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(71) Applicant: **RHENOVIA PHARMA** [FR/FR]; Technopole Mer Rouge Plaza, 20C Rue de Chemnitz, F-68200 Mulhouse (FR).

(72) Inventors: **BISCHOFF, Serge**; 937 Route de Cavaillon, F-84440 Robion (FR). **GEORGE, Florian**; 35 Rue Du General Offenstein, F-67000 Strasboourg (FR). **MOUSSAOUI, Saliha**; 24, rue des Ecureuils, F-68870 Bartenheim (FR). **GREGET, Renaud**; 4 Rue de Masevaux, F-68210 Traubach-le-haut (FR). **FAUPEL, Michel, D.**; 14, Rue de Bale, F-68440 Eschentzwiller (FR). **BAUDRY, Michel**; 1437 Burnett Circle, Corona, CA 92882 (US).

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(54) **Title**: TREATMENT FOR PARKINSON'S DISEASE

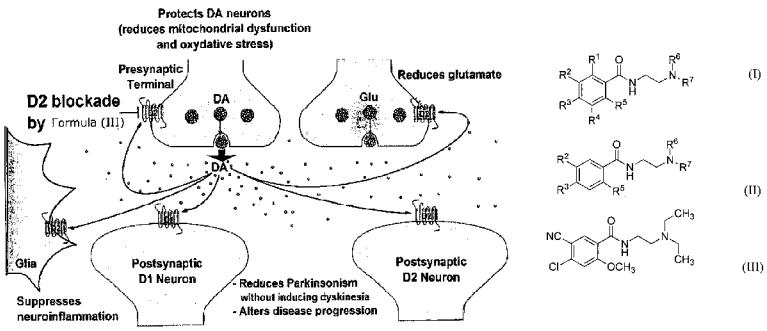


FIG. 1

(57) **Abstract**: A method for treating Parkinson's disease in a mammal in need thereof is disclosed. The method comprises administering to the mammal an effective amount of a compound of any one of Structural Formulas (I-III), or a pharmaceutically acceptable salt thereof. The values and alternative values for the variables in Structural Formulas (I) and (II) are described herein.

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TREATMENT FOR PARKINSON'S DISEASE

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/806,306, filed on March 28, 2013. The entire teachings of this application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Parkinson's disease (PD) is a degenerative disorder of the central nervous system. Early symptoms of PD include tremors, rigidity and slow movement, and progress in later stages of the disease to include cognitive and behavioral problems. There are approved therapies for treating the motor symptoms associated with PD. For example, levodopa (L-DOPA, L-3,4-dihydroxyphenylalanine) and other D2 receptor agonists are commonly used to treat PD. However, L-DOPA is associated with L-DOPA-induced dyskinesia, and researchers have found that while L-DOPA treatment of non-dyskinetic parkinsonian animals reverses glutamatergic overactivity and hypersensitivity of D2 receptors at corticostriatal terminals (Picconi *et al.*, Brain 2004; 127:1661-1669), L-DOPA has no effect in dyskinetic animals. NMDA receptor antagonists, such as amantadine (MK801), and mGluR5 antagonists only mitigate dyskinetic behavior (Nevalainen *et al.*, PLoS ONE 2013; 8:e55706).

[0003] Despite the fact that reduced dopaminergic transmission is known to be the mechanistic basis for the underlying pathological manifestations of PD, most prescribed drug treatments targeting dopaminergic transmission are far from satisfactory.

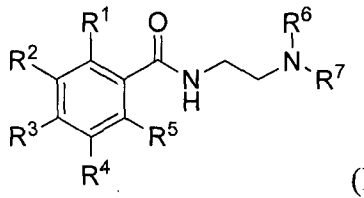
[0004] Thus, there is an acute need for alternative drugs for treating PD. In particular, there is a need for drugs that can modulate and equilibrate dopamine (DA) neurotransmission, for example, by preferentially antagonizing pre-synaptic DA D2 receptors.

SUMMARY OF THE INVENTION

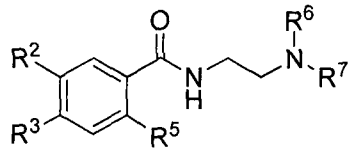
[0005] The present invention is related to the unexpected discovery that an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and a 5- to 100-fold preferential affinity for pre-synaptic DA D2 receptors versus post-synaptic DA D2

receptors are important determinants of a compound's ability to restore DA homeostasis and thereby treat Parkinson's disease (PD) in a mammal.

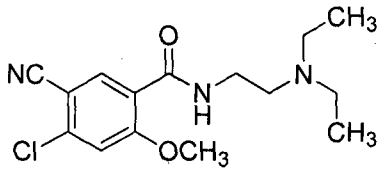
[0006] One embodiment of the invention is a method for treating PD in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of any one of Formulas I-III:



(I),



(II),



(III),

or a pharmaceutically acceptable salt thereof, wherein the values and alternative values for the variables in Formulas I and II are as described hereinbelow.

[0007] Another embodiment of the invention is a method for treating PD in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of any one of Formulas I-III, or a pharmaceutically acceptable salt thereof, having an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and/or an affinity for a pre-synaptic DA D2 receptor, as characterized by K_d, that is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d.

[0008] Another embodiment of the invention is a compound of any one of Formulas I-III, or a pharmaceutically acceptable salt thereof, for use in treating PD in a mammal in need thereof.

[0009] Another embodiment of the invention is a compound of any one of Formulas I-III, or a pharmaceutically acceptable salt thereof, having an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and/or an affinity for a pre-synaptic DA D2 receptor, as characterized by K_d, that is about 5 to about 100 times greater

than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d, for use in treating PD in a mammal in need thereof.

[0010] Another embodiment of the invention is use of a compound of any one of Formulas I-III, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of PD.

[0011] Another embodiment of the invention is use of a compound of any one of Formulas I-III, or a pharmaceutically acceptable salt thereof, having an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and/or an affinity for a pre-synaptic DA D2 receptor, as characterized by K_d, that is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d, in the manufacture of a medicament for the treatment of PD.

[0012] Another embodiment of the invention is a pharmaceutical composition comprising a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof; and a second therapeutic agent for treating PD.

[0013] Another embodiment of the invention is a pharmaceutical composition comprising a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, having an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and/or an affinity for a pre-synaptic DA D2 receptor, as characterized by K_d, that is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d; and a second therapeutic agent for treating PD.

[0014] The compounds of Formulas I-III (also referred to herein as benzamide compounds) exhibit a dual, biphasic mode of action due, at least in part, to a preferential affinity for pre-synaptic D2 receptors versus post-synaptic D2 receptors. The benzamide compounds described herein act directly on pre-synaptic DA nigrostriatal neurons and are expected to alter disease progression by enhancing DA release (a key function for normal neurotransmission and for reducing DA-induced oxidative stress) and DA transport and synthesis, thereby restoring normal function to DA neurons. The benzamide compounds also have a post-synaptic effect, which they exert by enhancing the release of DA, which acts on both GABAergic striato-pallidal neurons and glutamatergic cortico-striatal nerve terminals. This is a critical mechanism for controlling motor symptoms and dyskinesia, and is a clinically validated mechanism for approved DA-based therapies (*e.g.*, L-DOPA, D2 receptor agonists) and anti-glutamate drugs, respectively. Action of the benzamide compounds on

post-synaptic medium spiny neurons (MSNs) is also expected to alter disease progression by modulating pathogenic pathways (*e.g.*, calpain/cdk5/DAPP-32/PKA/mitochondria fragmentation/neuronal degeneration) and by reducing astrocyte neuroinflammation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

[0016] FIG. 1 is a schematic representation of the role of a benzamide compound, such as a compound of Formula III, in the treatment of PD.

