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DIPYRAZOLES AS CENTRAL NERVOUS SYSTEM AGENTS

FIELD OF THE INVENTION

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The present invention relates to novel dipyrazole compounds, compositions, and methods for the treatment and/or prevention of, neuropsychiatric disorders that result primarily from dysfunction at the glutamate receptors AMPA and NMDA.

BACKGROUND OF THE INVENTION

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Glutamate is the most abundant excitatory neurotransmitter in the mammalian central nervous system (CNS) and mediates the fast and slow neurotransmission responsible for such normal neurophysiological processes as memory acquisition and processing, and synaptic plasticity. Postmortem and pharmacological findings strongly implicate dysregulation of glutamate neurotransmission in the pathophysiology of several neuropsychiatric disorders including schizophrenia, Alzheimer disease, Parkinson disease, Huntington disease, epilepsy, attention-deficit hyperactivity disorder, AIDS-related dementia, neuropathic pain, depression, mild cognitive impairment, learning and memory disorders, and others (Lehohla, et al., *Metab Brian Dis*, 2004; Coyle, et al., *Ann. NY Acad. Sci.*, 2003; Coyle, et al., *Curr. Drug Targets CNS Neurol. Disord.*, 2002; Krystal, et al., *Arch Gen Psychiatry*, 2002; Dingledine et al., *Pharmacol. Rev.*, 1999; and Ozawa, et al., *Prog. Neurobiol.*, 1998).

Glutamate neurotransmission is mediated by three ionotropic glutamate receptors. These receptors are cation-specific ion channels which regulate fast synaptic neurotransmission. The ionotropic glutamate receptors have been classified into three types: the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, the kainic

acid (KA) receptors, and the N-methyl-D-aspartate (NMDA) receptors based on their unique pharmacological, electrophysiological and biochemical properties (Nakanishi, *Science*, 1992). Furthermore, each of these ionotropic glutamate receptors is made up of multiple heteromeric subunits, contributing to receptor heterogeneity in different tissues (Ozawa, et al., *Prog Neurobiol*, 1998). However, each of the ionotropic glutamate receptors contain predominant subunits, some requisite for functionality and thought to be most responsible for the regulation of function.

Regulation of the ionotropic glutamate receptors is partly achieved through phosphorylation of specific tyrosine, threonine and serine residues by several kinases and, conversely, through dephosphorylation of those residues by specific phosphatases (Carvalho, et al., *Neurochem. Res.*, 2000 and Swope, et al., *Adv Second Messenger Phosphoprotein Res.* 1999). The phosphorylation state of receptor subunits plays a critical role in receptor activity. For example, NMDA receptors are regulated by several kinases and phosphatases acting on its NR1 subunit. Protein kinase C (PKC), and cAMP-dependent protein kinase (PKA) have been shown to phosphorylate serine residues 896 and 897 of the NR1 subunit, respectively (Tingley, et al., *J. Biol. Chem.*, 1997 and Snyder, et al., *Neuropharmacology*, 2003). Likewise, AMPA receptors are regulated by several kinases and phosphatases acting on the GluR1 subunit; PKA phosphorylates serine residue 845 (Roche, et al., *Neuron* 16: 1179-1188, 1999; Wang, et al., *Science* 253: 1132-1135, 1991). Protein phosphatase I (PP1) dephosphorylates these serine residues, thus leading to a molecular switch for receptor activity.

Spinophilin (also named Neurabin II) is a scaffold protein, which is enriched in the dendritic spines of CNS neurons that serve as the major site of glutamatergic synapses in the brain (Allen, et al., *Proc. Natl. Acad. Sci. USA*, 1997; Hsieh-Wilson, et al., *Biochemistry*, 1999). Spinophilin was originally identified based on its ability to bind F-actin and protein phosphatase I (PP1). The interaction of spinophilin with PP1 is especially important for the function of ionotropic glutamate receptors as spinophilin acts as a modulator of glutamatergic synaptic neurotransmission by regulating PP1's ability to dephosphorylate the ionotropic glutamate receptors via localization. Evidence for such a function has been demonstrated using voltage whole-cell recordings of kainic acid-induced rundown of AMPA currents in individual acutely dissociated prefrontal cortical neurons (Yan, et al., *Nature Neurosci.* 1999). In these experiments, agonist-induced rundown of kainic-acid-evoked currents was inhibited by a peptide corresponding to the PP1 binding domain of spinophilin, but not by the same

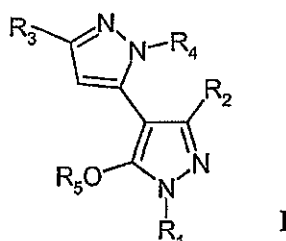
peptide containing a point mutation, thus indicating that when spinophilin no longer interacts with PP1, AMPA receptors (in this example) are no longer dephosphorylated to reduce function; therefore, they remain more active.

In order to discover small molecule compounds that would mimic the action of the spinophilin peptide described above, a novel protein interaction assay between PP1 and spinophilin was utilized to discover inhibitors of binding. These compounds were then evaluated in a whole-cell voltage clamp assay for the ability to inhibit the agonist-induced rundown of AMPA currents and for modulation of NMDA-evoked currents.

Thus, compounds discovered here should have utility in the treatment of several neuropsychiatric disorders which have been linked to the dysfunction of glutamate neurotransmission.

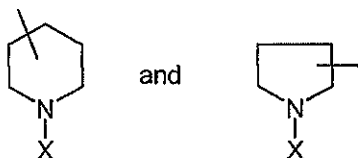
SUMMARY OF THE INVENTION

The present invention is a compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of aryl, benzyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, C₃₋₈cycloalkylC₁₋₆alkyl, heteroaryl, arylcarbonyl, arylC₁₋₆alkylC₃₋₈cycloalkylcarbonyl, C₁₋₁₀alkylcarbonyl, heteroarylcarbonyl and



wherein X is hydrogen, benzyl, arylC₂₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, or C₃₋₈cycloalkylC₁₋₆alkyl;

wherein said aryl, benzyl, or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, or aryl;

R₂ is selected from the group consisting of C₁₋₆alkyl, C₃₋₈cycloalkyl, and aryl wherein said

5 aryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₃ is selected from the group consisting of aryl, C₃₋₈cycloalkyl, C₁₋₆alkyl and heteroaryl

10 wherein said aryl or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₄ is selected from the group consisting of H, aryl, arylC₂₋₆alkyl, benzyl, hydroxyC₂₋₆alkyl, C₁₋₆perfluoroalkyl, C₃₋₈cycloalkyl and C₁₋₆alkyl wherein said aryl or benzyl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋

15 6perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₅ is H, C₁₋₆alkyl, or C₃₋₈cycloalkyl; and

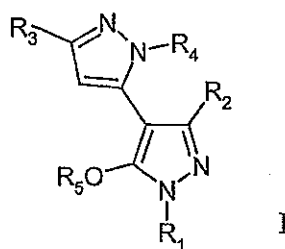
with the proviso that

(a) when R₁ and R₄ are phenyl or 4-chlorophenyl, and R₅ is hydrogen then R₂ and R₃ are
20 other than methyl simultaneously;

(b) when R₁ is phenyl or 4-chlorophenyl and R₄ and R₅ are hydrogen then R₂ and R₃ are other than methyl simultaneously.

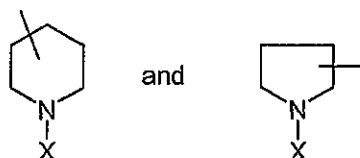
The present invention is also directed to pharmaceutical compositions of formula (I).

Another aspect of this invention is disclosed a method of treating a neuropsychiatric
25 disorder responsive to modulation of AMPA and NMDA receptors, comprising administering to a mammal in need of said treatment a therapeutically effective amount of a compound of formula I



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of aryl, benzyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, C₃₋₈cycloalkylC₁₋₆alkyl, heteroaryl, arylcarbonyl, arylC₁₋₆alkylC₃₋₈cycloalkylcarbonyl, C₁₋₁₀alkylcarbonyl, heteroarylcarbonyl and



wherein X is hydrogen, benzyl, arylC₂₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, or C₃₋₈cycloalkylC₁₋₆alkyl;

wherein said aryl, benzyl, or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, or aryl;

R₂ is selected from the group consisting of C₁₋₆alkyl, C₃₋₈cycloalkyl, and aryl wherein said aryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₃ is selected from the group consisting of aryl, C₃₋₈cycloalkyl, C₁₋₆alkyl and heteroaryl wherein said aryl or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₄ is selected from the group consisting of H, aryl, arylC₂₋₆alkyl, benzyl, hydroxyC₂₋₆alkyl, C₁₋₆perfluoroalkyl, C₃₋₈cycloalkyl and C₁₋₆alkyl wherein said aryl or benzyl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_y-alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

R₅ is H, C₁₋₆alkyl, or C₃₋₈cycloalkyl.

DETAILED DESCRIPTION OF THE INVENTION

The terms as used herein have the following meanings:

As used herein, the expression "C₁₋₆ alkyl" used alone or in combination with other terms means an alkyl (or alkylene as appropriate), straight or branched-chain and includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "C₁₋₆alkoxy", "C₁₋₆alkoxyC₁₋₆alkyl", "hydroxyC₁₋₆alkyl", "C₁₋₆alkylcarbonyl", "C₁₋₆alkoxycarbonylC₁₋₆alkyl", "C₁₋₆alkoxycarbonyl", "aminoC₁₋₆alkyl", "C₁₋₆alkylcarbamoylC₁₋₆alkyl", "C₁₋₆dialkylcarbamoylC₁₋₆alkyl" "mono- or di-C₁₋₆alkylaminoC₁₋₆alkyl", aminoC₁₋₆alkylcarbonyl", "diphenylC₁₋₆alkyl", "phenylC₁₋₆alkyl", "phenylcarbonylC₁₋₆alkyl" and "phenoxyC₁₋₆alkyl" are to be construed accordingly.

As used herein, the expression "C₂₋₆alkenyl" includes ethenyl and straight-chained or branched propenyl, butenyl, pentenyl and hexenyl groups. Similarly, the expression "C₂₋₆alkynyl" includes ethynyl and propynyl, and straight-chained or branched butynyl, pentynyl and hexynyl groups.

