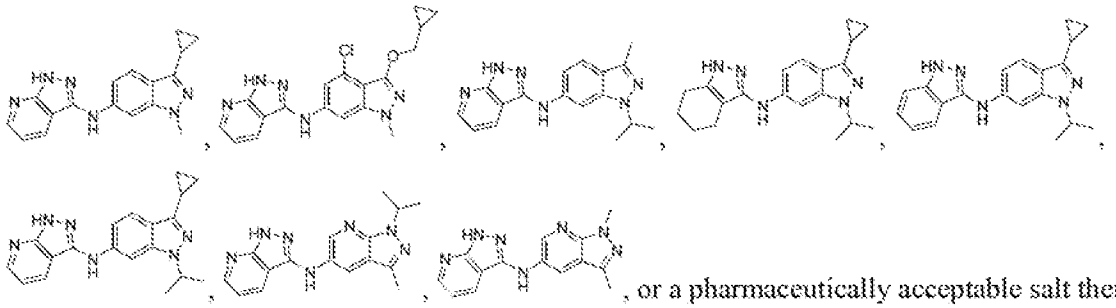




, or a pharmaceutically acceptable salt thereof.

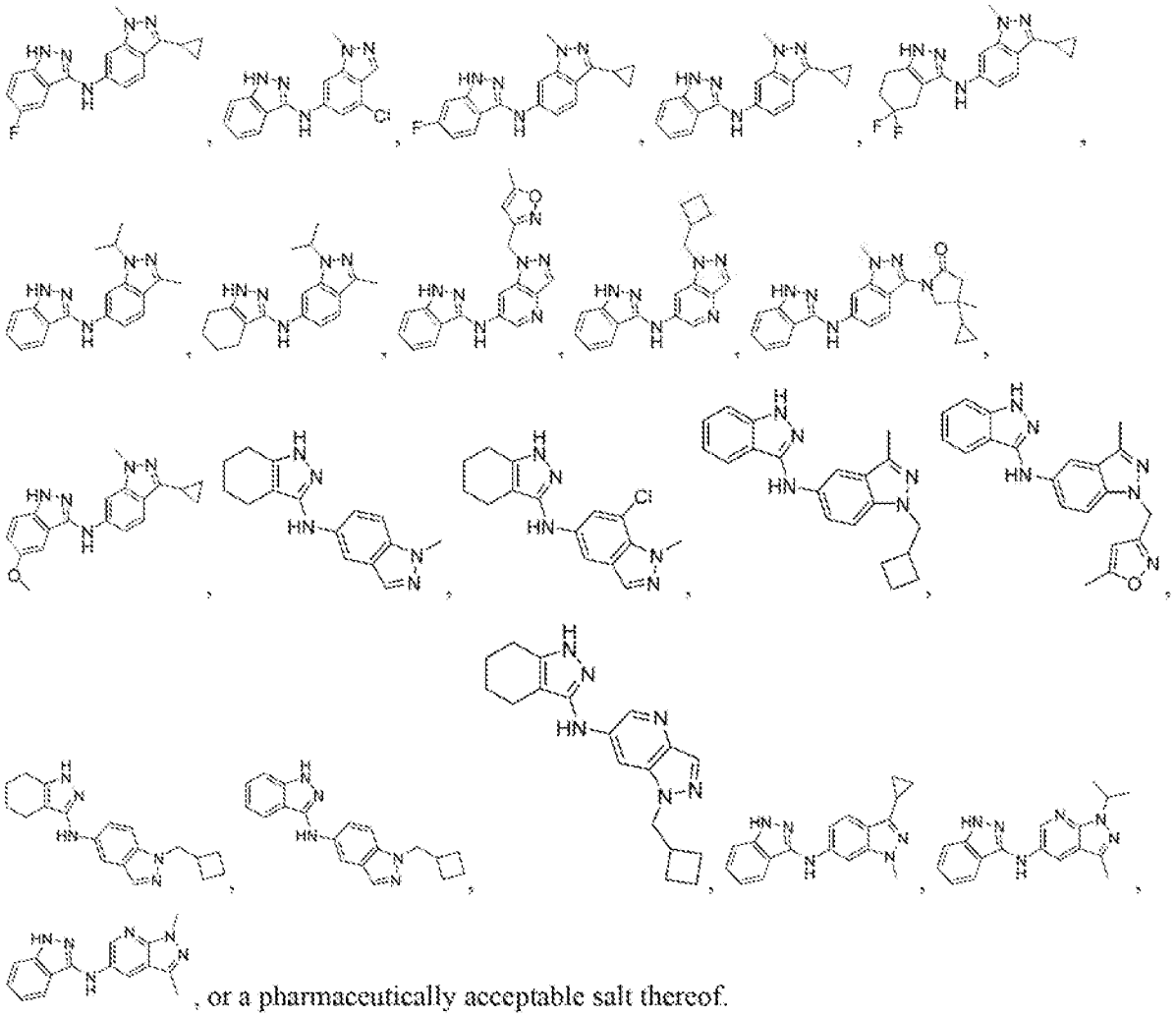
49. A compound of claim 1, of the following formula:





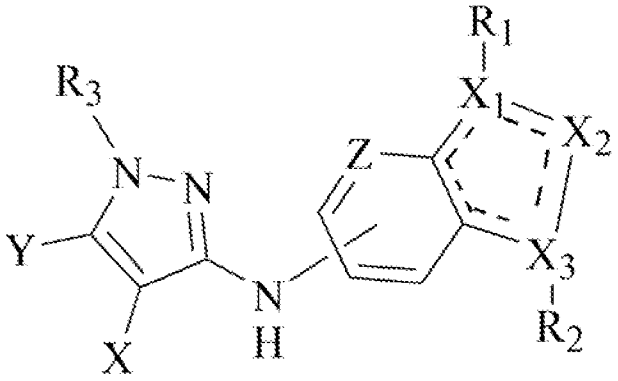
, or a pharmaceutically acceptable salt thereof.

50. A compound of claim 1, of the following formula:



, or a pharmaceutically acceptable salt thereof.

51. A method for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by a formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl,

CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

52. The method of claim 51, wherein the mammal is a human.

53. The method of claim 51, wherein the dysfunction is Parkinson's disease.

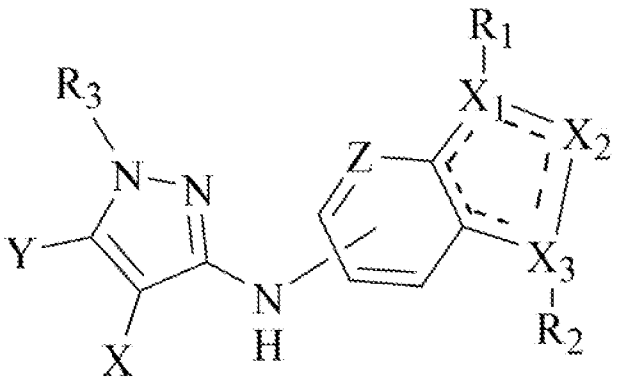
54. The method of claim 51, wherein the dysfunction is schizophrenia, psychosis, "schizophrenia-spectrum" disorder, depression, bipolar disorder, cognitive disorder, delirium, amnestic disorder, anxiety disorder, attention disorder, obesity, eating disorder, or NMDA receptor-related disorder.

55. The method of claim 51, wherein the dysfunction is Parkinson's disease; anxiety; motor effects after alcohol consumption; neurogenic fate commitment and neuronal survival; epilepsy; or certain cancers, for example, medulloblastoma, inflammation (for example, multiple sclerosis) and metabolic disorders (for example, diabetes) and taste enhancing associated with glutamatergic dysfunction and diseases in which mGluR4 receptor is involved.

56. The method of claim 51, wherein the mammal has been diagnosed with the dysfunction prior to the administering step.

57. The method of claim 51, further comprising the step of identifying a mammal having a need for treatment of the dysfunction.