[0017] FIG. 2A is a schematic representation of a pre-synaptic DA terminal in PD and a healthy pre-synaptic DA terminal, and shows a mechanistic basis for why a benzamide compound, such as a compound of Formula III, is expected to enhance DA release by binding to and blocking a pre-synaptic D2 receptor.

[0018] FIG. 2B is a schematic representation of a pre-synaptic DA terminal in PD and a healthy pre-synaptic DA terminal, and shows a mechanistic basis for why a benzamide compound, such as a compound of Formula III, is expected to enhance DA synthesis and transport by binding to and blocking a pre-synaptic D2 receptor.

[0019] FIG. 3 is a schematic representation of basal ganglia-thalamo-cortical neuronal circuitry controlling the indirect gamma-aminobutyric acid (GABA) pathway, and shows a mechanistic basis for: (a) the efficient antagonistic effect of D2 receptor (D2R) activation, counteracting glutamate/NMDA receptor effects on GABA striatopallidal neurotransmission when the nigrostriatal DA neuron is intact (as in a healthy subject); and (b) deficient antagonistic effect of D2 receptor (D2R) activation, less able to counteract glutamate/NMDA receptor effects on GABA striatopallidal neurotransmission when the nigrostriatal DA neuron is deficient (as in a PD subject).

[0020] FIG. 4 is a schematic representation of a synapse (between a DA nerve terminal and a GABA neuron), and shows a mechanistic basis for the expected effect of a benzamide compound, such as a compound of Formula III, on a signaling pathway leading to gene transcription, mitochondriogenesis and neuroprotection.

DETAILED DESCRIPTION OF THE INVENTION

[0021] A description of example embodiments of the invention follows.

[0022] One embodiment of the invention is a method for treating PD in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, having an affinity for a pre-synaptic DA D2 receptor, an affinity for a post-synaptic DA D2 receptor, and an averaged affinity for DA D2 receptors. The averaged affinity of the compound for DA D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8} M, and the affinity of the compound for a pre-synaptic DA D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d.

[0023] "Averaged affinity," as used herein, refers to a binding interaction between a sub-class of receptor types, such as D2 receptors (including pre- and post-synaptic D2 receptors), and a ligand, such as a compound of Formula I, II or III. The interaction can be characterized using methods known to those of skill in the art. Typically, the interaction is characterized by a dissociation constant (K_d), an inhibitor constant (K_i; the concentration of competing ligand in a competition assay which would occupy 50% of the receptors if no ligand were present), IC_{50} (the concentration at which an agent inhibits a biological process by half) or EC_{50} (the concentration at which an agent induces a response halfway between the baseline and the maximum for a biological process after a specified exposure time). IC_{50}, K_d, K_i and EC_{50} can be measured using receptor binding techniques, such as saturation binding assays, binding kinetics, or competition, including inhibition and displacement, assays. Other methods for determining IC_{50}, K_d, K_i and EC_{50} are known to those of skill in the art.

[0024] In some embodiments of the invention, the averaged affinity of the compound for DA D2 receptors is characterized by a K_d. Preferably, the K_d is about 10^{-5} to about 10^{-8} M. More preferably, the K_d is about 10^{-6} to about 10^{-7} M. Alternatively, the K_d is about the K_d of a compound of Formula III.

[0025] In some embodiments of the invention, the averaged affinity of the compound for DA D2 receptors is characterized by an IC_{50}, for example, in a spiperone binding assay. Preferably, the IC_{50} of the compound in a spiperone binding assay is about 10^{-6} M. A spiperone binding assay is disclosed in Bischoff, S., *et al.*; *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1994) 350:230-238.

[0026] The IC_{50} of a binding interaction between a ligand and a receptor can be converted to K_i using the Cheng-Prussoff equation:

$$K_i = IC_{50}/(1+L^*/K_d),$$

where L* is the concentration of ligand and K_d is the equilibrium dissociation constant ligand (*see* Cheng Y., Prusoff, W.H. *Biochem. Pharmacol.* (1973); Munson, P.J., Rodbard, D. An exact correction to the "Cheng-Prusoff" correction. *J Recept. Res.* 8:533-46 (1988)). In some circumstances, this equation can be approximated:

(i) when $L^* = K_d$, then $K_i = IC_{50}/2$; and

(ii) when K_d is significantly greater than L*, L^*/K_d approaches zero and $K_i = IC_{50}$.

[0027] Because the present invention is related, in part, to the discovery that compounds exhibiting a preferential affinity for pre-synaptic D2 receptors versus post-synaptic D2 receptors may be useful for treating PD, it is necessary to discriminate between the affinity of a compound for a sub-class of receptors, such as D2 receptors, and the affinity of the compound for specific types of receptors in a sub-class, such as a pre- or a post-synaptic D2 receptor. Therefore, as used herein, "affinity" refers to a binding interaction between a specific type of receptor, such as a pre- or a post-synaptic D2 receptor, and a ligand, such as a compound of Formula I, II or III.

[0028] "Preferential affinity" means that a compound or ligand binds to one type of receptor in a sub-class to a greater extent than to another type of receptor in the sub-class (*i.e.*, the compound exhibits selectivity for one type of receptor over another type of receptor). In some cases, preferential affinity is measured at low concentrations (*e.g.*, non-saturating concentrations) of the compound. Therefore, in some embodiments, the affinity of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, for a pre-synaptic DA D2 receptor is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor at low concentrations of the compound.

[0029] In some embodiments, the affinity of the compound for a pre-synaptic DA D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d. In some embodiments, the affinity of the compound for a pre-synaptic DA D2 receptor, as characterized by K_d, is about 5 to about 15, or about 10 to about 15 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d. In some embodiments, the preferential affinity of the compound for a pre-synaptic DA D2

receptor versus a post-synaptic DA D2 receptor is about the preferential affinity of a compound of Formula III for a pre-synaptic DA D2 receptor versus a post-synaptic DA D2 receptor (*e.g.*, the compound is approximately 13 times more selective for a pre-synaptic D2 receptor than for a post-synaptic D2 receptor).

[0030] Methods of assessing the averaged affinity of a D2 receptor antagonist, as well as the preferential affinity of a D2 receptor antagonist for $D2_{pre}$ versus $D2_{post}$, are disclosed in Bischoff, S., *et al.*; *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1994) 350:230-238. Methods of determining dissociation constants are known to those of skill in the art.

[0031] In some embodiments, the affinity or averaged affinity is the affinity or averaged affinity of a compound of Formula I, II or III for a D2 receptor, such as a pre- or a post-synaptic D2 receptor, or D2 receptors, including pre- and post-synaptic receptors, found in neuronal tissue.

[0032] In some embodiments, the compound of Formula I, II or III, or a pharmaceutically acceptable salt or a metabolite thereof, crosses the blood-brain barrier.

[0033] As used herein, the term "mammal" means a mammal in need of treatment or prevention, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the mammal is a human in need of the specified treatment.

[0034] As used herein, the term "treating" or "treatment" refers to obtaining desired pharmacological and/or physiological effect. The effect can include achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

[0035] "Effective amount" means that amount of active compound that elicits the desired biological response in a mammal. Desired biological responses include, for example, control of some or all motor symptoms of PD, control of motor and non-motor symptoms of PD, and/or alteration of disease progression. PD is a progressive, neurodegenerative disease characterized by partial loss and hypofunction of nigrostriatal DA neurons, and is associated with motor symptoms such as resting tremors, muscular rigidity, and slow movements. Additional PD symptoms include postural abnormalities, dysautonomia, dystonic cramps, and dementia. Common treatments for PD are typically able to control some symptoms of PD,

but are unable to alter disease progression, and can cause additional symptoms associated with abnormal dopaminergic transmission. For example, L-DOPA can cause dyskinesia.