As used herein, the expression "C₁₋₆ perfluoroalkyl" means that all of the hydrogen atoms in said alkyl group are replaced with fluorine atoms. Illustrative examples include trifluoromethyl and pentafluoroethyl, and straight-chained or branched heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl groups. Derived expression, "C₁₋₆ perfluoroalkoxy", is to be construed accordingly.

As used herein, the expression "C₃₋₈cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, the expression "C₃₋₈cycloalkylC₁₋₆alkyl" means that the C₃₋₈cycloalkyl as defined herein is further attached to C₁₋₆alkyl as defined herein. Representative examples include cyclopropylmethyl, 1-cyclobutylethyl, 2-cyclopentylpropyl, cyclohexylmethyl, 2-cycloheptylethyl and 2-cyclooctylbutyl and the like.

As used herein "halogen" or "halo" means chloro, fluoro, bromo, and iodo.

As used herein the expression "carbamoyl" means an --NC(O)-- group where the radical is bonded at two positions connecting two separate additional groups.

As used herein "aryl" represents a carbocyclic aromatic ring system such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic aromatic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

As used herein "heteroaryl" represents a heterocyclic aromatic ring system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinoliziny, quinoliny, isoquinoliny, quinoxaliny, naphthyridiny, pteridinyl, carbazolyl, azepiny, diazepiny, acridiny and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrroliny, pyrazoliny, indoliny, oxazolidiny, oxazoliny, oxazepiny and the like.

As used herein "heterocyclyl" represents a saturated 3 to 8 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidyl, piperidyl, piperaziny, morpholiny, thiomorpholiny, aziridiny, tetrahydrofuranyl and the like.

As used herein, "tautomer" or "tautomerism" refers to the coexistence of two (or more) compounds that differ from each other only in the position of one (or more) mobile atoms and in electron distribution, for example, keto-enol tautomers or tautomerism.

As used herein, 'treat' or 'treating' means any treatment, including but not limited to, alleviating symptoms, eliminating the causation of the symptoms either on a temporary or permanent basis, or to preventing or slowing the appearance of symptoms and progression of the named disease, disorder or condition.

"Therapeutically effective amount" means an amount of the compound which is effective in treating the named disorder or condition.

As used herein, "patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

As used herein, the expression "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present invention in order to permit the formation of a pharmaceutical

composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is a pharmaceutically acceptable oil typically used for parenteral administration.

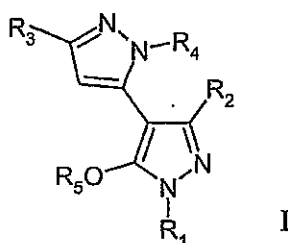
The term "pharmaceutically acceptable salts" as used herein means that the salts of the compounds of the present invention can be used in medicinal preparations. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, 2-hydroxyethanesulfonic acid, p-toluenesulfonic acid, fumaric acid, maleic acid, hydroxymaleic acid, malic acid, ascorbic acid, succinic acid, glutaric acid, acetic acid, salicylic acid, cinnamic acid, 2-phenoxybenzoic acid, hydroxybenzoic acid, phenylacetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, carbonic acid or phosphoric acid. The acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate can also be formed. Also, the salts so formed may present either as mono- or di- acid salts and can exist either as hydrated or can be substantially anhydrous. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The expression "stereoisomers" is a general term used for all isomers of the individual molecules that differ only in the orientation of their atoms in space. Typically it includes mirror image isomers that are usually formed due to at least one asymmetric center, (enantiomers). Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers, also certain individual molecules may exist as geometric isomers (cis/trans). It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

As used in the examples and preparations that follow, the terms used therein shall have the meanings indicated: "kg" refers to kilograms, "g" refers to grams, "mg" refers to milligrams, "µg" refers to micrograms, "pg" refers to picograms, "mol" refers to moles, "mmol" refers to millimoles, "nmole" refers to nanomoles, "L" refers to liters, "mL" or "ml" refers to milliliters, "µL" refers to microliters, "°C" refers to degrees Celsius, "R_f" refers to

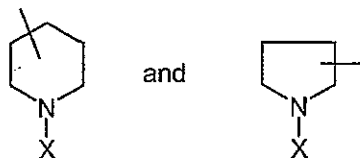
retention factor, "mp" or "m.p." refers to melting point, "dec" refers to decomposition, "bp" or "b.p." refers to boiling point, "mm of Hg" refers to pressure in millimeters of mercury, "cm" refers to centimeters, "nm" refers to nanometers, " $[\alpha]_D^{20}$ " refers to specific rotation of the D line of sodium at 20°C obtained in a 1 decimeter cell, "c" refers to concentration in g/mL, "THF" refers to tetrahydrofuran, "DMF" refers to dimethylformamide, "NMP" refers to 1-methyl-2-pyrrolidinone, "MP-carbonate" refers to a macroporous polystyrene anion exchange resin that is a resin bound equivalent to tetraalkylammonium carbonate, "brine" refers to a saturated aqueous sodium chloride solution, "M" refers to molar, "mM" refers to millimolar, "μM" refers to micromolar, "nM" refers to nanomolar, "TLC" refers to thin layer chromatography, "HPLC" refers to high performance liquid chromatography, "HRMS" refers to high resolution mass spectrum, "CIMS" refers to chemical ionization mass spectrometry, " t_R " refers to retention time, "lb" refers to pounds, "gal" refers to gallons, "L.O.D." refers to loss on drying, "μCi" refers to microcuries, "i.p." refers to intraperitoneally, "i.v." refers to intravenously.

In one aspect of this invention there is disclosed novel compounds having the general structure shown in formula I:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of aryl, benzyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, C₃₋₈cycloalkylC₁₋₆alkyl, heteroaryl, arylcarbonyl, arylC₁₋₆alkylC₃₋₈cycloalkylcarbonyl, C₁₋₁₀alkylcarbonyl, heteroarylcarbonyl and



wherein X is hydrogen, benzyl, arylC₂₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, or C₃₋₈cycloalkylC₁₋₆alkyl;

wherein said aryl, benzyl, or heteroaryl is optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, or aryl;

R_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and aryl wherein said

5 aryl is optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, aryl, or alkoxy;

R_3 is selected from the group consisting of aryl, C_{3-8} cycloalkyl, C_{1-6} alkyl and heteroaryl

wherein said aryl or heteroaryl is optionally substituted with one or more substituents each

10 independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, aryl, or alkoxy;

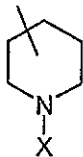
R_4 is selected from the group consisting of H, aryl, aryl- C_{2-6} alkyl, benzyl, hydroxy- C_{2-6} alkyl, C_{1-6} perfluoroalkyl, C_{3-8} cycloalkyl and C_{1-6} alkyl wherein said aryl or benzyl is optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, aryl, or alkoxy; R_5 is H, C_{1-6} alkyl, or C_{3-8} cycloalkyl; and

15 with the proviso that

(a) when R_1 and R_4 are phenyl or 4-chlorophenyl, and R_5 is hydrogen then R_2 and R_3 are other than methyl simultaneously;

20 (b) when R_1 is phenyl or 4-chlorophenyl and R_4 and R_5 are hydrogen then R_2 and R_3 are other than methyl simultaneously.

In a further embodiment of the compound of formula I of this invention, R_1 is selected from the group consisting of aryl, benzyl, C_{3-8} cycloalkyl, C_{1-10} alkyl, aryl- C_{1-6} alkyl and



25 wherein X is benzyl, R_2 and R_3 are C_{1-6} alkyl and R_5 is hydrogen or C_{1-6} alkyl.

In another embodiment of the compound of formula I of this invention, R_1 is aryl, R_2 and R_3 are C_{1-6} alkyl, R_4 is hydrogen, and R_5 is hydrogen or C_{1-6} alkyl.

Representative examples of compounds of this embodiment of the compound of

'formula I are selected from the group consisting of: 2'-(2-Fluoro-phenyl)-5,5'-dimethyl-2H,

30 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(4-Isopropyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(4-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-

trifluoromethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5, 5'-Dimethyl-2'-(4-methoxy-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(3-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(2-Methyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-trifluoromethoxy-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(2-ethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3,4-dichloro-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3-chlorophenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(4-tert-Butyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3-trifluoromethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 5'-Methoxy-5, 3'-dimethyl-1'-phenyl-2H, 1'H-[3,4']bipyrazolyl.

In a further embodiment of the compound of formula I of this invention, R₁ is aryl, R₂ and R₃ are C₁₋₆alkyl, R₄ is arylC₂₋₆alkyl, or benzyl and R₅ is hydrogen or C₁₋₆alkyl.

Representative examples of compounds of this embodiment of the compound of formula I are selected from the group consisting of: 5,5'-Dimethyl-2-phenethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-Benzyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2-Benzyl-5'-methoxy-5,3'-dimethyl-1'-phenyl-2H, 1'H-[3,4']bipyrazole, and 2-(3-Hydroxy-benzyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

In another embodiment of the compound of formula I of this invention, R₁ is aryl, R₂ and R₃ are C₁₋₆alkyl, R₄ is hydroxyC₁₋₆alkyl C₁₋₆perfluoroalkyl, C₃₋₈cycloalkyl or C₁₋₆alkyl and R₅ is hydrogen.

Compounds exemplary of this embodiment of the compound of formula I are selected from the group consisting of: 5,5'-Dimethyl-2'-phenyl-2- (2,2,2-trifluoro-ethyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-Cyclohexyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-(2-Hydroxy-ethyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2,5,5'-Trimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

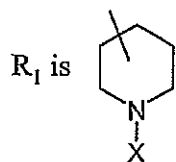
In yet another embodiment of the compound of formula I of this invention, R₁ is aryl, R₂ and R₃ are C₁₋₆alkyl, R₄ is aryl, and R₅ is hydrogen.

Representative examples of compounds of this embodiment of the compound of formula I are selected from the group consisting of: 2-(4-Methoxy-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol and 2-(4-Fluoro-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

In another embodiment of the compound of formula I of this invention, R₁ is arylC₂₋₆alkyl or benzyl, R₂ and R₃ are C₁₋₆alkyl, and R₄ and R₅ are hydrogen.