58. A method for potentiating mGluR4 activity in a subject comprising the step of administering to the subject at least one compound at least one compound having a structure represented by a formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine;

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, in a dosage and amount effective to potentiate mGluR4 receptor activity in the subject.

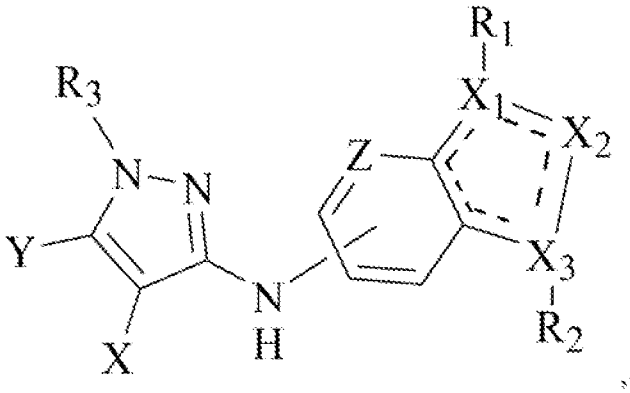
59. The method of claim 58, wherein the subject is a mammal.

60. The method of claim 58, wherein the subject is a human.

61. The method of claim 58, wherein the subject has been diagnosed with a need for potentiation of mGluR4 receptor activity prior to the administering step.

62. The method of claim 58, further comprising the step of identifying a subject having a need for potentiation of mGluR4 receptor activity.

63. A pharmaceutical composition comprising a compound having a structure represented by a formula:



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_3;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

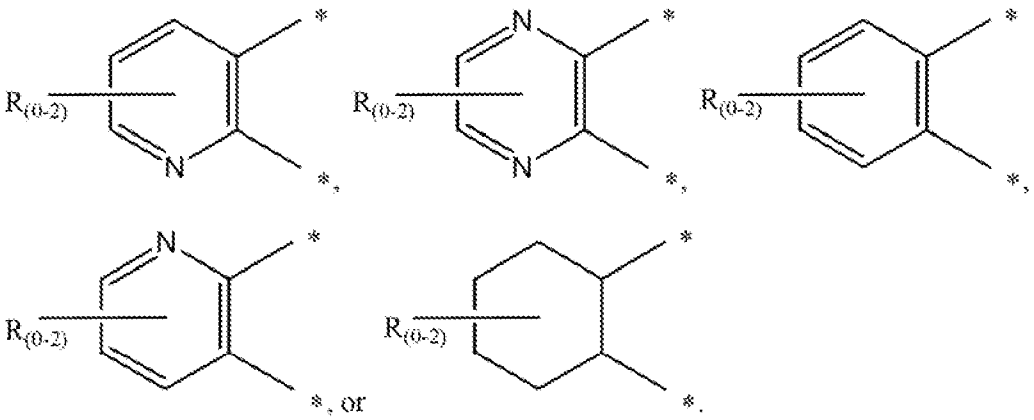
R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine;

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, and

a pharmaceutically acceptable carrier.

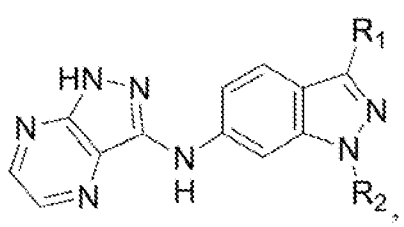
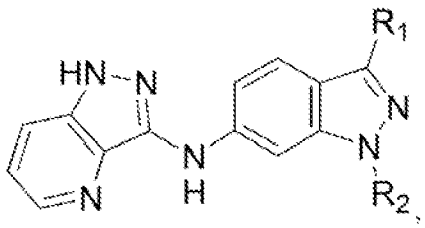
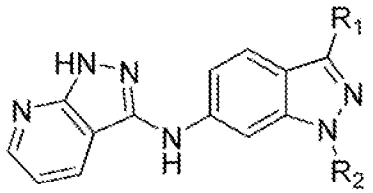
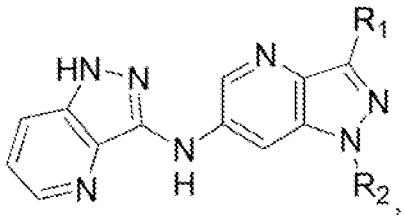
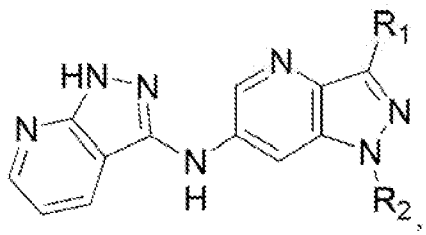
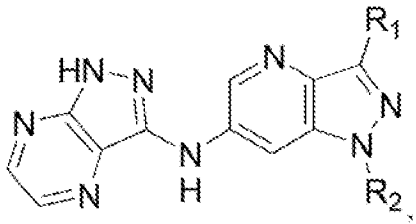
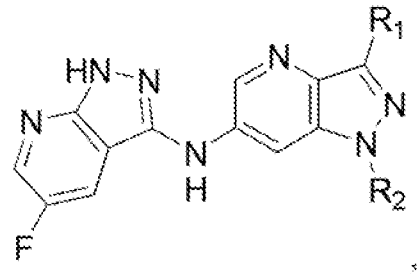
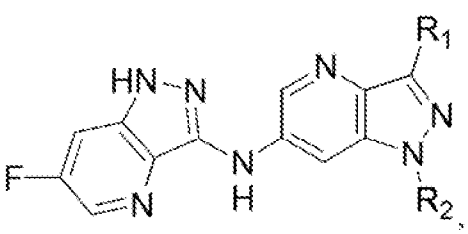
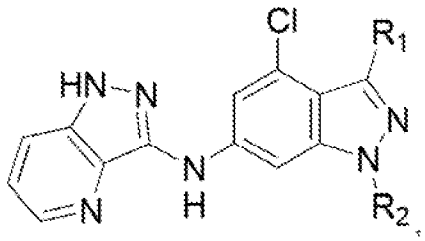
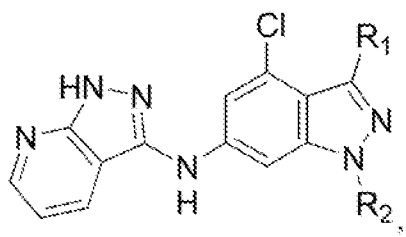
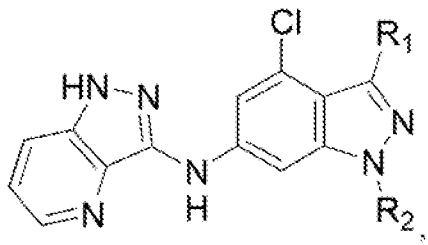
64. The composition of claim 63, wherein in the compound X and Y together form:

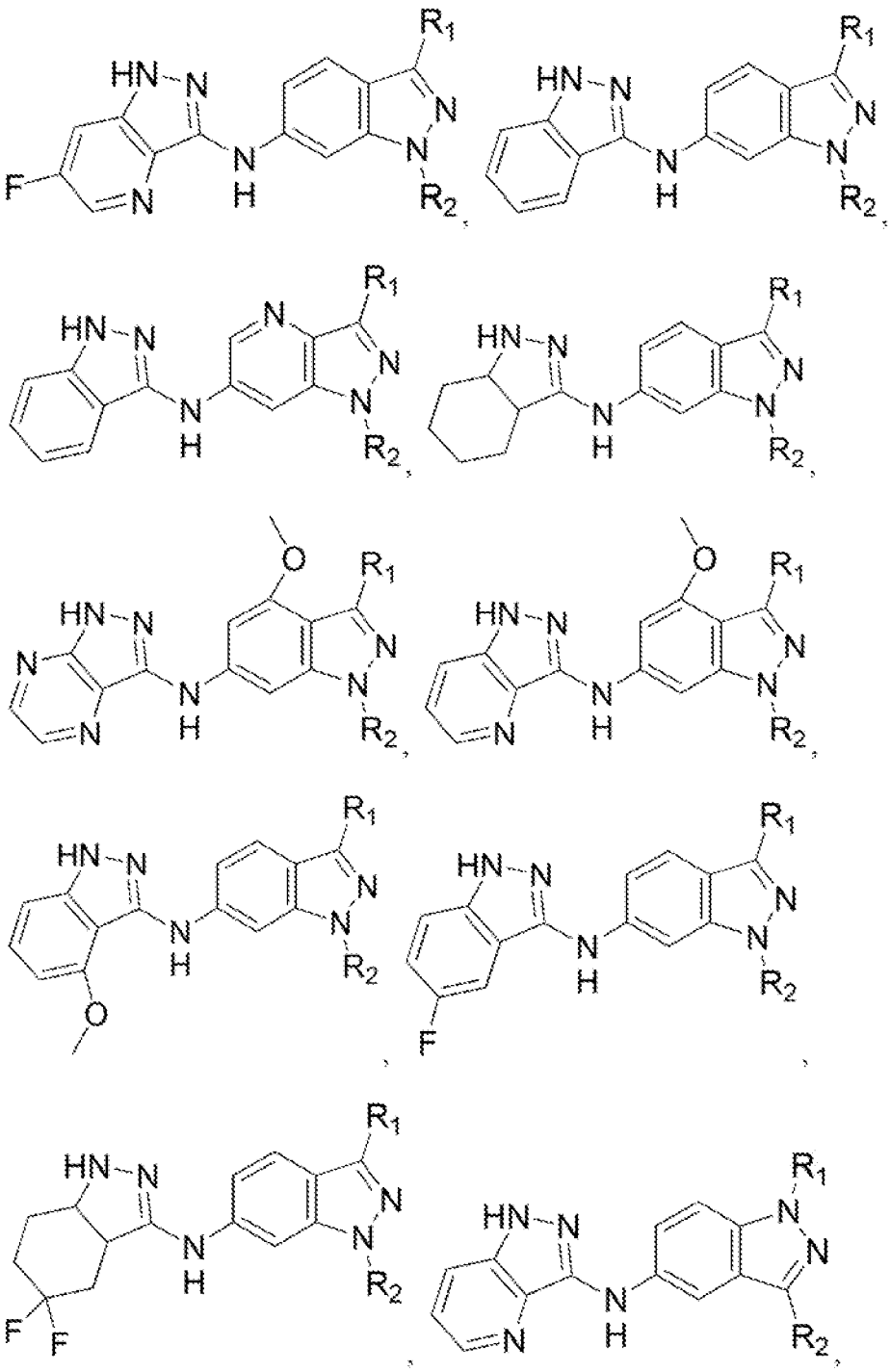


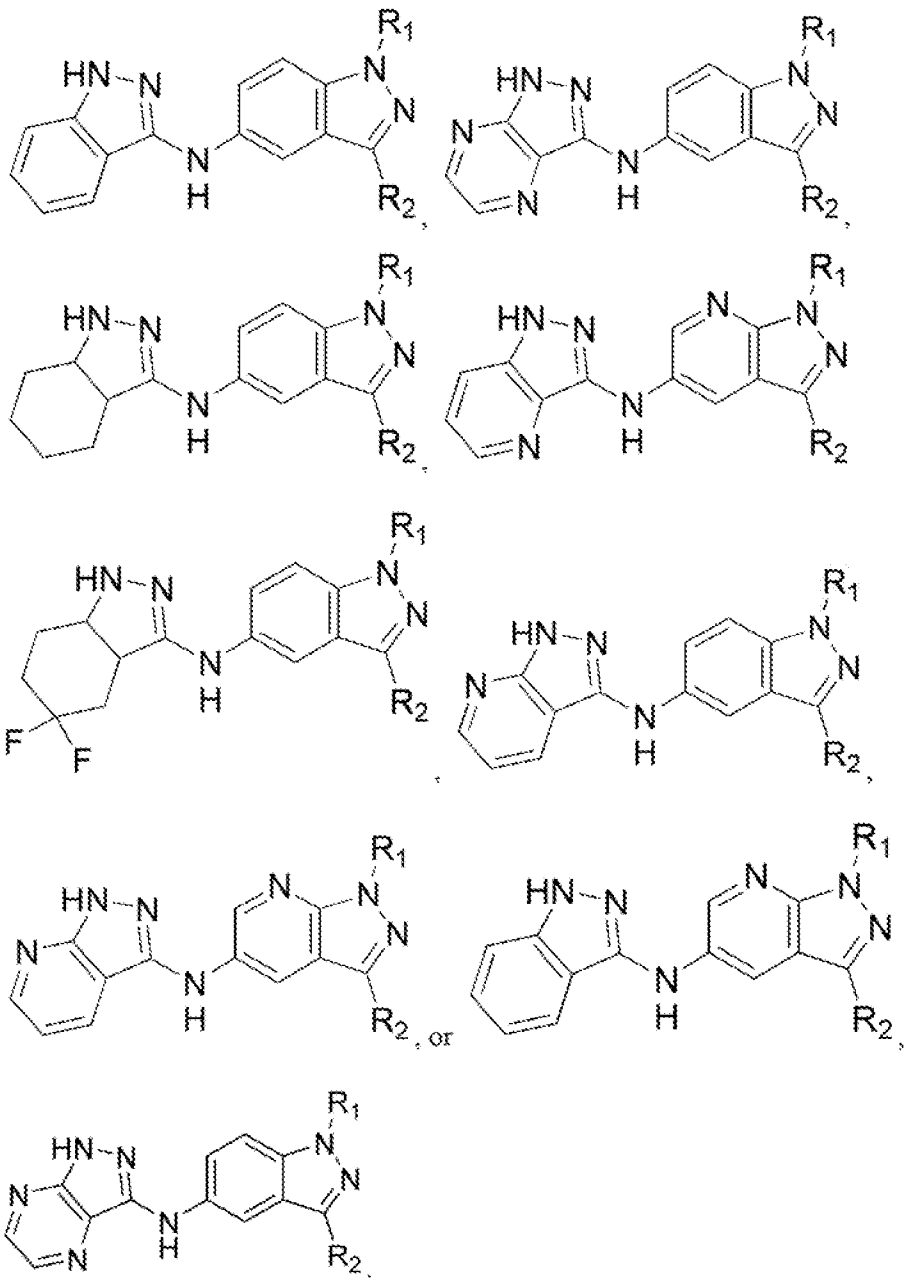
65. The composition of claim 63, wherein the in the compound R, when present, is F.

66. The composition of claim 63, wherein Z is N, CH, CD, or C-Cl.

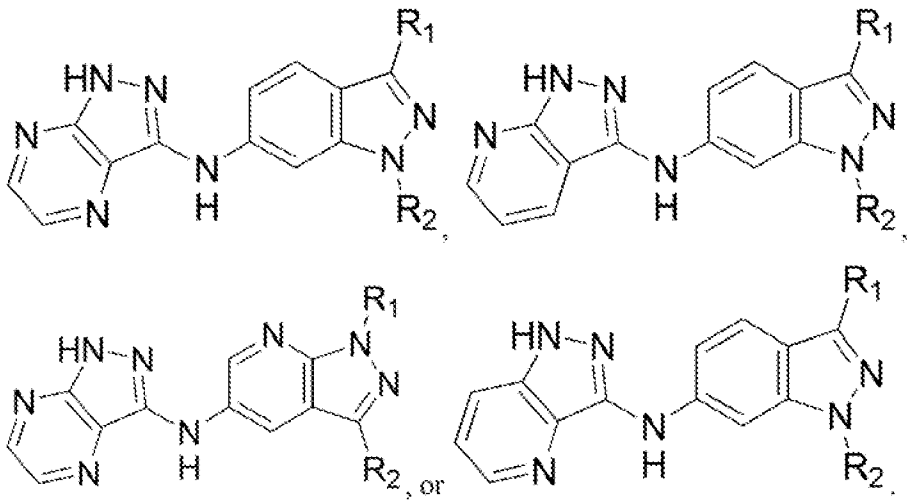
67. The composition of claim 63, wherein the compound is of the following formula:





68. The composition of claim 63, wherein the compound is of the following formula:



69. The composition of claim 63, wherein R_1 is H, alkyl, cycloalkyl, alkyl-cycloalkyl; and R_2 is H, alkyl, cycloalkyl, alkyl-cycloalkyl.