[0036] Although not wishing to be bound by any particular theory, it is expected that the symptoms associated with PD can be controlled by stimulating DA release into the synaptic cleft, thereby stimulating post-synaptic DA receptors. Thus, in some embodiments, the effective amount of a compound is an effective amount to stimulate dopaminergic transmission.

[0037] Although not wishing to be bound by any particular theory, it is expected that the restoration of normal function to DA neurons by selective modulation of pre-synaptic DA synthesis and transport in addition to pre-synaptic DA release will be able to alter disease progression and control PD symptoms. Thus, in some embodiments, the effective amount of a compound is an effective amount to restore pre-synaptic DA neuronal function, for example, via selective modulation of pre-synaptic D2R. In some embodiments, the effective amount of a compound is an effective amount to restore DA homeostasis, for example, via dual modulation of both presynaptic and postsynaptic D2R. In some embodiments, the effective amount of a compound is an effective amount to restore DA neuronal function.

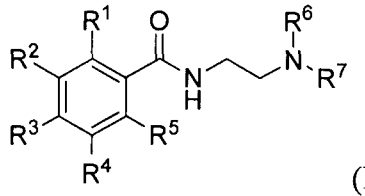
[0038] Examples of effective amounts are about 0.1 to about 150 mg/kg, about 0.1 to about 25 mg/kg, about 1 to about 25 mg/kg, about 5 to about 15 mg/kg, about 30 to about 100 mg/kg, and about 70 to about 100 mg/kg.

[0039] As used herein, "dopamine homeostasis" or "DA homeostasis" refers to mechanisms maintaining dopaminergic transmission in equilibrium. Dopamine is an important factor in the regulation of many biological processes, from addiction, cognition and motivation to balance and locomotion and, therefore, its function is tightly regulated. The delicate balance between DA release into the synaptic cleft and pre- or post-synaptic receptor transduction in response to DA binding (which together contribute to dopamine transmission), is disrupted in PD. Thus, "to restore DA homeostasis" means to re-equilibrate the biological processes governing or contributing to physiologically controlled dopaminergic transmission. To keep the system in equilibrium, extracellular DA concentration should be maintained in a range that correlates with a post-synaptic cAMP response in the midrange of physiological variations.

[0040] The activity state of a neuron and, therefore, whether the neuron is functioning under DA homeostatic conditions, can be measured, for example, as output current, or as

amount or concentration of released DA. The activity state of the neuron is also referred to herein as the "tone" of the neuron.

[0041] The compound of Formula I is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof.

R^1 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy, (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy, (C_1-C_8)aliphatic-OC(O)-, (C_1-C_8)aliphatic-C(O)O-, (C_1-C_8)aliphatic- or $N(R^8)_2$. Preferably, R^1 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. More preferably, R^1 is hydrogen.

[0042] R^3 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy, (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy, (C_1-C_8)aliphatic-OC(O)-, (C_1-C_8)aliphatic-C(O)O-, (C_1-C_8)aliphatic- or $N(R^8)_2$. Preferably, R^3 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. More preferably, R^3 is halogen. Yet more preferably, R^3 is fluoro or chloro.

[0043] R^5 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy, (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy, (C_1-C_8)aliphatic-OC(O)-, (C_1-C_8)aliphatic-C(O)O-, (C_1-C_8)aliphatic- or $N(R^8)_2$. Preferably, R^5 is hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. More preferably, R^5 is hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. Yet more preferably, R^5 is (C_1-C_8)aliphatic-O-. Yet more preferably, R^5 is (C_1-C_8)alkoxy or (C_1-C_8)alkenyloxy.

[0044] Each aliphatic, carbocyclyl, or alkyl group represented by R^1, R^3 and R^5 is optionally and independently substituted, for example, with one or more (*e.g.*, one, two, three, four or five, typically, one, two or three) suitable substituent groups. Alternatively, each aliphatic, carbocyclyl, or alkyl group represented by R^1, R^3 and R^5 is unsubstituted.

[0045] R^2 is hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O-. Preferably, R^2 is cyano.

[0046] R^4 is hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O-. Preferably, R^4 is hydrogen.

[0047] R^6 and R^7 are each independently hydrogen, (C_1-C_{30})aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl. Preferably, R^6 and R^7 are each independently (C_1-C_{30})aliphatic-. More preferably, R^6 and R^7 are each independently (C_1-C_8)aliphatic-. Yet more preferably, R^6 and R^7 are each independently (C_1-C_8)alkyl-. Yet more preferably, R^6 and R^7 are each independently (C_1-C_4)alkyl-.

[0048] Alternatively, R^6 and R^7 are each hydrogen, (C_1-C_{30})aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl. Preferably, R^6 and R^7 are each (C_1-C_{30})aliphatic-. More preferably, R^6 and R^7 are each (C_1-C_8)aliphatic-. Yet more preferably, R^6 and R^7 are each (C_1-C_8)alkyl-. Yet more preferably, R^6 and R^7 are each (C_1-C_4)alkyl-.

[0049] At least one C in each aliphatic or alkyl group represented by R^6 and R^7 is optionally and independently replaced by a heteroatom selected from oxygen, sulfur and nitrogen.

[0050] Each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl represented by R^6 and R^7 is optionally and independently substituted, for example, with one or more (*e.g.*, one, two, three, four or five, typically, one, two or three) suitable substituent groups. Alternatively, each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl represented by R^6 and R^7 is unsubstituted.

[0051] R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl. Preferably, R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl. More preferably, R^6 and R^7, together with the N to which they are bound, form a 5-7-membered, optionally substituted heterocyclyl.

[0052] The heterocyclyl or heteroaryl formed by R^6 and R^7, together with the N to which they are bound, is optionally and independently substituted, for example, with one or more (*e.g.*, one, two, three, four or five, typically, one, two or three) suitable substituent groups. Alternatively, the heterocyclyl or heteroaryl formed by R^6 and R^7, together with the N to which they are bound, is unsubstituted.

[0053] Each R^8 is independently hydrogen or (C_1-C_8)aliphatic-. Preferably, each R^8 is independently hydrogen or (C_1-C_8)alkyl. More preferably, each R^8 is independently hydrogen or (C_1-C_4)alkyl.

[0054] Two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl. Preferably, two R^8, together with the N to which they are bound, form a 5-7-membered heterocyclyl.

[0055] An "aliphatic group" is a non-aromatic monovalent radical consisting solely of carbon and hydrogen and can optionally contain one or more units of unsaturation, *e.g.*, double and/or triple bonds. An aliphatic group can be straight-chained or branched. An aliphatic group can contain between about one and about thirty carbon atoms, between about one and about ten carbon atoms, between about one and about eight càrbon atoms, or between about one and about four carbon atoms. Exemplary aliphatic groups include alkyl and alkenyl groups. A "substituted aliphatic group" is substituted at any one or more "substitutable carbon atoms." A "substitutable carbon atom" in an aliphatic, alkyl, alkenyl, carbocyclyl, cycloalkyl, or heterocyclyl group is a carbon in atom that is bonded to one or more hydrogen atoms. The one or more hydrogen atoms can optionally be replaced with a suitable substituent group.