Representative examples of compounds of this embodiment of the compound of formula I are selected from the group consisting of: 5,5'-Dimethyl-2'-phenethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(3-Hydroxy-benzyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2'-Benzyl-5, 5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

5 In a further embodiment of the compound of formula I of this invention,



wherein X is benzyl, R₂ and R₃ are C₁₋₆alkyl, and R₄ and R₅ are hydrogen.

A compound exemplary of this embodiment of the compound of formula I is 2'-(1-Benzyl-piperidin-4-yl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

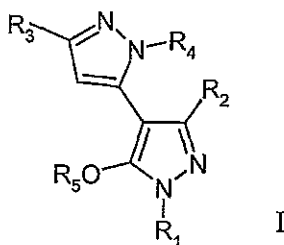
10 In another embodiment of the compound of formula I of this invention, R₁ is C₃₋₈cycloalkyl, R₂ and R₃ are C₁₋₆alkyl, and R₄ and R₅ are hydrogen.

A compound exemplary of this embodiment of the compound of formula I is 2'-Cyclohexyl-5,5'-dimethyl-2H-2'H-[3,4]bipyrazolyl-3'-ol.

In another embodiment of this invention is disclosed a compound which is 5,1',5'-trimethyl-2'-phenyl-1', 2'-dihydro-2H-[3,4'] bipyrazolyl-3'-one.

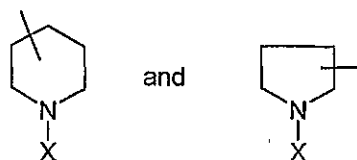
15 In another embodiment of the present invention is disclosed a pharmaceutical composition comprising an effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

20 In still another embodiment of the present invention, is disclosed a method of treating a neuropsychiatric disorder responsive to modulation of AMPA and NMDA receptors, comprising administering to a mammal in need of said treatment a therapeutically effective amount of a compound of formula I



25 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of aryl, benzyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, C₃₋₈cycloalkylC₁₋₆alkyl, heteroaryl, arylcarbonyl, arylC₁₋₆alkylC₃₋₈cycloalkylcarbonyl, C₁₋₁₀alkylcarbonyl, heteroarylcarbonyl and



5 wherein X is hydrogen, benzyl, arylC₂₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, or C₃₋₈cycloalkylC₁₋₆alkyl;

wherein said aryl, benzyl, or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, or aryl;

10 R₂ is selected from the group consisting of C₁₋₆alkyl, C₃₋₈cycloalkyl, and aryl wherein said aryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

15 R₃ is selected from the group consisting of aryl, C₃₋₈cycloalkyl, C₁₋₆alkyl and heteroaryl wherein said aryl or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy;

20 R₄ is selected from the group consisting of H, aryl, arylC₂₋₆alkyl, benzyl, hydroxyC₂₋₆alkyl, C₁₋₆perfluoroalkyl, C₃₋₈cycloalkyl and C₁₋₆alkyl wherein said aryl or benzyl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁₋₆alkoxy, nitro, aryl, or alkoxy; and

R₅ is H, C₁₋₆alkyl, or C₃₋₈cycloalkyl.

25 In another embodiment of the method of this invention, said neuropsychiatric disorder is selected from the group consisting of depression, epilepsy, schizophrenia, Alzheimer's, disease, learning and memory disorders; and mild cognitive impairment.

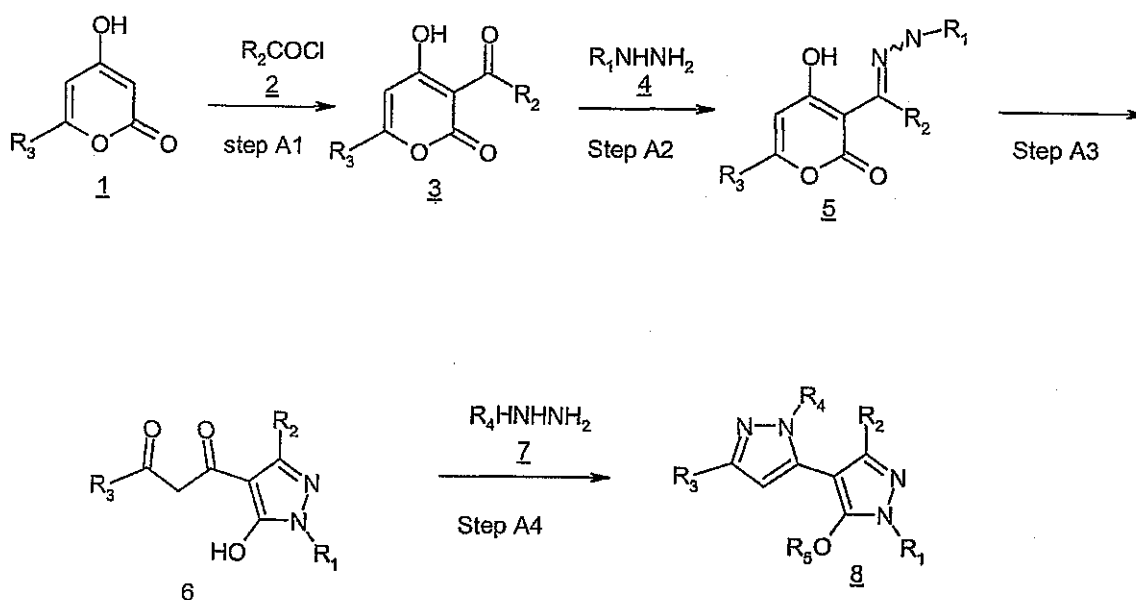
In a further embodiment of the method of this invention, said disorder is schizophrenia.

In yet another embodiment of the method of this invention, said disorder is depression.

30 In still another embodiment of the method of this invention, said disorder is learning and memory disorder.

The compounds of the invention may be prepared by the synthetic routes described below in the Schemes or by other methods, which may be apparent to those skilled in the art. The R substituents are as identified for formula (I), above unless otherwise noted. If necessary, in the following synthetic schemes, reactive functional groups present in the compounds described in this invention may be protected by suitable protecting groups. The protecting group may be removed at a later stage of the synthesis. Procedures for protecting reactive functional groups and their subsequent removal may be found in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley and Sons, 1991.

Scheme A



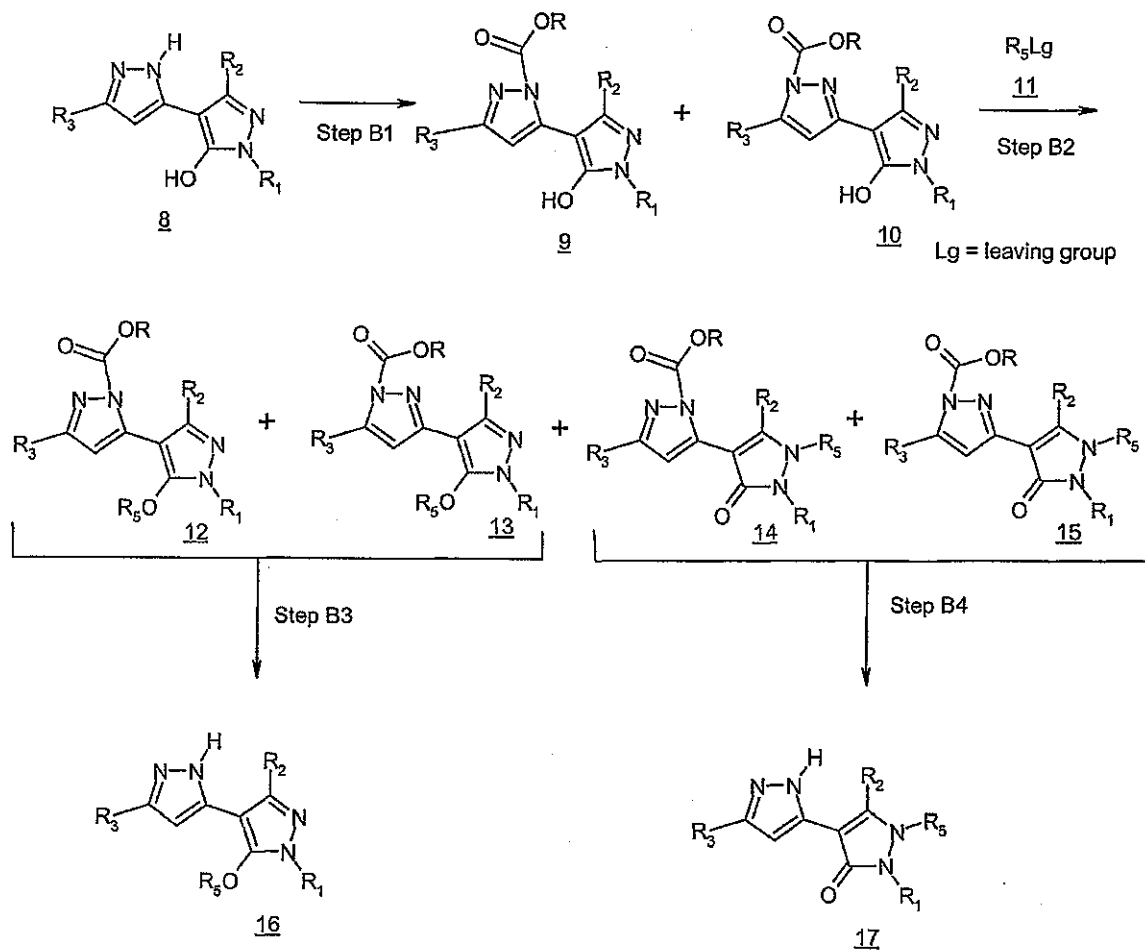
Scheme A shows the synthesis of a compound of formula I wherein R_4 and R_5 are hydrogen. In Step A1, the 6-substituted pyrone 1, a compound which is either commercially available or can readily be synthesized by methods well known in the art (Lokot, et al, *Tetrahedron*, 55, 4783-4792, 1999), is reacted with a carboxylic acid chloride, compound 2, in the presence of a strong organic acid, to give the 3-acylated derivative 3. Suitable strong organic acids that may be used in the reaction are for example, a trihaloacetic acid such as trifluoroacetic acid or a trifluoroalkylsulfonic acid. The reaction is typically run at temperatures of from 50°C to the reflux temperature of the acid.