70. A method for the treatment of a disorder associated with mGluR4 neurotransmission dysfunction and other disease states in a mammal comprising the step of administering to the mammal at least one compound of claim 1, in a dosage and amount effective to treat the disorder in the mammal.

71. The method of claim 70, wherein the disorder is selected from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

72. The method of claim 70, wherein the disorder is Parkinson's disease.

73. The method of claim 70, wherein the disorder is a neurological and/or psychiatric disorder associated with mGluR4 receptor activity dysfunction.

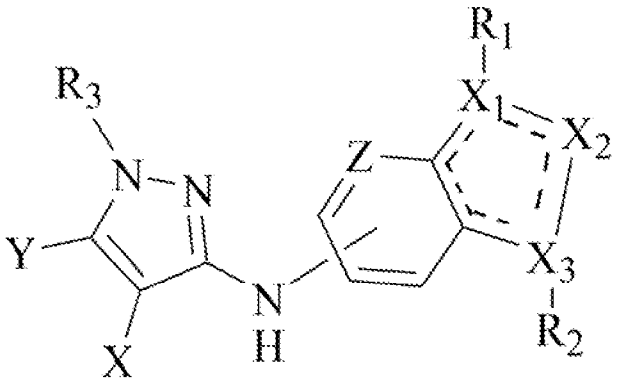
74. The method of claim 70, wherein the disorder is a neurological or psychiatric disorder associated with mGluR4 neurotransmission dysfunction selected from: schizophrenia, psychosis, "schizophrenia-spectrum" disorders, depression, bipolar disorder, cognitive disorders, delirium, amnestic disorders, anxiety disorders, attention disorders, obesity, eating disorders, and NMDA receptor-related disorders.

75. The method of claim 70, wherein the mammal is a human.

76. The method of claim 70, wherein the mammal has been diagnosed with the disorder prior to the administering step.

77. The method of claim 70, further comprising the step of identifying a mammal having a need for treatment of the disorder.

78. A method for the manufacture of a medicament for potentiating mGluR4 receptor activity in a mammal comprising combining a compound having a structure represented by a formula (I):



inwherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-

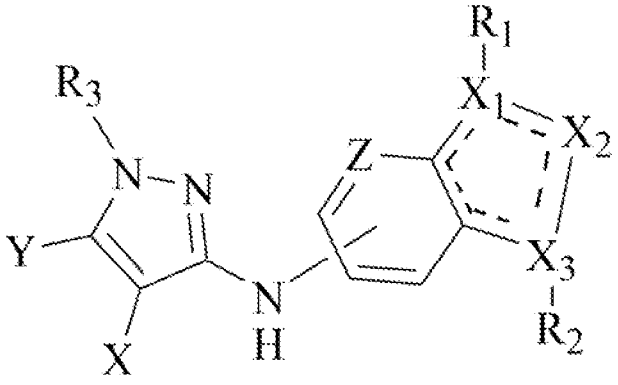
dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof,

with a pharmaceutically acceptable carrier.

79. Use of a compound for potentiating mGluR4 receptor activity in a mammal, wherein the compound has a structure represented by a formula (*I*):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_1R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine;or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof,

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

80. The use of claim 79, wherein the mammal is a human.

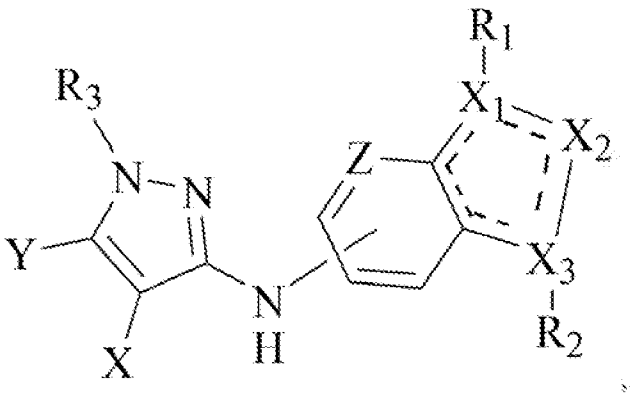
81. The use of claim 80, as a taste enhancer.

82. The use of claim 79, as a treatment of a disorder in a mammal.

83. The use of claim 82, wherein the disorder is a neurological and/or psychiatric disorder or other disease state associated with mGluR4 receptor activity dysfunction.

84. The use of claim 79, wherein the disorder is Parkinson's disease.

85. A method for the treatment of a neurotransmission dysfunction or other disease state associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by a formula (I):



wherein the variables are substituted or unsubstituted and:

X is N, alkyl, alkoxy, or CH, CD, and optionally together with Y forms a six membered ring optionally substituted with one or more R;

Y is N, alkyl, alkoxy, or CH and optionally together with X forms a six membered ring optionally substituted with one or more R;

Z is N, CH, CD, or C-halogen, C-Me, C-O-Me, C-CN;

R is independently chosen from H, Cl, F, CN, alkyl, cycloalkyl, Me, OMe, alkoxy;

X_1 is N, NH, CH, CD, CR_1;

X_2 is N, NR_1, or NR_2;

X_3 is N, NH, CH, CD, CR_1;

provided that one of X_1 or X_3 is CH or CR_1;

R_1 is independently H, alkyl, cycloalkyl, phenyl, cycloheteroalkyl, halogen, CF_3, Cl, CD_3, CD_2R, $CDRR_2$, aryl, heteroaryl, SO_2R3. O-R, O-aryl, O-heteroaryl, NHR, NR_2R_2, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, O-alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-

cycloalkyl, CN, alkoxy-cycloalkyl, alkoxy-cycloheteroalkyl, O-alkoxy, O-phenyl, O-alkoxyphenyl- O-dioxothian, hydroxyl, alkoxy, O-alkyl-heteroaryl, O-alkyl-cycloheteroalkyl, alkoxy-heteroalkyl, methylsulfonyl, O-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, alkoxy-heteroaryl, alkoxy, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, CO-alkyl, CO-cycloalkyl, CO-alkyl-cycloalkyl, CO-amino-alkyl-sulfonylmethyl, CO-amino-cycloalkyl ;

R_2 is independently H, heteroaryl, alkyl, phenyl, aryl, O-cycloheteroalkyl, alkoxy-cycloheteroalkyl, O-alkoxy-cycloheteroalkyl, O-alkoxyaryl, O-heteroaryl, alkoxy-heteroaryl, alkoxy, alkoxycycloheteroalkyl, alkyl-phenyl, cycloheteroalkyl, O-CD_3, O-CD_2R, hydroxyl, amino, cycloalkyl, CH_2-cycloalkyl, CO-alkyl; cycloheteroalkyl, H, CF_3, halogen,, CD_3, CD_2R, $CDRR_2$, aryl, SO_2R_3, OR, Oaryl, NHR, NR_3R_1, perfluorinated alkyl, heteroalkyl, benzyl, heteroaryl benzyl (CH_2heteroaryl), alkene, alkyl-cycloalkyl, CH_2-cycloalkyl, CH_2-CF_3, hydroxyalkyl, alkyl-alkoxy, alkyl-cycloheteroalkyl, alkyl-heteroaryl, O-alkyl-heteroaryl, alkyl-carboxylic acid, CO-CF_3, alkyl-CO-O-alkyl, CO-alkyl-sulfonyl-alkyl, CO-cycloheteroalkyl, CO-NH-cycloalkyl, CN, alkoxy-cycloalkyl, O-dioxothian, hydroxyl, methylsulfonyl;

R_3 is H, alkyl, alkoxyphenyl, pyridine, nitrilepyridine, chloropyridine; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with (i) a drug having a known side-effect of increasing metabotropic glutamate receptor activity, (ii) a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or (iii) a drug known to treat the neurotransmission dysfunction or other disease state associated with potentiation of mGluR4.