[0056] "Alkyl" means a saturated aliphatic branched or straight-chain monovalent hydrocarbon radical. "(C_1-C_8)alkyl" means a radical having from 1-8 carbon atoms in a linear or branched arrangement. "(C_1-C_8)alkyl" includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl.

[0057] "Alkylthio" means an alkyl radical attached through a sulfur linking atom. "Alkylthio" can also be depicted as -S-alkyl.

[0058] "Alkylsulfinyl" means an alkyl radical attached through a sulfinyl (*i.e.*, -S(O)-) group. "Alkylsulfinyl" can be depicted as -S(O)-alkyl.

[0059] "Alkylsulfonyl" means an alkyl radical attached through a sulfonyl (*i.e.*, -$S(O)_2$-) group. "Alkylsulfonyl" can be depicted as -$S(O)_2$-alkyl.

[0060] The term "alkoxy" means an alkyl radical attached through an oxygen linking atom. "Alkoxy" can be depicted as -O-alkyl. "Hydroxyalkyl" means alkyl substituted with hydroxy; "aralkyl" means alkyl substituted with an aryl group; "alkoxyalkyl" means alkyl substituted with an alkoxy group; "alkylaryl" means aryl substituted with an alkyl group;

"cycloalkylalkyl" means alkyl substituted with cycloalkyl; where alkyl, cycloalkyl and aryl are as defined herein.

[0061] "Carbocyclyl" means a non-aromatic monocyclic or polycyclic ring system consisting solely of carbon and hydrogen. A carbocyclyl can optionally contain one or more units of unsaturation, *e.g.*, double and/or triple bonds. In some embodiments, a carbocyclyl contains three to ten carbon atoms, three to eight carbon atoms, or three to seven carbon atoms.

[0062] The term "carbocyclyloxy" means -O-carbocycylyl; "carbocyclylalkoxy" means -O-alkyl-carbocyclyl; where carbocyclyl and alkyl are as defined above.

[0063] "Cycloalkyl" means a saturated monocyclic or polycyclic carbocyclic ring. In some embodiments, a carbocyclyl includes three to ten carbon atoms, or three to seven carbon atoms.

[0064] "Cycloalkoxy" means a cycloalkyl radical attached through an oxygen linking atom. "Cycloalkoxy" can also be depicted as -O-cycloalkyl.

[0065] "Halogen" or "halo," as used herein, refers to fluorine, chlorine, bromine, or iodine. Preferably, the halogen is fluorine or chlorine. More preferably, the halogen is chlorine.

[0066] As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon group that contains one or more double bonds between carbon atoms. Suitable alkenyl groups include, *e.g.*, *n*-butenyl, allyl, and the like. Suitable substituents for an alkenyl group include those for an aliphatic group.

[0067] "Alkenyloxy" means an alkenyl radical attached through an oxygen linking atom. "Alkenyloxy" can be depicted as -O-alkenyl.

[0068] "Aryl" means an aromatic monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) carbocyclic ring system. In one embodiment, "aryl" is a 6-12 membered monocylic or bicyclic ring system. Aryl systems include, but are not limited to, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, and anthracenyl. A "substituted aryl group" is substituted at any one or more "substitutable ring atom."

[0069] "Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. When the heteroatom is S, the S can be oxidized (*i.e.*, -S(O)- or -SO_2-). A hetero ring system can have 1, 2, or 3 carbon atom members replaced by a heteroatom.

[0070] The term "heteroaryl" refers to an aromatic monocyclic or polycyclic ring system in which one or more ring carbons are replaced with a heteroatom independently selected from N, O, and S. In one embodiment, "heteroaryl" is a 5-12-membered, preferably a 5-6-membered ring system. Typically, a heteroaryl contains 1, 2, or 3 heteroatoms. Heteroaryls include, but are not limited to pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole 1,1-dioxide, 1,3,4-thiadiazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-triazine, 1,3,5-triazine, and tetrazole.

[0071] The term "heterocyclyl" refers to a non-aromatic monocyclic or polycyclic ring system in which one or more ring carbons, preferably one or two, are each replaced by a heteroatom independently selected from N, O, and S. A heterocyclyl can optionally contain one or more units of unsaturation, *e.g.*, double and/or triple bonds. In some embodiments, "heterocyclyl" is a 4-12-membered, a 4-8-membered, or a 5-7-membered ring system. Examples of heterocyclic groups include tetrahydrofuranyl, azetidinyl, oxazolidinyl, morpholinyl, pyrrolidinyl, piperazinyl and piperidinyl.

[0072] A "substitutable ring atom" in an aromatic or heteroaromatic group is a ring carbon or nitrogen atom bonded to a hydrogen atom. The hydrogen can optionally be replaced with a suitable substituent group.

[0073] Suitable substituent groups for an aliphatic, alkyl, aryl, carbocyclyl, cycloalkyl, heteroaryl and heterocyclyl include, but are not limited to, halogen, hydroxy, nitro, cyano, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkylthio, $(C_1\text{-}C_4)$alkylsulfinyl, $(C_1\text{-}C_4)$alkylsulfonyl, $(C_1\text{-}C_4)$alkoxy$(C_1\text{-}C_4)$alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, and $-N(R^8)_2$, wherein each R^8 is independently as described above. Examples of suitable substituents for a substitutable carbon of an aliphatic, alkyl, carbocyclyl, cycloalkyl, and heterocyclyl that is bonded to two or more hydrogen atoms include those listed above and the following: =O and =S.

[0074] In a first embodiment, the compound is represented by Structural Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy, $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$aliphatic-OC(O)-, $(C_1\text{-}C_8)$aliphatic-C(O)O-, $(C_1\text{-}C_8)$aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or (C_1-C_8)aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

R^2 and R^4 are each independently hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, (C_1-C_{30})aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl.

[0075] In a first aspect of the first embodiment, R^1 is hydrogen; R^3 is halogen; and R^5 is hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. The values and alternative values for the remaining variables are as described in the first embodiment.

[0076] In a second aspect of the first embodiment, R^2 is hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O- and R^4 is hydrogen. The values and alternative values for the remaining variables are as described in the first embodiment, or first aspect thereof.

[0077] In a third aspect of the first embodiment, R^1 is hydrogen and R^3 and R^5 are each independently hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy or (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy. The values and alternative values for the remaining variables are as described in the first embodiment, or first or second aspect thereof.

[0078] In a fourth aspect of the first embodiment, R^2 is cyano and R^3 is halogen. The values and alternative values for the remaining variables are as described in the first embodiment, or first through third aspects thereof.

[0079] In a fifth aspect of the first embodiment, R^6 and R^7 are each $(C_1\text{-}C_8)$aliphatic. The values and alternative values for the remaining variables are as described in the first embodiment, or first through fourth aspects thereof.

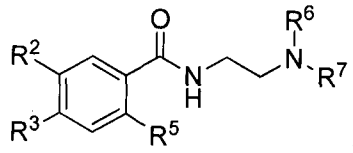
[0080] In a sixth aspect of the first embodiment, R^6 and R^7 are each independently $(C_1\text{-}C_8)$alkyl. The values and alternative values for the remaining variables are as described in the first embodiment, or first through fifth aspects thereof.

[0081] In a seventh aspect of the first embodiment, R^5 is hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy or $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy. The values and alternative values for the remaining variables are as described in the first embodiment, or first through sixth aspects thereof.

[0082] In an eighth aspect of the first embodiment, R^5 is $(C_1\text{-}C_8)$alkoxy or $(C_1\text{-}C_8)$alkenyloxy. The values and alternative values for the remaining variables are as described in the first embodiment, or first through seventh aspects thereof.