In Step A2, compound 3 is reacted with a hydrazine 4 to form the hydrazone, compound 5. The reaction is typically performed in an inert organic solvent such as an alcohol, optionally in the presence of a suitable base if a hydrazine salt is used as a reactant. Suitable alcohols include methanol, ethanol, isopropanol or ethylene glycol and suitable bases include alkali carbonates such as sodium, potassium or cesium carbonates, or resin bound carbonates such as MP-carbonate. The temperature at which the reaction can be run is from ambient to the reflux temperature of the organic solvent.

As shown in Step A3 the hydrazone, compound 5, can be converted to the pyrazolyl dione 6 by affecting an intramolecular cyclization of 5 in the presence of a suitable organic acid such as acetic, propionic or trifluoroacetic acid. The reaction is typically run at elevated temperatures from about 50°C to the reflux temperature of the organic acid.

In Step A4, reaction of the dione 6 with hydrazine 7 gives the desired bipyrazole 8. The reaction is typically run in an inert organic solvent such as an alcohol at or near the reflux temperature of the solvent.

Scheme B



5

Scheme B illustrates a method that can be used to synthesize compounds of formula I wherein R_5 is C_{1-6} alkyl, C_{3-8} cycloalkyl. In Step B1 the unsubstituted ring nitrogen of the bipyrrole 8 is protected with an alkoxy carbonyl group to give a mixture of positional isomers, compounds 9 and 10. The reaction is accomplished by using methods well known in the art for instance treatment of 8 with t-butylcarbazate can give compound 9. See Kashuma, et al, *Tetrahedron*, 54, 14679, 1998.

10

In Step B2 the mixture of isomers 9 and 10 are reacted with an alkylating/cycloalkylating agent 11 wherein Lg is a leaving group such as halogen, alkylsulfonate or arylsulfonate to produce a mixture of the O-alkylated compounds 12 and 13 and the N-alkylated compounds 14 and 15. The reaction can be run in a polar aprotic solvent such as DMF, DMSO or acetonitrile in the presence of a suitable base. Suitable

15

bases include the alkaline and alkali carbonates and bicarbonates such as potassium and sodium carbonate and bicarbonate. The temperature at which the reaction can be run is from ambient to the reflux temperature of the organic solvent. Following workup of the reaction, chromatography on silica gel gives two separate mixtures. One mixture consists of the O-alkylated compounds 12 and 13 the other consists of N-alkylated compounds 14 and 15.

The O-alkylated target compound 16 can be obtained as depicted in StepB3 by cleavage of the N-alkoxycarbonyl from the positional isomers 12 and 13. The cleavage can be accomplished by methods that are well known in the art, for example by acid or base treatment of 12 and 13.

Similarly, StepB4 employs identical conditions as Step B3 to give the N-alkylated compound 17.

BIOLOGICAL EXAMPLES

The following test protocols are used to ascertain the biological properties of the compounds of this invention. The following examples are being presented to further illustrate the invention. However, they should not be construed as limiting the invention in any manner.

Spinophilin/Protein Phosphatase-I Interaction Assay:

Materials:

10X stock TBS (Tris-Buffered Saline) is from Bio-Rad. Spinophilin (6xHis) and GST-PP1 proteins are cloned, expressed, and purified in house by protein production. Eu-anti-GST antibody, DELFIA assay buffer and DELFIA Enhancement solution are from Wallac (now Perkin Elmer). High binding 384 well plates are from Greiner.

Methods for ELISA Time-resolved Fluorescence 384-well Assay:

Plates are coated with 50ul of Spinophilin/TBS solution (50ug/ml) or 50ul of TBS buffer (0 control) and incubated overnight @ 4°C. Test compounds are prepared and diluted in 96-well polypropylene plates using a Labsystems Wellpro Liquid Handler. After washing the plates 3 times with TBS using the Elx-405 (Biotek) plate washer, the compounds are transferred from the 96-well plate to the 384-well plate using a Multimek (Beckman) liquid handler. GST-PP1, 50ul (2.5ug/ml) is then added to the plate. Plates are incubated for 3-6 h @

room temperature. The plates are washed 3 times as above and 50ul of Eu-anti-GST antibody (~50 ng/ml) are added using a Multidrop (Titertek) module and allowed to incubate for 30 min at room temperature. The plates are washed 3 times as above and 100ul of Enhancement Solution are added with the Multidrop module and allowed to incubate for 1 h @ room temperature. Plates are read in the Farcyte (Tecan) Fluorescence reader using Europium setting. Compounds are evaluated for their ability to inhibit the interaction of Spinophilin (6xHis) and GST-PP1 by measuring a reduction in the fluorescence signal.

Voltage Whole-cell Recording of AMPA and NMDA Currents in Prefrontal Cortical Neurons:

Neuronal Acute-dissociation Method:

Prefrontal cortical (PFC) neurons from young adult (3-5 weeks postnatal) rats are acutely dissociated using procedures similar to those described previously (Feng, et al., *J Neurosci*, 2001; Chen, et al., *Proc Natl Acad Sci USA*, 2004). After incubation of brain slices in a NaHCO₃-buffered saline, PFC is dissected and placed in an oxygenated chamber containing papain (Sigma, 0.8 mg/ml) in HEPES-buffered Hank's balanced salt solution (HBSS, Sigma) at room temperature. After 40 minutes of enzyme digestion, tissue is rinsed three times in the low Ca⁺², HEPES-buffered saline and mechanically dissociated with a graded series of fire-polished Pasteur pipettes. The cell suspension is then plated into a 35 mm Lux Petri dish, which is then placed on the stage of a Nikon inverted microscope.

Whole-cell Recording of AMPA and NMDA:

Whole-cell recordings of whole-cell ion channel currents employ standard voltage clamp techniques (Yan et al., *Nat Neuroscience*, 1999; Wang et al., *J Neurosci*, 2003; Tyszkiewicz et al., *J Physiol.*, 2004). The internal solution (inside the patch pipette) consists of (in mM): 180 N-methyl-d-glucamine (NMG), 40 HEPES, 4 MgCl₂, 0.1 BAPTA, 12 phosphocreatine, 3 Na₂ATP, 0.5 Na₂GTP, 0.1 leupeptin, pH = 7.2-7.3, 265-270 mosm/L. The external solution consists of (in mM): 127 NaCl, 20 CsCl, 10 HEPES, 1 CaCl₂, 5 BaCl₂, 12 glucose, 0.001 TTX, 0.02 glycine, pH = 7.3-7.4, 300-305 mOsm/L. Recordings are obtained with an Axon Instruments 200B patch clamp amplifier that is controlled and monitored with an IBM PC running pCLAMP (v. 8) with a DigiData 1320 series interface (Axon instruments). Electrode resistances are typically 2-4 MΩ in the bath. After seal rupture to

attain whole-cell recording conditions, series resistance (4-10 M Ω) is compensated (70-90%) and periodically monitored. The cell membrane potential is held at -60 mV.

The application of KA (200 μ M) or NMDA (100 μ M, in Mg²⁺-free solution) evokes a partially desensitizing inward current. KA or NMDA is applied for 2 seconds every 30
5 seconds to minimize desensitization-induced decrease of current amplitude. Drugs are applied with a gravity-fed 'sewer pipe' system. The array of application capillaries (ca. 150 μ m i.d.) is positioned a few hundred microns from the cell under study. Solution changes are effected by the SF-77B fast-step solution stimulus delivery device (Warner Instruments). Data are collected with PCLAMP software and analyzed with AXOGRAPH, KALEIDOGRAPH, and
10 STATVIEW.

Compounds described herein inhibit the KA-induced rundown of AMPA current by either stabilizing the agonist-evoked current or increasing the current. Likewise, compounds described herein increase the NMDA-evoked current. The minimum effective dose (MED) was identified by determining the lowest concentration of inhibitor that was effective in each
15 functional assay.

The results of these assays are shown in Table I and Table II.

Table I

20 Inhibition of KA-Induced Rundown of AMPA Current

Example No.	Minimal Effective Concentration (μ M)
4	0.1 *
5	0.1 *
15	1.0
18	1.0
25	1.0

* Lowest concentration tested (MED possibly less than 100nM).

Table II
Increase of NMDA-Evoked Current

EXAMPLE #	Minimal Effective Concentration (μM)	Average percent increase in NMDA current (10 μM)
8	1	303% (n=3 neurons)
18	5	55% (n=4 neurons)

5 Porsolt's Forced Swim Test:

The effects measured in this model have been correlated to antidepressant efficacy for drugs. The paradigm of this model is that an effective antidepressant compound will cause a rat to make greater attempts to escape a water-filled cylinder than a rat given vehicle only.

10 Animals used in this study are non-naive male Sprague Dawley rats weighing between 225-350 grams. The test apparatus consists of 6 clear PLEXIGLAS[®] cylinders 40 cm high x 19 cm wide. Cylinders are filled to 18 cm with 25°C water. Each rat is placed in a cylinder for a 15-minute training session. Following either subchronic or acute dosing of either vehicle (0.5% methylcellulose) or compound, animals are brought back 24 hours later for a 5-minute test session. These test sessions are videotaped for later scoring.

15 Subchronic dosing consists of administering drug three times in the 24-hour period between training and testing. The drug is administered 24 hrs., 5 hrs., and 1 hr. prior to the test session. Acute dosing consists of administering the drug once, 1 hour prior to the test session. Scoring is done using a time-sampling computer program. Every five seconds, animals are rated as demonstrating one of three behaviors: immobility, mild swim, or
20 climbing. These sampling scores are then converted into percentages of the test session.

This invention is further illustrated by the following examples of compounds used herein, which are provided for illustration purposes and in no way limit the scope of the present invention.

25 Object Recognition Test:

The object recognition test is a memory test. It measures the ability of mice (and rats) to differentiate between known and unknown objects and is therefore suitable for the determination of the memory-improving action of the compounds according to the invention.

The test can generally be carried out as described in the literature. (Blokland et al. *NeuroReport* 1998, 9, 4205-4208; Ennaceur, A., Delacour, J., *Behav. Brain Res.* 1988, 31, 47-59; Ennaceur, A., Meliani, K., *Psychopharmacology* 1992, 109, 321-330; Prickaerts, et al. *Eur. J. Pharmacol.* 1997, 337, 125-136).