86. The method of any one of claims 85, wherein co-administration is sequential.

87. The method of any one of claims 85, wherein the mammal is a human.

88. The method of any one of claims 85, wherein the dysfunction is Parkinson's disease.

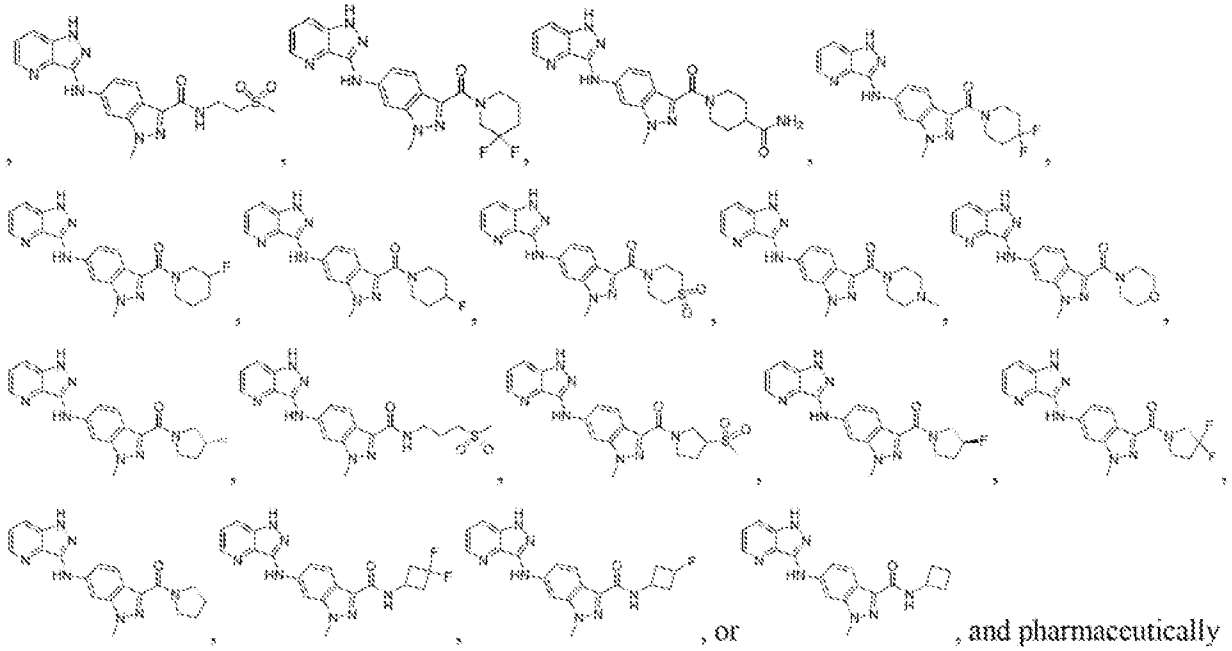
89. The method of any one of claims 85, wherein the dysfunction is schizophrenia, psychosis, "schizophrenia-spectrum" disorder, depression, bipolar disorder, cognitive disorder, delirium, amnestic disorder, anxiety disorder, attention disorder, obesity, eating disorder, or NMDA receptor-related disorder.

90. A compound of claim 1, wherein heteroaryl is substituted or unsubstituted and chosen from isoxazole, methyl-isoxazole, alkyl-isoxazole, benzoisoxazole, quinnoline, pyridine, nitrilepyridine, or chloropyridine.

91. A compound of claim 1, wherein cycloheteroaryl is substituted or unsubstituted and chosen from pyrolidin-one, methyl-pyrolidin-one, alkyl-pyrolidin-one, piperidine, fluoro-piperidine, di-fluoro-

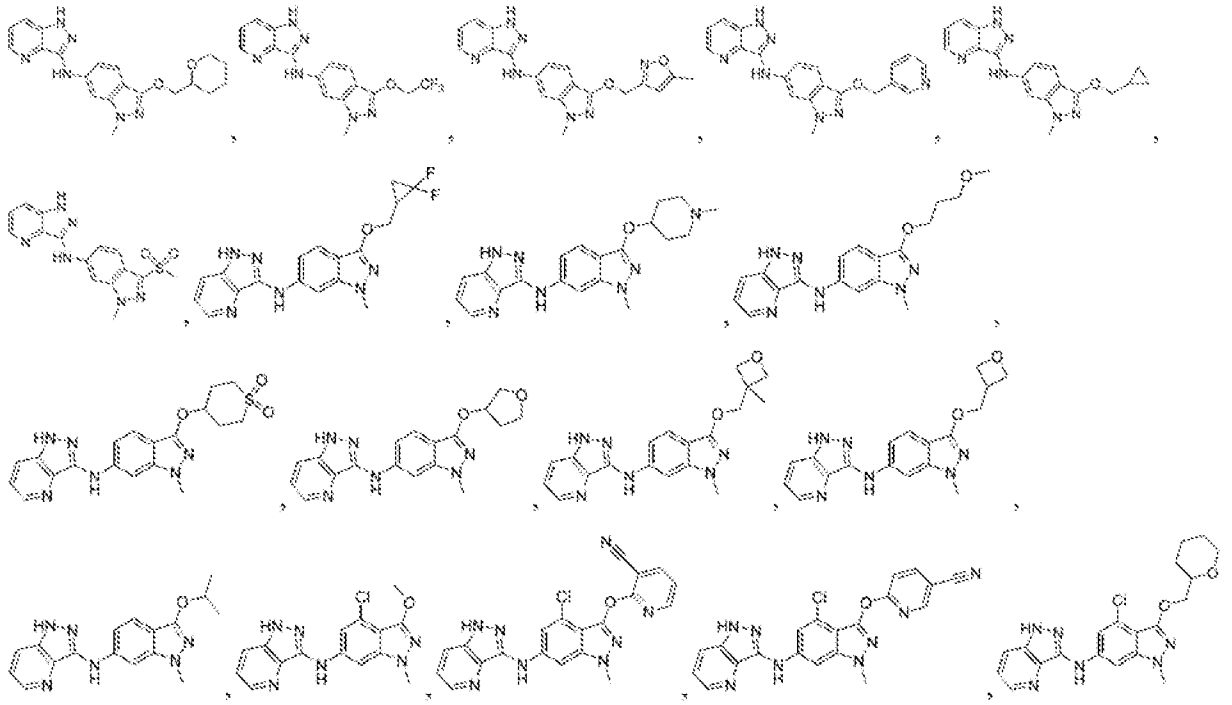
piperidine, tetrahydropyran, piperazine, methyl-piperazine, thiomorpholine-dioxide, morpholine, pyrolidine, or oxetane.

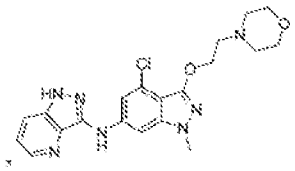
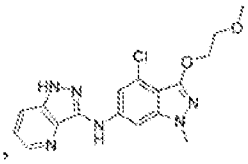
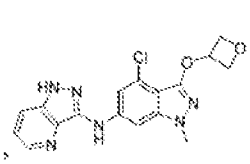
92. A compound of claim 21, of the following formula:

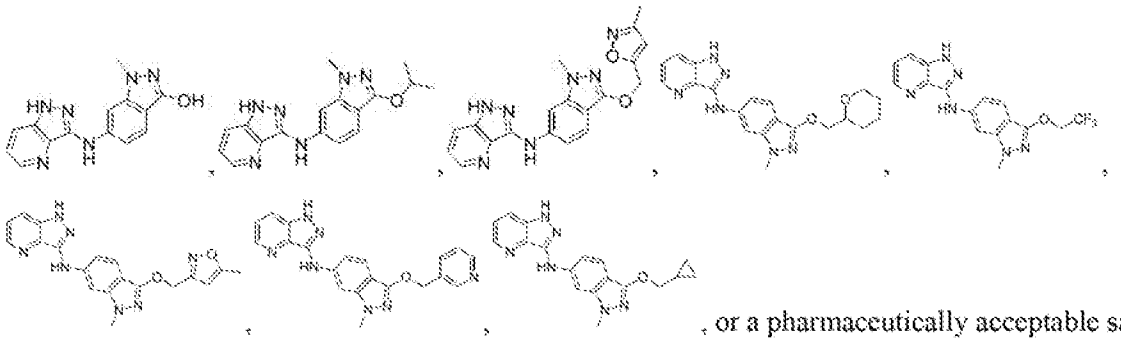


, and pharmaceutically acceptable salts thereof.