[0083] In a ninth aspect of the first embodiment, R^2 is cyano and R^3 is chloro. The values and alternative values for the remaining variables are as described in the first embodiment, or first through eighth aspects thereof.

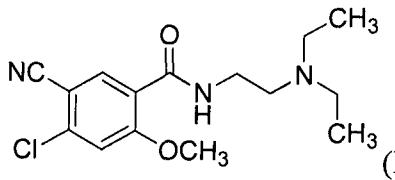
[0084] In a second embodiment, the compound is represented by Structural Formula II:



(II),

or a pharmaceutically acceptable salt thereof. The values and alternative values for the remaining variables are as described in the first embodiment, or any aspect thereof.

[0085] In a third embodiment, the compound is represented by Structural Formula III:



(III),

or a pharmaceutically acceptable salt thereof.

[0086] In a first aspect of the third embodiment, the compound is the hydrochloride salt of the compound of Structural Formula III.

[0087] Methods of making a compound of Structural Formulas I-III, as well as exemplary compounds useful in the methods of the invention, are disclosed in U.S. Patent No. 4,772,630.

[0088] A pharmaceutically acceptable salt of a compound for use in the methods of the present invention can be obtained, for example, by reacting an amine or other basic group in the compound with a suitable organic or inorganic acid. Examples of salts include the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts. In some embodiments, the compound of Formula I, II, or III is the hydrochloride salt of the compound of Formula I, II, or III, respectively.

[0089] Another embodiment of the present invention is a method for treating PD in a mammal in need thereof, comprising administering to the mammal a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof.

[0090] "Pharmaceutically acceptable carrier" and "pharmaceutically acceptable diluent" mean non-therapeutic components that are of sufficient purity and quality for use in the formulation of a composition of the invention that, when appropriately administered to a mammal or human, typically do not produce an adverse reaction, and that are used as a vehicle for a drug substance.

[0091] The compositions for use in the methods of the invention include oral, transdermal, topical with or without occlusion, intravenous (both bolus and infusion), and injection (intraperitoneally, subcutaneously, intramuscularly or parenterally) formulations. The composition can be in a dosage unit such as a tablet, pill, capsule, powder, granule, liposome, parenteral solution or suspension, ampoule, auto-injector device, or suppository for administration orally, transdermally, topically, or intravenously.

[0092] Compositions for use in the methods of the invention suitable for oral administration include solid forms such as pills, tablets, caplets, capsules (each including

immediate release, timed release, and sustained release formulations), granules and powders; and, liquid forms such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

[0093] The dosage form containing the composition for use in the methods of the invention contains an effective amount of the active ingredient necessary to provide a therapeutic effect. The composition can contain from about 5,000 mg to about 0.1 mg (preferably, from about 1,000 mg to about 0.1 mg) of a compound of any one of Formulas I-III, or a salt form thereof, and can be constituted into any form suitable for the selected mode of administration. The composition can be administered about 1 to about 5 times per day. Daily administration or post-periodic dosing can be employed.

[0094] For oral administration, the composition is preferably in the form of a tablet or capsule containing, *e.g.*, 100 to 1 milligrams of the active compound. Dosages will vary depending on factors associated with the symptoms of the particular mammal being treated, the severity of the condition being treated, the mode of administration, and the strength of the preparation.

[0095] The oral composition is preferably formulated as a homogeneous composition, wherein the active ingredient is dispersed evenly throughout the mixture, which can be readily subdivided into dosage units containing equal amounts of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof. Preferably, the compositions are prepared by mixing a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, with one or more optionally present pharmaceutical carriers (such as a starch, sugar, diluent, granulating agent, lubricant, glidant, binding agent, and disintegrating agent), one or more optionally present inert pharmaceutical excipients (such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and syrup), one or more optionally present conventional tableting ingredients (such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, and any of a variety of gums), and an optional diluent (such as water).

[0096] Binder agents include starch, gelatin, natural sugars (*e.g.*, glucose and beta-lactose), corn sweeteners and natural and synthetic gums (*e.g.*, acacia and tragacanth). Disintegrating agents include starch, methyl cellulose, agar, and bentonite.

[0097] Tablets and capsules represent an advantageous oral dosage unit form. Tablets can be sugar-coated or film-coated using standard techniques. Tablets can also be coated or

otherwise compounded to provide a prolonged, controlled-release therapeutic effect. The dosage form can comprise an inner dosage and an outer dosage component, wherein the outer component is in the form of an envelope over the inner component. The two components can further be separated by a layer which resists disintegration in the stomach (such as an enteric layer) and permits the inner component to pass intact into the duodenum or a layer which delays or sustains release. A variety of enteric and non-enteric layer or coating materials (such as polymeric acids, shellacs, acetyl alcohol, and cellulose acetate or combinations thereof) can be used.

[0098] Compositions for use in the methods of the invention can also be administered via a slow release composition; wherein the composition includes a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and a biodegradable slow release carrier (*e.g.*, a polymeric carrier) or a pharmaceutically acceptable non-biodegradable slow release carrier (*e.g.*, an ion exchange carrier).

[0099] Biodegradable and non-biodegradable slow release carriers are well known in the art. Biodegradable carriers are used to form particles or matrices which retain active agent(s) and which slowly degrade/dissolve in a suitable environment (*e.g.*, aqueous, acidic, basic and the like) to release the agent. Such particles degrade/dissolve in body fluids to release the active compound therein. The particles are preferably nanoparticles or nanoemulsions (*e.g.*, in the range of about 1 to 500 nm in diameter, preferably about 50-200 nm in diameter, and most preferably about 100 nm in diameter). In a process for preparing a slow release composition, a slow release carrier and a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, are first dissolved or dispersed in an organic solvent. The resulting mixture is added into an aqueous solution containing an optional surface-active agent(s) to produce an emulsion. The organic solvent is then evaporated from the emulsion to provide a colloidal suspension of particles containing the slow release carrier and the compound of the invention.

[00100] The compound disclosed herein can be incorporated for administration orally or by injection in a liquid form such as aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil and the like, or in elixirs or similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose,

methylcellulose, polyvinyl-pyrrolidone, and gelatin. The liquid forms in suitably flavored suspending or dispersing agents can also include synthetic and natural gums. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations, which generally contain suitable preservatives, are employed when intravenous administration is desired.

[00101] The compounds can be administered parenterally via injection. A parenteral formulation can consist of the active ingredient dissolved in or mixed with an appropriate inert liquid carrier. Acceptable liquid carriers usually comprise aqueous solvents and other optional ingredients for aiding solubility or preservation. Such aqueous solvents include sterile water, Ringer's solution, or an isotonic aqueous saline solution. Other optional ingredients include vegetable oils (such as peanut oil, cottonseed oil, and sesame oil), and organic solvents (such as solketal, glycerol, and formyl). A sterile, non-volatile oil can be employed as a solvent or suspending agent. The parenteral formulation is prepared by dissolving or suspending the active ingredient in the liquid carrier whereby the final dosage unit contains from 0.005 to 10% by weight of the active ingredient. Other additives include preservatives, isotonizers, solubilizers, stabilizers, and pain-soothing agents. Injectable suspensions can also be prepared, in which case appropriate liquid carriers, suspending agents and the like can be employed.

[00102] The compounds of Formulas I-III, and pharmaceutically acceptable salts thereof, can also be administered topically or enhanced by using a suitable topical transdermal vehicle or a transdermal patch.