In a first passage, a mouse in an otherwise empty, relatively large observation arena is confronted with two identical objects. The mouse will extensively examine, i.e. sniff and touch, both objects. The amount of time the mouse spends with each object is scored. In a second passage, after an interval of 24 hours, the mouse is again tested in the observation arena. One of the known objects is now replaced by a new, unknown object. When a mouse recognizes the known object, it will especially examine the unknown object. After 24 hours, a mouse, however, has normally forgotten which object it has already examined in the first passage, and will therefore inspect both objects equally intensively. The administration of a substance having learning- and memory-improving action will lead to a mouse recognizing the object already seen 24 hours beforehand, in the first passage, as known. It will examine the new, unknown object in greater detail than the already known one. This memory power is expressed in a discrimination index. A discrimination index of zero means that the mouse examines both objects, the old and the new one, for the same length of time; i.e. it has not recognized the old object and reacts to both objects as if they are both unknown and new. A discrimination index of greater than zero means that the mouse has inspected the new object for longer than the old one; i.e. the mouse has recognized the old object.

25 MK-801-Induced Psychosis Model:

The non-competitive NMDA receptor antagonist MK-801 induces stereotypies and hyperactivity in rodents (Contreras et al., *Synapse* 2: 240-243, 1988) by interacting with the NMDA receptor-associated ion channel. Phencyclidine, which also interferes with the NMDA receptor, produces psychotic effects in humans similar in many respects to schizophrenia. These findings suggest that a deficiency in glutamate transmission may be responsible in the pathology of schizophrenia (Javitt & Zukin, *Am. J. Psychiatr.*, 48: 1301-1308, 1991). The neuroleptics haloperidol, clozapine and raclopride are able to reverse the behavioral changes induced by MK-801 in rats (Carlsson et al., *Biol. Psychiatr.* 46: 1388-1395, 1999). Therefore

the MK-801-induced activity and stereotypies in rats may represent an appropriate animal model to test the potential efficacy of antipsychotic drugs.

Experimental Procedures

5 Male Wistar rats, weight 250-300 g are housed 2 per cage on a 12 h/12 h light dark cycle (lights on at 7.00 a.m.) at a room temperature of 21.±.2.degree. C. for a minimum of 5 days before testing. All animals are given access to commercial food and tap water ad libitum.

On the day of the experiment, rats are treated with reference drug vehicle, the reference drugs haloperidol or clozapine, the test compound vehicle, or test compounds. After administration, the rats are returned to their home cages for 15 minutes. The haloperidol, 10 clozapine, test compound and vehicle treated animals receive an i.p. injection of 0.3 mg/kg MK-801. The remaining rats treated with placebo receive a second injection of vehicle. The standard injection volume is 2.0 ml/kg. After 10 minutes in the home cages, rats are transferred to the test box (Plexiglas, 29.times.12.times.12 cm), 5 minutes before the assessment for accommodation. The test box is cleaned with 70% ethanol before each 15 assessment. Stereotypies, defined as wall-contacts with the snout, and locomotion, defined as turn-rounds of 180.degree., are assessed during 5 minute periods.

Metrazole Potentiation Assay

Male CD-1 mice (20-30 grams) are used. On the day of testing, animals are brought to 20 the laboratory and randomly assigned to groups. For a primary screen, the test compound is administered intraperitoneally (i.p., 10 ml/kg) to groups of 10 mice 60 minutes prior to challenge with metrazol (55 mg/kg sc). Post-metrazol administration animals are placed individually into clear plastic cylinders (12 X 5 inches) and then observed for clonic seizures. A clonic seizure is defined as a single episode of clonic spasms of at least 3-second duration. 25 The mice treated with metrazol are considered "potentiated" when these clonic seizures occur.

A dose range is necessary when 50% of the animals demonstrate potentiation in the primary screen. Test compounds are tested at the 60-minute pretreatment time using 3 or more doses with a vehicle control group. The ED50 value is determined by linear regression.

30
$$\frac{\% \text{ Rx group} - \% \text{ vehicle group}}{100 - \% \text{ vehicle group}}$$

Supramaximal Electroshock Assay

Male CD-1 mice (18-30 g) are used. Drugs are prepared using distilled water and if insoluble a surfactant is added. Control animals receive vehicle. Drugs are routinely administered intraperitoneally. The route of administration may be varied (p.o., s.c.). The dosage volume is 10 ml/kg.

5 A constant current stimulator, similar to the apparatus described by Woodbury and Davenport (*Arch. Int. Pharmacodyn.* 92: 97-107, 1952) delivers a 60 Hz shock of variable current and duration through corneal electrodes. A 0.3 s, 25 mA shock (50V) is sufficient to produce extensor tonus in 95% of control mice.

10 A compound is considered to give protection if the mouse does not exhibit extensor tonus. Protection is expressed as normalized percent inhibition relative to vehicle control. A time response is carried out using 6 animals per group. Animals are tested at 30, 60, and 120 min post-drug. Additional time periods are tested if indicated by previous tests. When peak activity has been determined, a dose-response is initiated, using 10 animals per group at that time period. The ED50 and 95% confidence interval are calculated by computerized probit
15 analysis.

Synthetic Examples

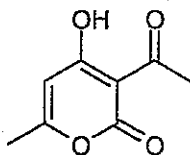
General

20 Commercial reagents and solvents are used as received. ¹H NMR spectra are recorded on a Varian MercuryPlus-300 (300 MHz) or Varian Unity Inova (400 MHz) spectrometer as indicated. Proton chemical shifts are reported in δ ppm relative to internal tetramethylsilane (0.0 ppm). MS (LC-MS) data is obtained using a Micromass LCT time of flight mass spectrometer with electrospray ionization and 5 min data acquisition time for m/z 100 to 1000.

25 LC (LC-MS) is performed using a Hypersil C18 column (4.6x50mm, 3.5 μ) with mobile phase of 0.1 % TFA in H₂O (A) and 0.1% TFA in ACN (B) and a gradient of 5% to 100% B over 3 min followed by 2 min at 100% B. Alternatively, a Platform LC-MS with electrospray source may be used with a HP1100 LC system running at 2.0 ml/min, 200 μ L/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection. A Luna C18(2)

30 column (30x4.6mm 3 μ) is used with a gradient of 5% to 95% B over 4.5 min with mobile phase of 0.1% formic acid in H₂O and 0.1% formic acid in ACN (B). HPLC purification is performed on a Varian ProStar system using a reversed-phase C18 column with a linear gradient of ACN /H₂O containing 0.1% trifluoroacetic acid.

Example 1



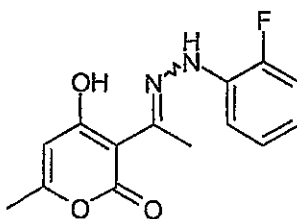
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3-Acetyl-4-hydroxy-6-methyl-pyran-2-one

Dissolve 4-hydroxy-6-methyl-pyran-2-one (12.6g, 100mmol) in trifluoroacetic acid (50ml), and add 7.8g (100mmol) of acetyl chloride dropwise. Heat this mixture at reflux for 5
10 hours. Evaporate the reaction mixture under reduced pressure. Add 50ml of water, extract with ethyl acetate (50ml x3) and combine the organic layers. Wash with brine and dry (sodium sulfate). Chromatograph on silica gel, eluting with chloroform to provide 5.8g (34.5mmol) of 3-acetyl-4-hydroxy-6-methyl-pyran-2-one.
LCMS (M+H): m/z 169, retention time 3.24 min.

15

Example 2



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3-{1-[(2-Fluorophenyl)-hydrazono]-ethyl}-4-hydroxy-6-methyl-pyran-2-one

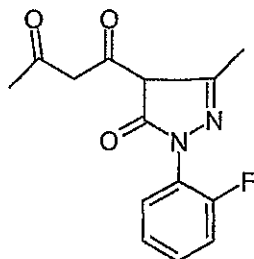
To 2-fluorophenyl hydrazine hydrochloride (0.16g, 1.0 mmol) in methanol (8ml) add MP-carbonate (1.0g, 3.3 equivalents). Shake this mixture at room temperature for 1 hour. Filter the resin and wash with methanol. To the filtrate add (2-fluorophenyl)-hydrazine (0.134g,
25 0.80mmol). Shake the reaction mixture at room temperature for 2 hours after which evaporate the solvent under reduced pressure. Recrystallize the solid from a minimum amount of

methanol and obtain 0.185g (0.67mmol) of 3-{1-[(2-fluoro-phenyl)-hydrazono]-ethyl}-4-hydroxy-6-methyl-pyran-2-one.

LCMS (M+H): m/z 277, retention time 2.74 min.

5

Example 3



1-[1-(2-Fluoro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl]-butane-1,3-dione

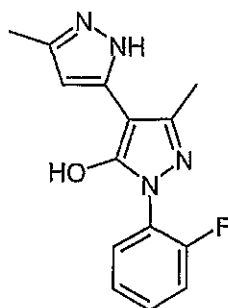
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Heat at reflux for 1 hour 3-{1-[(2-fluoro-phenyl)-hydrazono]-ethyl}-4-hydroxy-6-methyl-pyran-2-one (0.045g, 0.163mmol) in acetic acid (0.3ml). Add heptane (3ml) and evaporate the mixture to dryness to give 1-[1-(2-fluoro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl]-butane-1,3-dione (0.045g, 0.163 mmol). Use this material for the next step without further purification.

15

LCMS (M+H): m/z 277, retention time 2.05min.

Example 4



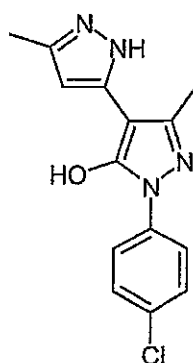
20

2'-(2-Fluoro-phenyl)-5,5'-dimethyl-2H,2'H-[3,4'] bipyrazolyl-3'-ol

Add to 1-[1-(2-fluoro-phenyl)-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione (0.045g, 0.163mmol) hydrazine hydrate (0.016g, 0.32mmol) in ethanol (1.6ml). Heat the reaction mixture at reflux for 1.5 hours after which evaporate the ethanol. Wash the
5 residue with dichloromethane to give 2'-(2-fluorophenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol (0.028g, 0.102mmol).
LCMS (M+H): m/z 273, retention time 2.16 min.