Claim 93. A compound of claim 22, of the following formula:

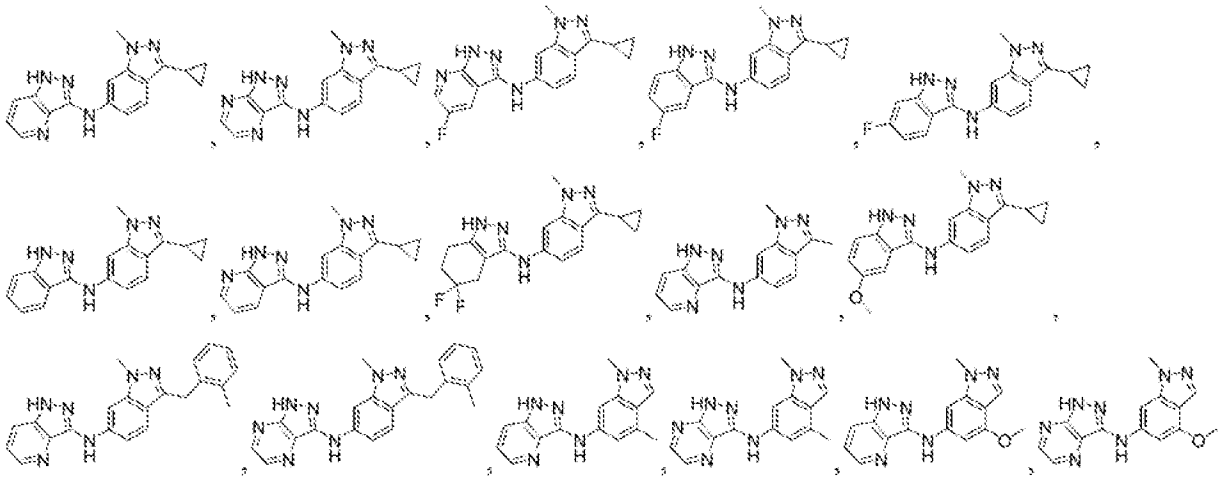




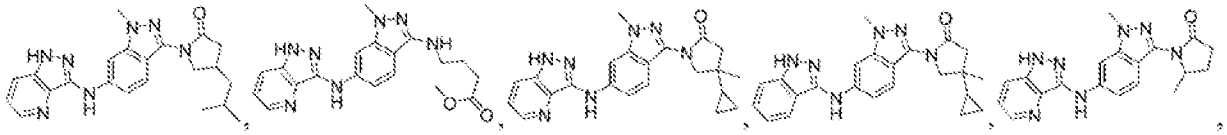
, or a pharmaceutically acceptable salt thereof.

95. A compound of claim 1, of the following formula:



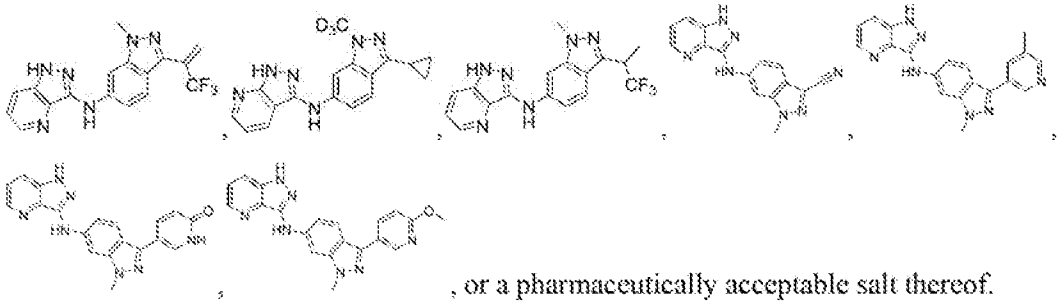
, or a pharmaceutically acceptable salt thereof.

96. A compound of claim 1, of the following formula:



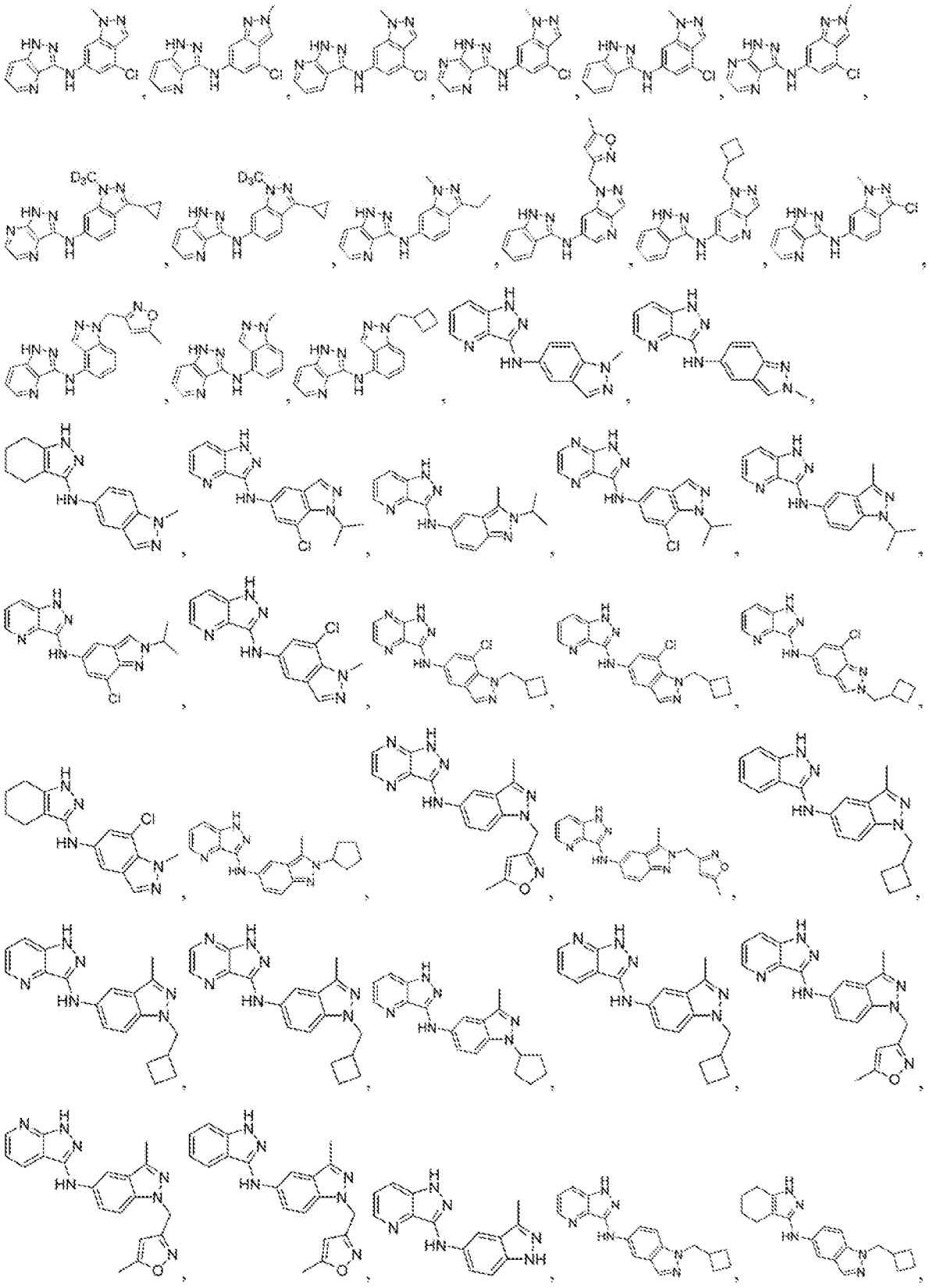
or a pharmaceutically acceptable salt thereof.