[00103] The compounds described herein can be administered as a monotherapy or as part of a combination therapy. For example, the benzamide compounds described herein can be administered in combination with L-DOPA, or a formulation thereof; a therapeutic agent that blocks degradation of endogenous DA; L-DOPA and a therapeutic agent that blocks endogenous DA (*e.g.*, a pharmaceutical composition comprising L-DOPA and an agent that block endogenous DA); a therapeutic agent that blocks glutamate receptors (*e.g.*, a glutamate receptor antagonist, such as an mGluR5 antagonist); an NMDA receptor antagonist; or with another therapeutic agent for treating PD (*e.g.*, an antioxidant, an inhibitor of calpain, c-Abl or cdk5). Thus, in some embodiments, an effective amount of a compound of Formula I, II or III is administered in combination with an effective amount of a second therapeutic agent for treating PD. Preferably, the second therapeutic agent is or contains L-DOPA.

[00104] When a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is administered in combination with L-DOPA, for example, to treat L-DOPA-induced dyskinesia, the effective amount of the compound of Formula I, II or III, or the pharmaceutically acceptable salt thereof, can be about 0.1 mg/kg to about 25 mg/kg.

[00105] In some embodiments, the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is administered simultaneously with the second therapeutic agent for treating PD, for example, in a single unit dose. In one example, when the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent are in solution, simultaneous administration can be achieved by administering a solution containing the combination of compounds. In another example, simultaneous administration of separate solutions, one of which contains the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and the other of which contains the second therapeutic agent, can be employed. In yet another example, when the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent are in solid form, simultaneous administration can be achieved by administering a composition containing the combination of compound and agent.

[00106] In other embodiments, the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent for treating PD are not administered simultaneously. For example, the compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, can be administered before the second therapeutic agent. Alternatively, the second therapeutic agent can be administered before the compound of Formula I, II or III, or pharmaceutically acceptable salt thereof. The time difference in non-simultaneous administrations can be greater than 1 minute, and can be, for example, precisely, at least, up to, or less than 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 60 minutes, two hours, three hours, six hours, nine hours, 12 hours, 24 hours, 36 hours, or 48 hours. In another embodiment, the first administered compound or agent is provided time to take effect on the mammal before the second administered compound or agent is administered. Generally, the difference in time does not extend beyond the time for the first administered compound or agent to complete its effect in the mammal, or beyond the time the first administered compound or agent is completely or substantially eliminated or deactivated in the mammal.

[00107] Another embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and an effective amount of a second therapeutic agent for treating PD, for example, L-DOPA.

[00108] Another embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Formula I-III, or a pharmaceutically acceptable salt thereof, having an averaged affinity for DA D2 receptors characterized by a K_d of about 10^{-5} to about 10^{-8} M, and an affinity for a pre-synaptic DA D2 receptor, as characterized by K_d, that is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic DA D2 receptor, as characterized by K_d; and an effective amount of a second therapeutic agent for treating PD, for example, L-DOPA.

[00109] In some embodiments of a pharmaceutical composition, the effective amount of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is an effective amount to stimulate dopaminergic transmission in a mammal in need thereof. In some embodiments of a pharmaceutical composition, the effective amount of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is an effective to restore pre-synaptic DA neuronal function in a mammal in need thereof. In some embodiments of a pharmaceutical composition, the effective amount of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is an effective to restore DA neuronal function in a mammal in need thereof. In some embodiments of a pharmaceutical composition, the effective amount of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, is an effective amount to restore DA homeostasis in a mammal in need thereof. Examples of effective amounts of a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, are about 0.1 to about 150 mg/kg, about 0.1 to about 25 mg/kg, about 1 to about 25 mg/kg, about 5 to about 15 mg/kg, about 30 to about 100 mg/kg, and about 70 to about 100 mg/kg.

[00110] A pharmaceutical composition comprising a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent for treating PD can further comprise one or more pharmaceutically acceptable carriers and/or diluents, and can be formulated and/or administered in accordance with the compositions for use in the methods of the invention described herein.

Identification of a Compound for Treatment of Parkinson's Disease Using In Silico Screening

[00111] Based on both biosimulation studies and experimental data, it has been demonstrated that a compound of Formula III is a DA enhancer and has several unique properties: i) it is a highly selective ligand of DA D2 receptors (D2R), and a highly preferential antagonist of pre-synaptic D2R, with an affinity for D2R similar to that of DA, thereby efficiently modulating and equilibrating DA neurotransmission; ii) it elicits biphasic changes in postsynaptic cAMP levels; iii) it enhances DA release from striatal DA nerve terminals; and iv) it has a unique *in vivo* behavioral profile. All of these properties make a compound of Formula III an excellent drug candidate for the treatment of PD. Of importance, the DA-enhancing mechanism of a compound of Formula III is not only clinically validated for treatment of PD motor symptoms (as shown by existing DA therapies), but it also has a high potential for exhibiting superior efficacy and safety to control PD symptoms and to alter disease progression, as compared to any existing therapy.

[00112] Methods of making a compound of Formula III are described in U.S. Patent No. 4,772,630 to Storni *et al.* Methods of assessing the K_d of the compound of Formula III, as well as the preferential affinity of the compound of Formula III for $D2_{pre}$ versus $D2_{post}$, are disclosed in Bischoff, S., *et al.*; *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1994) 350:230-238.

[00113] A compound of Formula III can be used as a monotherapy to treat motor and other behavioral and psychiatric symptoms of PD and to alter the course of disease progression. A compound of Formula III can also be used in combination with L-DOPA and other drugs that block degradation of endogenous DA for increased efficacy and safety, or with other disease-modifying medications.

[00114] FIG. 1 is a schematic representation of the role of a benzamide compound, such as a compound of Formula III, in the treatment of PD, and shows a mechanistic basis for why a preferential blockade of pre-synaptic D2R coupled to DA enhancement, such as that observed with a compound of Formula III, is expected to lead to a unique combination of beneficial effects at the pre-synaptic, post-synaptic and glial levels.

Pre-synaptic modulatory effects of a compound of Formula III

[00115] A compound of Formula III, by increasing DA release, synthesis and transport, is expected to protect nigrostriatal DA neurons and to help restore normal function to

nigrostriatal DA neurons. For example, DA neurons in various forms of PD, including familial forms caused by gene mutations (alpha-synuclein, parkin, DJ1, *etc.*) are highly sensitive to mitochondrial dysfunction and oxidative stress, including DA-induced oxidative stress. If accumulated and/or stored improperly, DA can auto-oxidize to yield highly toxic free radicals, including hydrogen peroxide, superoxide radical, and DA-quinone, a cytotoxic DA by-product. Alternatively, DA can be oxidized by monoamine oxidase to yield hydrogen peroxide and an inert metabolite, 3,4-dihydroxyphenylacetic acid. Mutations in alpha-synuclein lead to impaired DA storage and intraneuronal DA accumulation, which, in turn, leads to increased levels of oxidative stress and, ultimately, death of DA neurons (Kurz *et al.*, PLoS One, 2010; 5:e11464; Thomas and Beal, Hum. Mol. Genet. 2007;16:R183-R94; Obeso *et al.*, Nature Medicine, 2010; 16:653-61; Madeo *et al.*, Neuroscience, 2012; 211:126-35). A compound of Formula III, by enhancing DA release, is expected to relieve DA neurons from intracellular DA-induced mitochondrial dysfunction, oxidative stress and degeneration.