Example 5

10



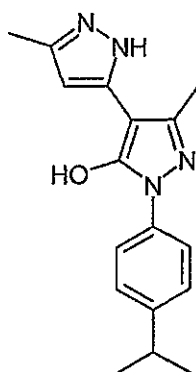
2'-(4-Chloro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

15 Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-chlorophenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 289, retention time 2.72 min.

20

Example 6



2'-(4-Isopropyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

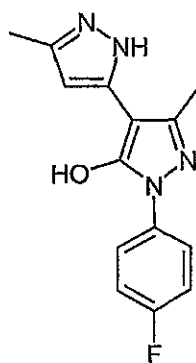
5

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-isopropylphenylhydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 297, retention time 2.85 min.

10

Example 7



2'-(4-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

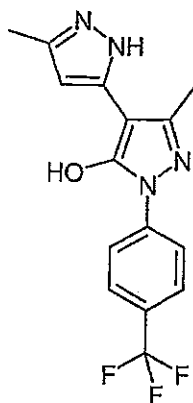
15

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-fluorophenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 273, retention time 2.00 min.

20

Example 8



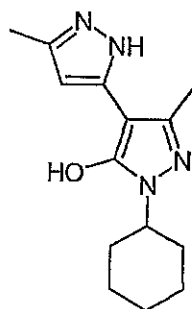
5

5,5'-Dimethyl-2'-(4-trifluoromethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-trifluoromethylphenyl hydrazine according to the procedure illustrated in Examples 2, 3 and 4.

10 LCMS (M+H): m/z 323, retention time 2.88 min.

Example 9



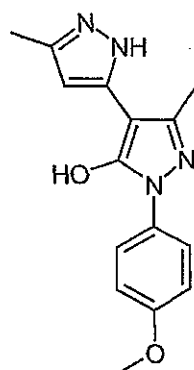
15

2'-Cyclohexyl-5,5'-dimethyl-2H-2'H-[3,4]bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and cyclohexylhydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

20 LCMS (M+H): m/z 261, retention time 1.80 min.

Example 10



5, 5'-Dimethyl-2'-(4-methoxy-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

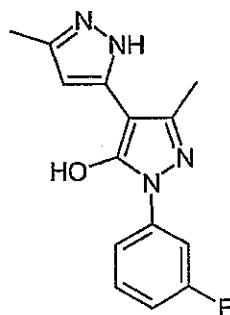
5

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-methoxyphenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 285, retention time 1.96 min.

10

Example 11



2'-(3-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

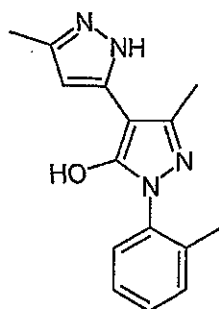
15

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3-fluorophenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 273, retention time 2.45 min.

20

Example 12



2'-(2-Methyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

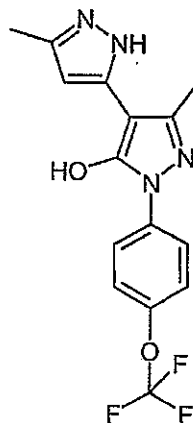
5

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 2-methylphenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 269, retention time 1.70 min.

10

Example 13



55'-Dimethyl-2'-(4-trifluoromethoxy-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

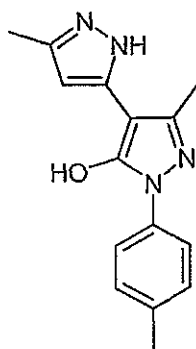
15

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-trifluoromethoxyphenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 339, retention time 3.02 min.

20

Example 14

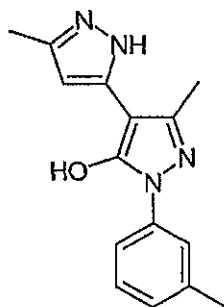


5 5,5'-Dimethyl-2'-(4-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-methyl-phenyl hydrazine hydrochloride according to the illustrated in Examples 2, 3 and 4. LCMS (M+H): m/z 269, retention time 2.44 min.

10

Example 15

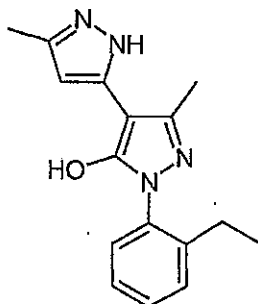


15 5,5'-Dimethyl-2'-(3-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3-methylphenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

20 LCMS (M+H): m/z 269, retention time 2.46 min.

Example 16

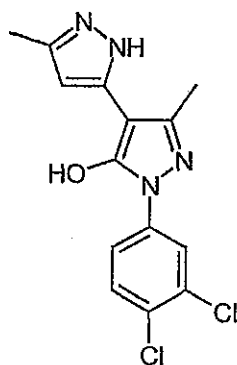


5 5,5'-Dimethyl-2'-(2-ethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 2-ethylphenylhydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

10 LCMS (M+H): m/z 283, retention time 2.32 min.

Example 17

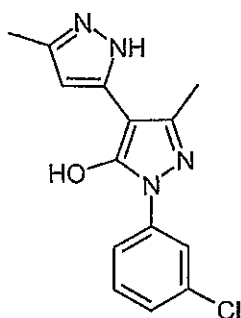


15 5,5'-Dimethyl-2'-(3,4-dichloro-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3,4-dichlorophenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

20 LCMS (M+H): m/z 323, retention time 3.04 min.

Example 18



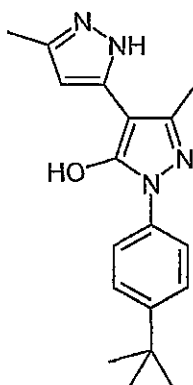
5,5'-Dimethyl-2'-(3-chlorophenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

- 5 Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3-chlorophenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 289, retention time 2.28 min.

10

Example 19



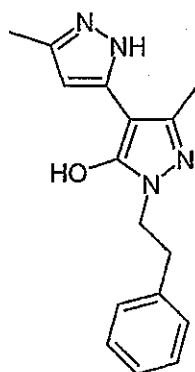
2'-(4-tert-Butyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

- 15 Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 4-tert-butylphenylhydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 311, retention time 2.62 min.

20

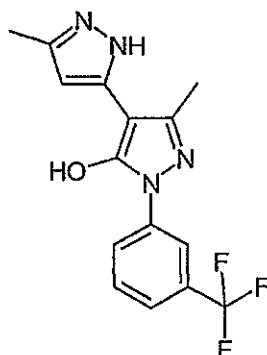
Example 20



5,5'-Dimethyl-2'-phenethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

- 5 Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and phenethylhydrazine sulfate according to the procedure illustrated in Examples 2, 3 and 4. LCMS (M+H): m/z 283, retention time 2.07 min.

Example 21



5,5'-Dimethyl-2'-(3-trifluoromethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

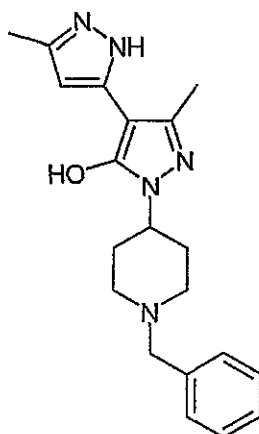
5

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3-trifluoromethylphenyl hydrazine hydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 323, retention time 2.62 min.

10

Example 22



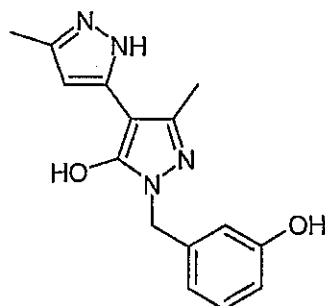
15

2'-(1-Benzyl-piperidin-4-yl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 1-benzylpiperidin-4-yl hydrazine dihydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

LCMS (M+H): m/z 352, retention time 1.52 min.

Example 23



5

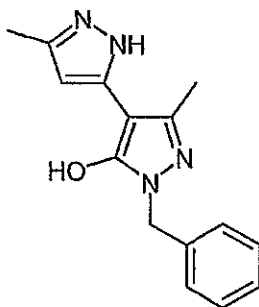
2'-(3-Hydroxy-benzyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and 3-hydrazinomethylphenol dihydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

10

LCMS (M+H): m/z 285, retention time 1.57 min.

Example 24



15

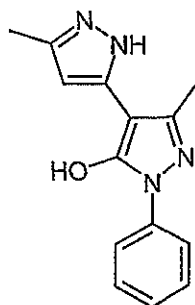
2'-Benzyl-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and benzylhydrazine dihydrochloride according to the procedure illustrated in Examples 2, 3 and 4.

20

LCMS (M+H): m/z 269, retention time 1.95 min.

Example 25

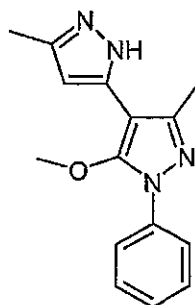


5,5'-Dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

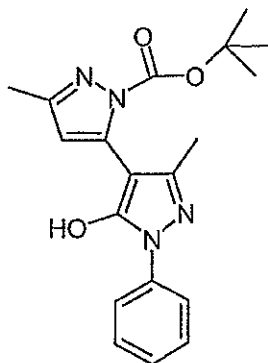
- 5 Prepare the title compound from 3-acetyl-4-hydroxy-6-methyl-pyran-2-one and phenylhydrazine according to the procedure illustrated in Examples 2, 3 and 4.
LCMS (M+H): m/z 255, retention time 1.77 min.