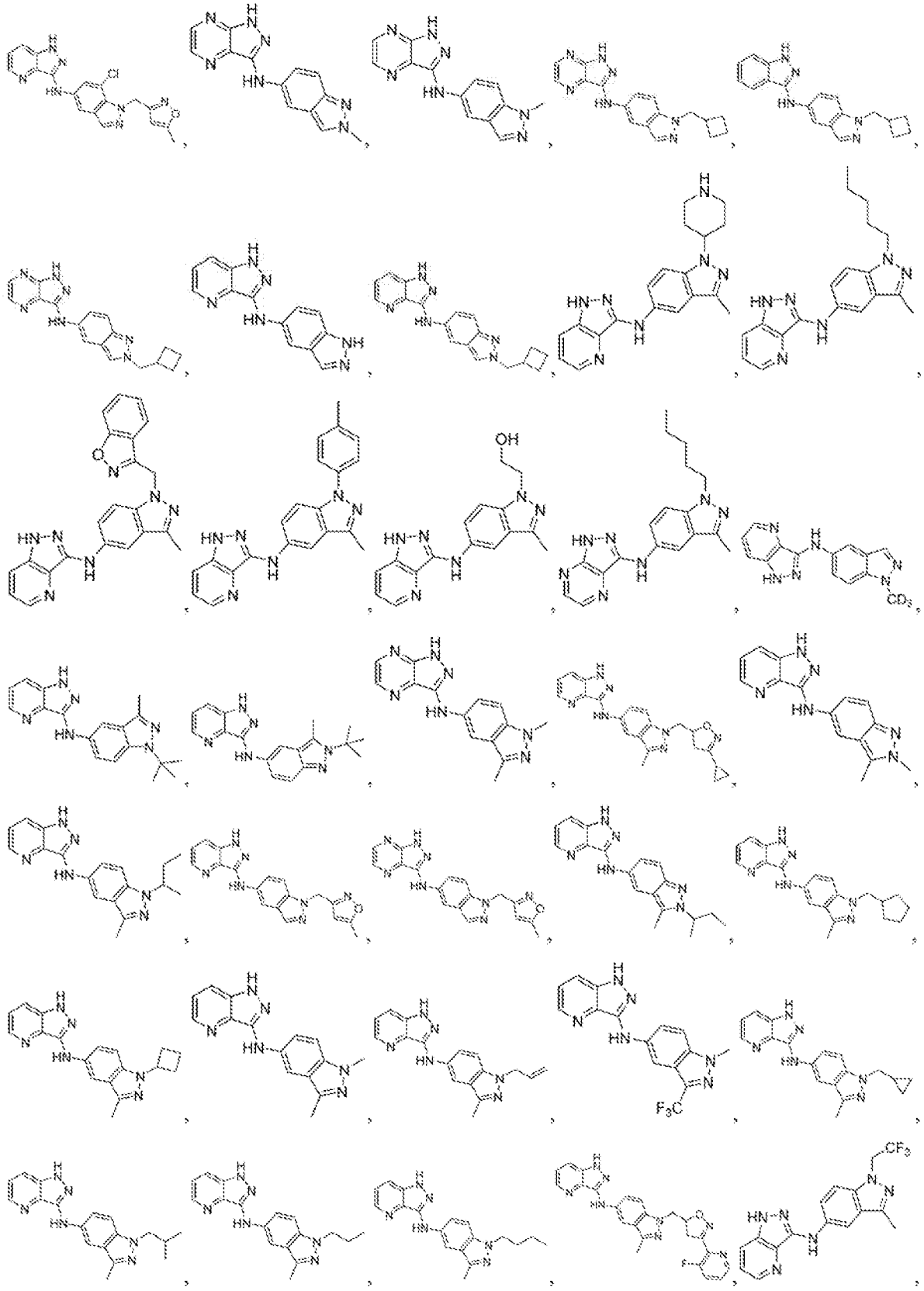
97. A compound of claim 1, of the following formula:

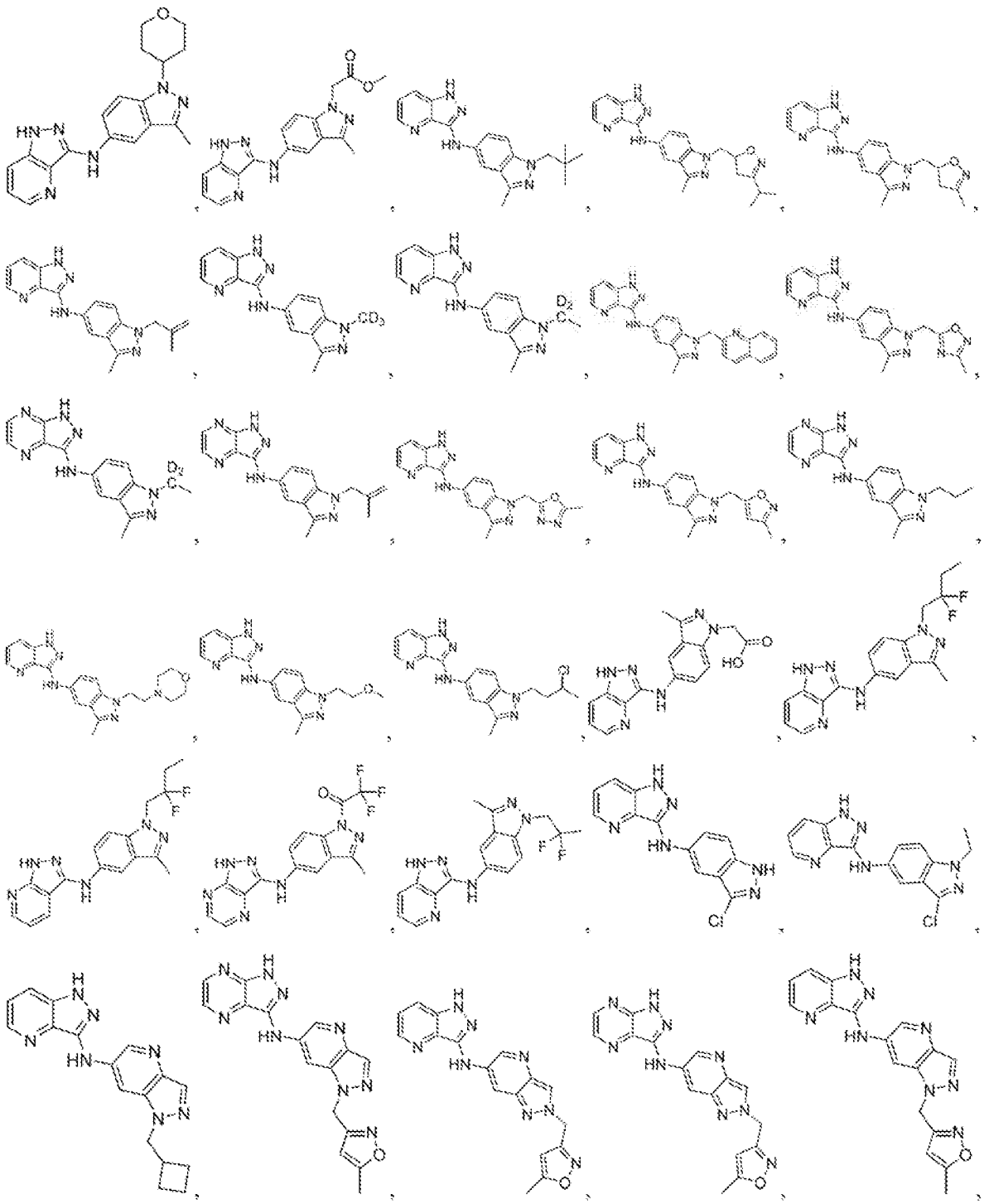


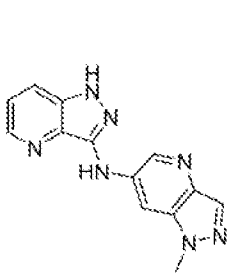
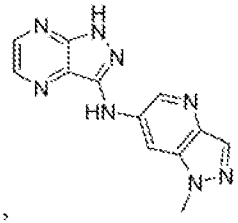
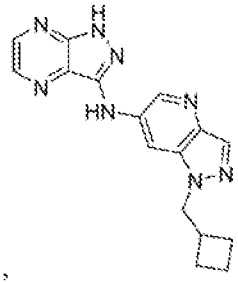
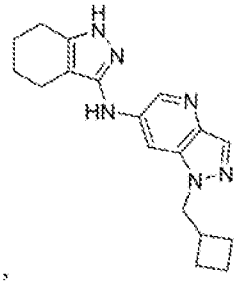
, or a pharmaceutically acceptable salt thereof.

98. A compound of claim 1, of the following formula:

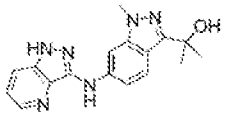




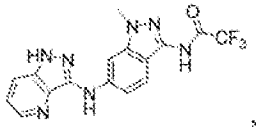


 ,  ,  ,  ,or a pharmaceutically acceptable salt thereof.

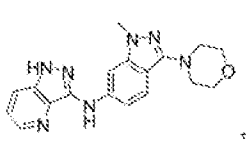
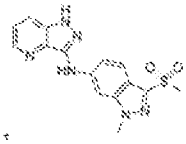
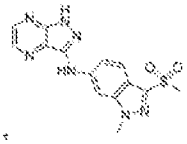
99. A compound of claim 1, of the following formula:

 , or a pharmaceutically acceptable salt thereof.

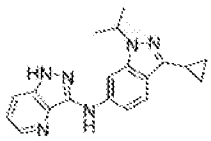
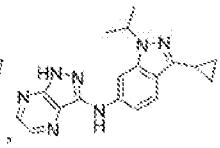
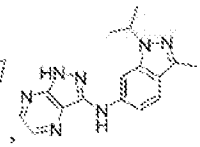
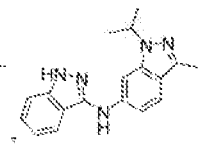
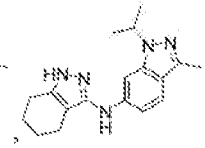
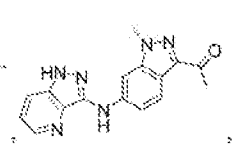
100. A compound of claim 1, of the following formula:

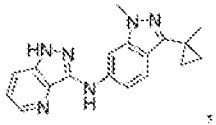
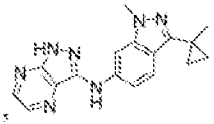
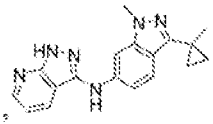
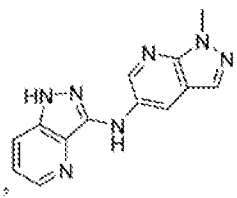
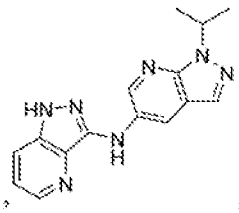
 , or a pharmaceutically acceptable salt thereof.

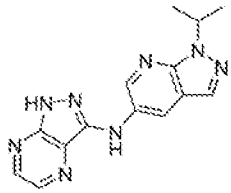
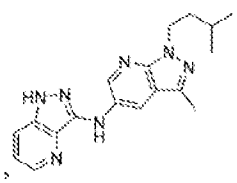
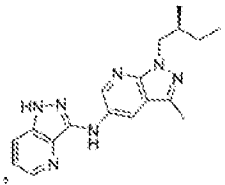
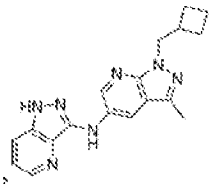
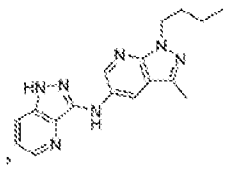
101. A compound of claim 1, of the following formula:

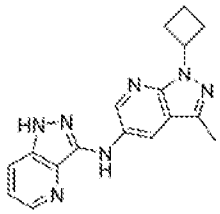
 ,  ,  , or a pharmaceutically acceptable salt thereof.

102. A compound of claim 1, of the following formula:

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 , or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/16018

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/519; C07D 471/04, 487/04 (2016.01)
CPC - A61K 31/415, 31/437; C07D 471/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/519; C07D 471/04, 487/04 (2016.01)
CPC: A61K 31/415, 31/437; C07D471/04 USPC: 514/262.1; 544/127, 262

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google Scholar; IP.com; SureChEMBL; KEYWORDS: pyrazolo pyridin*, pyrazolo pyrimidin*, mGluR*, mGluR4, treat* neurotransmission dysfunction*, mGluR4 activit*, diagnos* subject*, identif* subject*, potentiat* mGluR4 activit*, schizophrenia, Parkinson*, tast* enhanc*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2013/0096110 A1 (CONN, PJ et al.) 18 April 2013; paragraphs [0009]-[0011], [0014], [0037]-[0038], [0053], [0056], [0063], [0069]-[0070], [0088], [0190]-[0191], [0198], [0201]-[0202], [0209], [0212], [0218], [0220]-[0221]; claims 1, 5, 64-65	1-2, 3/1-2, 5-21, 23-24, 25A, 25B, 28-31, 33-39, 42-44, 46-92, 95, 97-99, 101-102 --- 22, 26-27, 40-41, 45, 93-94, 96
Y	US 2004/0127508 A1 (GERLACH, M et al.) 01 July 2004; paragraphs [0002], [0009], [0018]-[0019], [0026], [0028]	22, 26-27, 45, 93-94
Y	US 2008/0176904 A1 (GOVEK, SP et al.) 24 July 2008; paragraphs [0007], [0017], [0027]-[0028], [0044], [0050], [0068], [0195]	40-41
Y	US 7,704,994 B2 (SEHMI, SS et al.) 27 April 2010; column 13, lines 49-59; column 86, lines 1-16	96
A	US 2009/0048250 A1 (ARONOV, A et al.) 19 February 2009; paragraphs [0127], [0159]-[0160]	32
A	US 4,085,280 A (KRAPCHO, J et al.) 18 April 1978; abstract	32

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2016 (13.03.2016)	07 APR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/16018

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MINU, M et al., Synthesis, antimicrobial activity and QSAR studies of new 2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2H-indazoles, Bioorg. Med. Chem. Lett. 19, pages 2960-2964, 2009; [retrieved on 2016-03-11]. Retrieved from the Internet: <URL: https://www.researchgate.net/profile/Minu_Maninder3/publication/24397254_Synthesis_antimicrobial_activity_and_QSAR_studies_of_new_23-disubstituted-33a4567-hexahydro-2H-indazoles/links/551480660cf283ee0836dc2d.pdf> <DOI: 10.1016/j.bmcl.2009.04.052>; page 2960, Scheme 1, see structures 1-3	32
A	US 2010/0197665 A1 (BANDIERA, T et al.) 05 August 2010; paragraph [0287]	100
A	US 2010/0240618 A1 (PENNELL, AMK et al.) 23 September 2010; paragraphs [0390]-[0391]	100
A	US 2014/0303164 A1 (GILEAD SCIENCES, INC.) 09 October 2014; paragraph [0954]	100

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/16018

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

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.