[00116] FIG. 2A is a schematic representation of a pre-synaptic DA terminal in PD and a healthy pre-synaptic DA terminal, and shows a mechanistic basis for why a benzamide compound, such as a compound of Formula III, is expected to enhance DA release by blocking a pre-synaptic D2 receptor and thereby relieve PD DA neurons from intracellular DA-induced mitochondrial dysfunction, oxidative stress and degeneration.

[00117] Pre-synaptic D2R can not only regulate DA release, but also regulate DA uptake and synthesis (for review, *see* De Mei *et al.,* Curr Opin Pharmacol 2009; 9: 53-8). Stimulation of pre-synaptic D2R increases cell-surface expression of DAT, the DA transporter that terminates DA neurotransmission via either direct protein/protein interaction or via the ERK1/2-dependent pathway. Mice deficient in pre- but not post-synaptic D2R exhibit reduced TH phosphorylation. These data indicate that blockade of presynaptic D2R, such as by a compound of Formula III, could produce unique effects (combined increase in DA release, synthesis and transport), which are completely different from those of existing PD therapies. In contrast to a compound of Formula III, DA transport/uptake inhibitors would further deplete DA content in neurons, while D2R agonists (being non-selective for pre- and post-synaptic D2R) would also act on pre-synaptic D2R and, therefore, inhibit TH and DA synthesis. Therefore, Formula III-mediated release, synthesis and transport of endogenous DA via blocking pre-synaptic D2R could represent not only a symptomatic therapy, but also a disease-modifying therapy to alter the progression of PD.

[00118] FIG. 2B is a schematic representation of a pre-synaptic DA terminal in PD and a healthy pre-synaptic DA terminal, and shows a mechanistic basis for why a benzamide compound, such as a compound of Formula III, is expected to enhance DA synthesis and transport by blocking a pre-synaptic D2 receptor.

Post-synaptic modulatory effects of a compound of Formula III: treatment of PD symptoms

[00119] A compound of Formula III, by enhancing DA release, can facilitate natural and balanced DA neurotransmission and can, therefore, be useful for treating PD symptoms, including motor symptoms and dyskinesia. Following release from a pre-synaptic terminal, DA binds to and activates post-synaptic D1R and D2R located on GABA striatal neurons of the direct pathway, projecting from striatum (St) to substantia nigra reticulata (SNr), and of the indirect pathway, projecting from striatum (St) to globus pallidus (GP), as well as D2R located on glutamate corticostriatal nerve terminals. This is essential for a balanced control of the direct and indirect neuronal pathways and, therefore, for the appropriate execution and control of body movements. By preferentially antagonizing pre-synaptic D2 receptors and facilitating DAergic transmission (DA release, transport and synthesis), a compound of Formula III is expected to normalize striato-pallidal and striato-SNr GABA neurotransmission via the indirect and direct pathways, respectively, in PD.

[00120] FIG. 3 is a schematic representation of basal ganglia-thalamo-cortical neuronal circuitry controlling the indirect gamma-aminobutyric acid (GABA) pathway, and shows a mechanistic basis for: (a) the efficient antagonistic effect of D2 receptor (D2R) activation, counteracting glutamate/NMDA receptor effects on GABA striatopallidal neurotransmission when the nigrostriatal DA neuron is intact (as in a healthy subject); and (b) deficient antagonistic effect of D2 receptor (D2R) activation, less able to counteract glutamate/NMDA receptor effects on GABA striatopallidal neurotransmission when the nigrostriatal DA neuron is deficient (as in a PD subject). A benzamide compound, such as a compound of Formula III, by restoring DA function (DA synthesis, transport and release), normalizes the function of basal ganglia-thalamo-cortical neuronal circuitry, and consequently controls PD symptoms. In FIG. 3, mCx = motor cortex; St = striatum ; GP = globus pallidus; Th = thalamus; STN = subthalamic nucleus; SNc = substantia nigra compacta; and SNr = substantia nigra reticulata. For simplicity, the direct GABAergic pathway (direct neuronal projection from St to SNr) is not illustrated in FIG. 3.

[00121] A compound of Formula III can induce DA release and thereby stimulate post-synaptic D2 receptors on MSN, thus controlling PD motor symptoms; this mechanism is clinically validated with L-DOPA and D2R agonists approved as therapies to control PD motor symptoms.

[00122] Formula III-induced sustained DA release will stimulate continuously postsynaptic D2R and D1R on MSNs, which may be of importance for balanced execution and control of motor movements without inducing dyskinesia. Indeed, continuous synthesis and release of endogenous DA by a compound of Formula III allows a continuous presence of DA in the synapse cleft and is, therefore, not expected to be associated with up-regulation of postsynaptic D1R or D2R on MSNs of the direct and indirect pathways. In contrast, postsynaptic D1R up-regulation is associated with L-DOPA-induced dyskinesia (Aubert *et al.*, Ann Neurol. 2005; 57:17-22), likely because of a non-sustained DA production from L-DOPA.

[00123] Formula III-induced DA release is also expected to activate D2R located on glutamatergic corticostriatal terminals, thereby decreasing cortex-generated excitatory inputs to MSNs (Bamford *et al.*, Neuron 2004; 42:653-63). Thus, a compound of Formula III is expected to be superior to existing DA therapies because it incorporates effects of glutamate antagonists, which could be beneficial for controlling both PD motor symptoms and dyskinesia.

Post-synaptic modulatory effects of a compound of Formula III: protection of striatal MSNs

[00124] The pathogenic mechanism underlying the consequences of profound DA depletion (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model) on postsynaptic neurons (MSNs), such as that observed in PD, involves the calcium-dependent protease calpain, increased c-Abl-dependent cdk5 kinase activity (pY15-cdk5), and increased phosphorylation of DARPP-32 (pThr75-DARP-32) in striatum. This signaling cascade (impaired in MPTP model) is further impaired in the striatum during L-DOPA-induced dyskinesia (Yamamura *et al.*, Front. Cell Neurosci 2013; 7; Chagniel *et al.*, Neurobiol Dis. 2012; 45: 645-55), but is normalized by c-Abl and cdk5 inhibition, calpain inhibition and D2R stimulation, and has been shown to be pathogenic in human PD: c-Abl is up-regulated in the striatum of PD patients, and c-Abl-dependent phosphorylation of parkin is a major post-translational modification, which leads to loss of parkin function and disease progression (parkin gene mutations are the most common cause of autosomal-recessive PD) (Ko *et al.*,

PNAS, 2010; 107: 16691-6; Imam *et al.*, J. Neurosci. 2011; 31: 157-63). Therefore, Formula III-mediated control of this pathogenic pathway via modulation of an upstream target (D2R) could represent: i) a symptomatic therapy for the control of motor symptoms (alone as a monotherapy, or in combination with L-DOPA, for the prevention of L-DOPA-induced dyskinesia), and ii) a disease-modifying therapy, as a monotherapy or in combination with inhibitors of downstream targets (calpain, c-Abl or cdk5).

[00125] FIG. 4 is a schematic representation of a terminal, and shows a mechanistic basis for why a benzamide compound, such as a compound of Formula III, via pre-synaptic D2R blockade is expected to enhance synaptic DA release and stimulate post-synaptic D2R. This cascade is expected to lead to reduced Cdk-5 phophorylation, reduced p-Th75-DARPP-32 and reduced PKA activation, and result in enhanced gene transcription, mitochondriogenesis and neuroprotection.