10

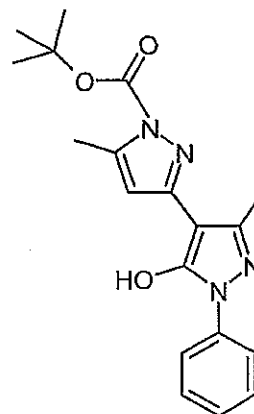
Example 26



5'-Methoxy-5, 3'-dimethyl-1'-phenyl-2H,1'H-[3,4']bipyrazolyl



(A)



(B)

15

(A) 5'-Hydroxy-5,3'-dimethyl-1'-phenyl-1'H-[3,4']bipyrazolyl-2-carboxylic acid tert-butyl ester

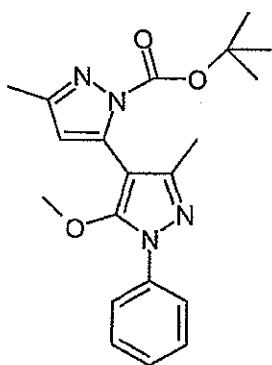
(B) 5'-Hydroxy-5,3'-dimethyl-1'-phenyl-1'H-[3,4']bipyrazolyl-1-carboxylic acid tert-butyl ester

5

To 5,5'-Dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol (0.118g, 0.457mmol) (Example 25) in ethanol (4 ml) add tert-butyl carbazate (0.120g, 0.914mmol). Heat at reflux for 1.5 hours, after which evaporate the ethanol. Chromatography on silica gel, eluting with 50% ethyl acetate/heptane provides 0.101g of a mixture of positional isomers A and B. Use the mixture for the next step.

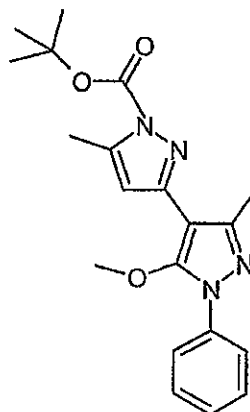
10

LCMS (M+H): m/z 355, retention time 1.97 min. and 3.24 min., respectively.



15

(C)

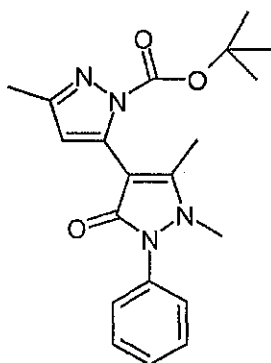


(D)

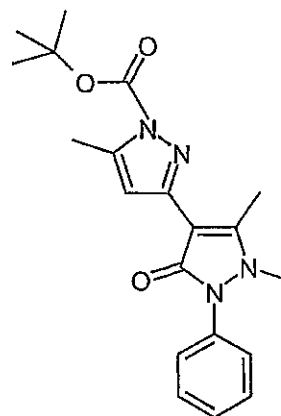
(C) 5'-Methoxy-5,3'-dimethyl-1'-phenyl-1'H-[3,4']bipyrazolyl-2-carboxylic acid tert-butyl ester

(D) 5'-Methoxy-5,3'-dimethyl-1'-phenyl-1'H-[3,4']bipyrazolyl-1-carboxylic acid tert-butyl ester

20



(E)



(F)

(E) 5,1',5'-Trimethyl-3'-oxo-2'-phenyl-2',3'-dihydro-1'H-[3,4']bipyrazolyl-2-carboxylic acid
tert-butyl ester

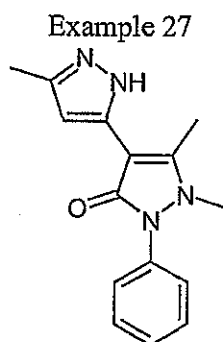
(F) 5,1',5'-Trimethyl-3'-oxo-2'-phenyl-2',3'-dihydro-1'H-[3,4']bipyrazolyl-1-carboxylic acid
tert-butyl ester

To a mixture of compounds (A) and (B) (0.100g, 0.282mmol) in DMF (5ml) add
 10 NaHCO₃ (0.071g, 0.845mmol) and iodomethane (0.40g, 2.82mmol). Stir the mixture at room
 temperature overnight. Dilute the reaction mixture with ethyl acetate (25ml), wash with water
 (30mlx5), and dry (sodium sulfate). Chromatography on silica gel, eluting with 50% ethyl
 acetate/heptane provided 0.013 g of O-methylated products ((C) and (D) LCMS (M+H): m/z
 369, retention time 3.30 min.) and 0.012g of N-methylated products ((E) and (F), LCMS
 15 (M+H): m/z 369, retention time 2.63 min.). Use the O-methylated products for the next step.

5'-Methoxy-5, 3'-dimethyl-1'-phenyl-2H,1'H-[3,4']bipyrazolyl

To the mixture of O-methylated products, compounds (C) and (D) (0.013g 0.035mmol), in dichloromethane (1ml) add trifluoroacetic acid (1ml). Stir this mixture at room temperature for 1 hour, and then evaporate the mixture to dryness. Dilute the residue with dichloromethane, wash sequentially with water, aqueous sodium bicarbonate solution, and water. Dry the organic layer (sodium sulfate) and concentrate to give 0.006g (0.022mmol) of the title compound.

LCMS (M+H): m/z 269, retention time 2.83 min.

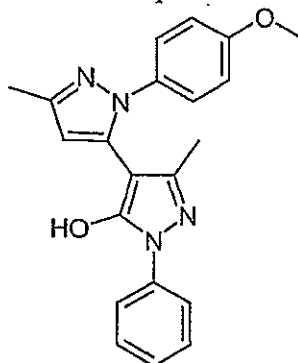


5,1', 5'-Trimethyl-2'-phenyl-1',2'-dihydro-2H-[3,4']bipyrazolyl-3'-one

To the mixture of the N-methyl isomers (E) and (F) of Example 26 (0.012g, 0.035mmol) in dichloromethane (1ml) add trifluoroacetic acid (1ml). Stir this mixture at room temperature for 1 hour, and then evaporate the mixture to dryness. Dilute the residue with dichloromethane, wash sequentially with water, aqueous sodium bicarbonate solution, and water. Dry the organic layer (sodium sulfate) and concentrate to give 0.009g (0.035mmol) of the title compound.

LCMS (M+H): m/z 269, retention time 2.06 min.

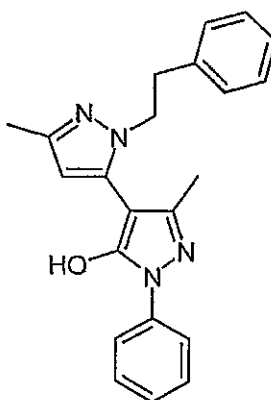
Example 28



2-(4-Methoxy-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

- 5 To (4-methoxyphenyl)-hydrazine hydrochloride (0.083g, 0.48mmol) in ethanol (5ml) add sodium bicarbonate (0.067g, 0.80mmol) after which stir the mixture for 10 min. Add 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione (0.103g, 0.40mmol). The mixture was heated at reflux for 1.5 hours after which it was evaporated to dryness. Chromatography on silica gel, eluting with 50 to 100% ethyl acetate / heptane
10 provided 0.071g of the title compound.
LCMS (M+H): m/z 361, retention time 2.43 min.

Example 29



15

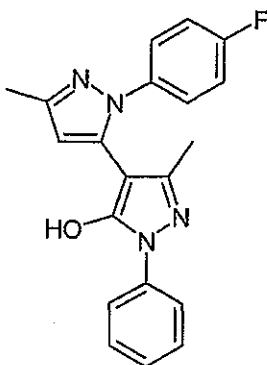
5,5'-Dimethyl-2-phenethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and phenethyl hydrazine sulfate according to the procedure of Example 28.

LCMS (M+H): m/z 359, retention time 2.55 min.

5

Example 30



2-(4-Fluoro-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

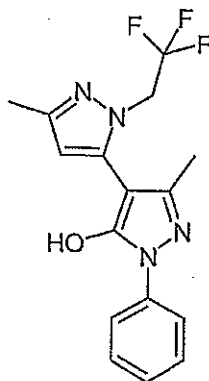
10

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and 4-fluorophenyl hydrazine hydrochloride according to the procedure of Example 28.

LCMS (M+H): m/z 349, retention time 2.48 min.

15

Example 31



5,5'-Dimethyl-2'-phenyl-2-(2,2,2-trifluoro-ethyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

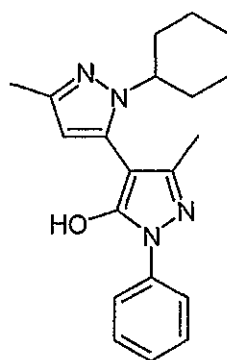
20

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and 2,2,2-trifluoro-ethyl hydrazine (70% in water) according to the procedure of Example 28.

LCMS (M+H): m/z 337, retention time 2.35 min.

5

Example 32



2-Cyclohexyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

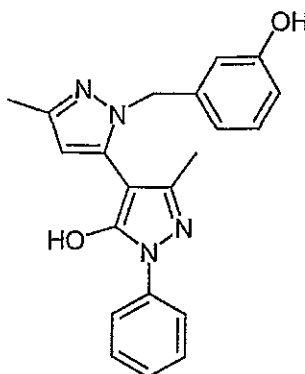
10

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and cyclohexylhydrazine hydrochloride according to the procedure of Example 28.

LCMS (M+H): m/z 337, retention time 2.50 min.

15

Example 33



2-(3-Hydroxy-benzyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

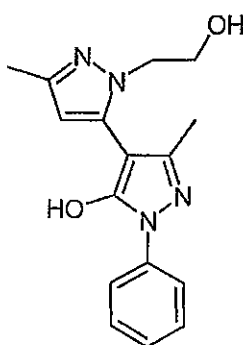
5

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and 3-hydroxybenzyl hydrazine dihydrochloride according to the procedure of Example 28.

LCMS (M+H): m/z 361, retention time 2.18 min.

10

Example 34



2-(2-Hydroxy-ethyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

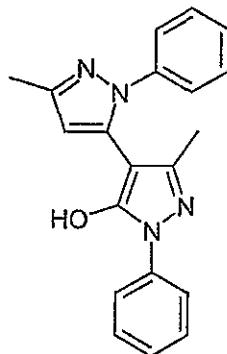
15

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and 2-hydroxy-ethyl hydrazine according to the procedure of Example 28.

LCMS (M+H): m/z 299, retention time 1.83min.

20

Example 35

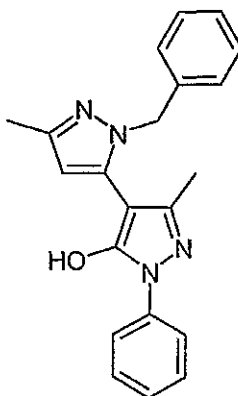


5 5,5'-Dimethyl-2, 2'-diphenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and phenyl hydrazine according to the procedure of Example 28.

10 LCMS (M+H): m/z 331, retention time 2.42 min.

Example 36



15

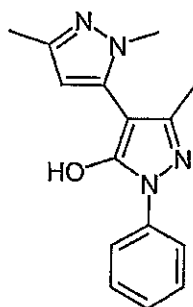
2-Benzyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

Prepare the compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and benzylhydrazine hydrochloride according to the procedure of Example 28.

LCMS (M+H): m/z 345, retention time 2.69 min.

5

Example 37



2,5,5'-Trimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol

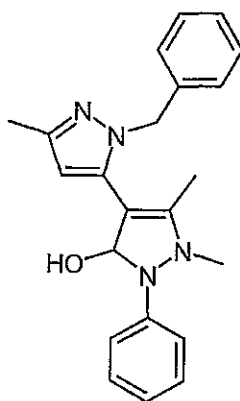
10

Prepare the title compound from 1-[1-phenyl-3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl]-butane-1, 3-dione and methylhydrazine according to the procedure of Example 28.

LCMS (M+H): m/z 269, retention time 2.10 min.

15

Example 38



2-Benzyl-5, 1', 5'-trimethyl-2'-phenyl-1', 2'-dihydro-2H-[3,4'] bipyrazolyl-3'-one

20

To 2-benzyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol (Example 36, 0.200g, 0.58mmol) in DMF add cesium carbonate (0.944g, 2.90mmol), and then iodomethane (0.823g, 5.8mmol). Stir this mixture at room temperature overnight. Dilute the reaction mixture with ethyl acetate, wash with water (25ml x 5) and dry (sodium sulfate).

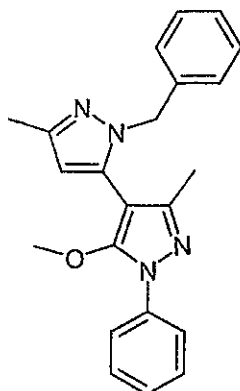
- 5 Chromatograph on silica gel, eluting with 50~100% ethyl acetate / heptane to provide 0.045g of the title compound.

LCMS (M+H): m/z 359 with retention time 2.84 min.

The reaction also affords an O-methyl compound. See Example 39 below.

10

Example 39



2-Benzyl-5'-methoxy-5,3'-dimethyl-1'-phenyl-2H,1'H-[3,4']bipyrazole

15

Isolate the title compound from the chromatography described in Example 38 to afford 0.033g of O-methylated isomer.

LCMS (M+H): m/z 359 with retention time 3.51 min.

20

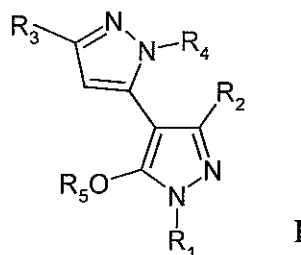
Although the invention has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof.

25

CLAIMS

What is claimed is:

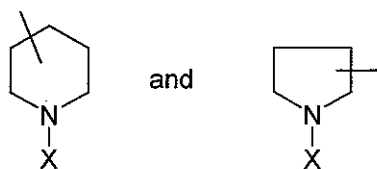
- 5 1. A compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

10

R₁ is selected from the group consisting of aryl, benzyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, C₃₋₈cycloalkylC₁₋₆alkyl, arylcarbonyl, arylC₁₋₆alkylC₃₋₈cycloalkylcarbonyl, C₁₋₁₀alkylcarbonyl, heteroarylcarbonyl and



15

wherein X is hydrogen, benzyl, arylC₂₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₁₀alkyl, or C₃₋₈cycloalkylC₁₋₆alkyl;

20

wherein said aryl, benzyl, or heteroaryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁-C₆alkoxy, nitro, or aryl;

25

R₂ is selected from the group consisting of C₁₋₆alkyl, C₃₋₈cycloalkyl, and aryl wherein said aryl is optionally substituted with one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆perfluoroalkyl, halogen, hydroxy, C_nH_xF_{y-6}alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and x + y is 2n+1, C₁-C₆alkoxy, nitro, aryl, or alkoxy;

R_3 is selected from the group consisting of aryl, C_{3-8} cycloalkyl, C_{1-6} alkyl and heteroaryl wherein said aryl or heteroaryl is optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, aryl, or alkoxy;

5

R_4 is selected from the group consisting of H, aryl C_{2-6} alkyl, benzyl, C_{1-6} perfluoroalkyl, C_{3-8} cycloalkyl and C_{2-6} alkyl wherein said aryl or benzyl is optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, halogen, hydroxy, $C_nH_xF_y$ -alkoxy wherein n is 1-4, x is 0-8, y is 1-9 and $x + y$ is $2n+1$, C_1 - C_6 alkoxy, nitro, aryl, or alkoxy;

10

R_5 is H, C_{1-6} alkyl, or C_{3-8} cycloalkyl; and

with the proviso that

(a) when R_1 and R_4 are phenyl or 4-chlorophenyl, and R_5 is hydrogen then R_2 and R_3 are other than methyl simultaneously;

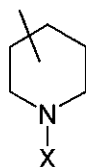
15

(b) when R_1 is phenyl or 4-chlorophenyl and R_4 and R_5 are hydrogen then R_2 and R_3 are other than methyl simultaneously.

2. The compound according to claim 1 wherein

20

R_1 is selected from the group consisting of aryl, benzyl, C_{3-8} cycloalkyl, C_{1-10} alkyl, aryl C_{1-6} alkyl and



wherein X is benzyl;

R_2 and R_3 are C_{1-6} alkyl; and

25

R_5 is hydrogen or C_{1-6} alkyl.

3. The compound according to claim 1 wherein

R_1 is aryl;

R_2 and R_3 are C_{1-6} alkyl;

30

R_4 is hydrogen; and

R_5 is hydrogen or C_{1-6} alkyl.

4. The compound according to claim 3 which is selected from the group consisting of:

2'-(2-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(4-Isopropyl-phenyl)-
 5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(4-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-
 5 [3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-trifluoromethyl-phenyl)-2H, 2'H-[3,4']
 bipyrazolyl-3'-ol, 5, 5'-Dimethyl-2'-(4-methoxy-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-
 (3-Fluoro-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(2-Methyl-phenyl)-5,5'-
 dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-trifluoromethoxy-phenyl)-2H,
 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(4-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-
 10 ol, 5,5'-Dimethyl-2'-(3-methyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(2-
 ethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3,4-dichloro-phenyl)-2H,
 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-(3-chlorophenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-
 ol, 2'-(4-tert-Butyl-phenyl)-5,5'-dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 5,5'-Dimethyl-2'-
 (3-trifluoromethyl-phenyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 5'-Methoxy-5, 3'-dimethyl-1'-
 15 phenyl-2H,1'H-[3,4']bipyrazolyl.

5. The compound according to claim 1 wherein

R₁ is aryl;

R₂ and R₃ are C₁₋₆alkyl;

20 R₄ is arylC₂₋₆alkyl, or benzyl; and

R₅ is hydrogen or C₁₋₆alkyl.

6. The compound according to claim 5 which is selected from the group consisting of:

5,5'-Dimethyl-2-phenethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-Benzyl-5, 5'-
 25 dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2-Benzyl-5'-methoxy-5,3'-dimethyl-
 1'-phenyl-2H,1'H-[3,4']bipyrazole, and 2-(3-Hydroxy-benzyl)-5,5'-dimethyl-2'-phenyl-2H,
 2'H-[3,4'] bipyrazolyl-3'-ol.

7. The compound according to claim 1 wherein

30 R₁ is aryl;

R₂ and R₃ are C₁₋₆alkyl;

R₄ is hydroxyC₂₋₆alkyl, C₃₋₈cycloalkyl or C₂₋₆alkyl and

R₅ is hydrogen.

8. The compound according to claim 7 which is selected from the group consisting of:

5,5'-Dimethyl-2'-phenyl-2- (2,2,2-trifluoro-ethyl)-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-Cyclohexyl-5, 5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2-(2-Hydroxy-ethyl)-
 5 5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2,5,5'-Trimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

9. A compound which is selected from the group consisting of:

2-(4-Methoxy-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol and 2-(4-
 10 Fluoro-phenyl)-5,5'-dimethyl-2'-phenyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

10. The compound according to claim 1 wherein

R₁ is arylC₂₋₆alkyl or benzyl;

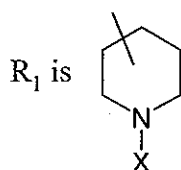
R₂ and R₃ are C₁₋₆alkyl; and

15 R₄ and R₅ are hydrogen.

11. The compound according to claim 10 which is selected from the group consisting of:

5,5'-Dimethyl-2'-phenethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, 2'-(3-Hydroxy-benzyl)-5,5'-
 20 dimethyl-2H, 2'H-[3,4'] bipyrazolyl-3'-ol, and 2'-Benzyl-5, 5'-dimethyl-2H, 2'H-[3,4']
 bipyrazolyl-3'-ol.

12. The compound according to claim 1 wherein



wherein X is benzyl;

25 R₂ and R₃ are C₁₋₆alkyl; and

R₄ and R₅ are hydrogen.

13. The compound according to claim 12 which is 2'-(1-Benzyl-piperidin-4-yl)-5,5'-dimethyl-
 2H, 2'H-[3,4'] bipyrazolyl-3'-ol.

14. The compound according to claim 1 wherein

R₁ is C₃₋₈cycloalkyl;

R₂ and R₃ are C₁₋₆alkyl; and

R₄ and R₅ are hydrogen.

5

15. The compound according to claim 14 which is 2'-Cyclohexyl-5,5'-dimethyl-2H-2'H-[3,4]bipyrazolyl-3'-ol.

16. A compound which is 5,1',5'-trimethyl-2'-phenyl-1', 2'-dihydro-2H-[3,4'] bipyrazolyl-3'-one.

10

17. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

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