Modulatory effects of a compound of Formula III at the glial level

[00126] Shao *et al.*, Nature 2013; 494: 90-4 have demonstrated that astrocytic D2 receptors modulate innate immunity through αB-crystallin, which is known to suppress neuroinflammation. Mice lacking D2R exhibited neuro-inflammatory responses and increased vulnerability of nigral DA neurons to MPTP-induced toxicity. A compound of Formula III, by enhancing DA release and thereby stimulating D2 receptors on astrocytes, is expected to reduce glial inflammation.

Identification of Additional Compounds for Treatment of Parkinson's Disease

[00127] Substituted benzamides of Formulas I and II can meet the pharmacological characteristics identified with respect to a compound of Formula III as being useful for treating PD.

[00128] Compounds of Formula I possess a high electron density at the oxygen of the amide functionality, which can enable them to discriminate between pre-and post-synaptic D2 receptors. The presence of electron-withdrawing groups meta to the amide funtionality and/or electron-donating groups ortho and para to the amide functionality can enhance this effect. Compounds of Formula II are, in some cases, preferred to minimize steric interactions that can cause the benzamide to distort into a non-planar configuration.

[00129] The relevant teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

[00130] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details can be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

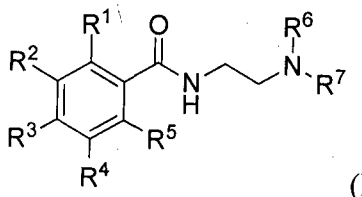
What is claimed is:

1. A method for treating Parkinson's disease in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a compound having an affinity for a pre-synaptic dopamine D2 receptor, an affinity for a post-synaptic dopamine D2 receptor, and an averaged affinity for dopamine D2 receptors, wherein:

the averaged affinity for dopamine D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8} M;

the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d; and

the compound is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy, $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$aliphatic-OC(O)-, $(C_1\text{-}C_8)$aliphatic-C(O)O-, $(C_1\text{-}C_8)$aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or $(C_1\text{-}C_8)$aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

R^2 and R^4 are each independently hydrogen, cyano, nitro, $(C_1\text{-}C_8)$aliphatic-S(O)- or $(C_1\text{-}C_8)$aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, $(C_1\text{-}C_{30})$aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom

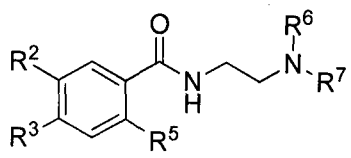
selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl.

2. The method of Claim 1, wherein the averaged affinity of the compound for the dopamine D2 receptor is characterized by a K_d of about 10^{-6} to about 10^{-7} M.

3. The method of Claim 1 or Claim 2, wherein the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 15 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d.

4. The method of any one of Claims 1-3, wherein the compound is represented by the following structural formula:



(II),

or a pharmaceutically acceptable salt thereof.

5. The method of any one of Claims 1-4, wherein R^2 is cyano and R^3 is chloro.

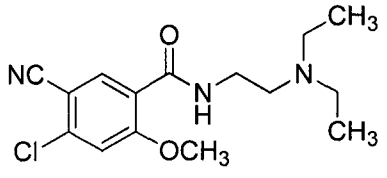
6. The method of any one of Claims 1-5, wherein R^6 and R^7 are each independently optionally substituted $(C_1\text{-}C_8)$aliphatic-.

7. The method of Claim 6, wherein R^6 and R^7 are each independently $(C_1\text{-}C_8)$alkyl.

8. The method of any one of Claims 1-7, wherein R^5 is hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy or $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy.

9. The method of Claim 8, wherein R^5 is $(C_1\text{-}C_8)$alkoxy or $(C_1\text{-}C_8)$alkenyloxy.

10. The method of any one of Claims 1-3, wherein the compound is represented by the following structural formula:



(III),

or a pharmaceutically acceptable salt thereof.

11. The method of Claim 10, wherein the compound is the hydrochloride salt of the compound of Structural Formula (III).

12. The method of any one of Claims 1-11, wherein the effective amount is an effective amount to stimulate dopaminergic transmission.

13. The method of any one of Claims 1-11, wherein the effective amount is about 0.1 mg/kg to about 25 mg/kg.

14. The method of any one of Claims 1-11, wherein the effective amount is an effective amount to restore dopamine homeostasis.

15. The method of any one of Claims 1-14, wherein the mammal is a human.

16. The method of any one of Claims 1-15, wherein the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d, at low concentrations of the compound.

17. The method of any one of Claims 1-16, wherein the compound is administered in combination with a second therapeutic agent for treating Parkinson's disease.

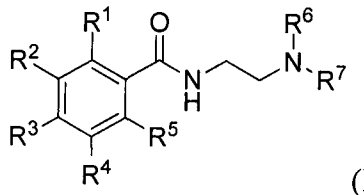
18. The method of Claim 17, wherein the second therapeutic agent is or contains levodopa.

19. A compound for use in treating Parkinson's disease in a mammal in need thereof, the compound having an affinity for a pre-synaptic dopamine D2 receptor, an affinity for a post-synaptic dopamine D2 receptor, and an averaged affinity for dopamine D2 receptors, wherein:

the averaged affinity for dopamine D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8};

the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d; and

the compound is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy, $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$aliphatic-OC(O)-, $(C_1\text{-}C_8)$aliphatic-C(O)O-, $(C_1\text{-}C_8)$aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or $(C_1\text{-}C_8)$aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

R^2 and R^4 are each independently hydrogen, cyano, nitro, $(C_1\text{-}C_8)$aliphatic-S(O)- or $(C_1\text{-}C_8)$aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, $(C_1\text{-}C_{30})$aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom

selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

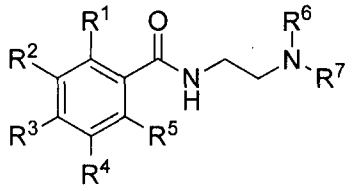
R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl.

20. Use of a compound in the manufacture of a medicament for the treatment of Parkinson's disease, the compound having an affinity for a pre-synaptic dopamine D2 receptor, an affinity for a post-synaptic dopamine D2 receptor, and an averaged affinity for dopamine D2 receptors, wherein:

the averaged affinity for dopamine D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8};

the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d; and

the compound is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy, $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$aliphatic-OC(O)-, $(C_1\text{-}C_8)$aliphatic-C(O)O-, $(C_1\text{-}C_8)$aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or $(C_1\text{-}C_8)$aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

R^2 and R^4 are each independently hydrogen, cyano, nitro, $(C_1\text{-}C_8)$aliphatic-S(O)- or $(C_1\text{-}C_8)$aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, $(C_1\text{-}C_{30})$aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl.

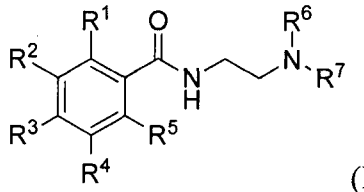
21. A method for treating Parkinson's disease in a human in need thereof, the method comprising administering to the human an effective amount of a compound having an affinity for a pre-synaptic dopamine D2 receptor, an affinity for a post-synaptic dopamine D2 receptor, and an averaged affinity for dopamine D2 receptors, wherein:

the effective amount is about 0.1 mg/kg to about 150 mg/kg;

the averaged affinity for dopamine D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8} M;

the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d; and

the compound is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, $(C_1\text{-}C_8)$aliphatic-O-, $(C_3\text{-}C_8)$carbocyclyloxy, $(C_3\text{-}C_8)$carbocyclyl$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$aliphatic-OC(O)-, $(C_1\text{-}C_8)$aliphatic-C(O)O-, $(C_1\text{-}C_8)$aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or (C_1-C_8)aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

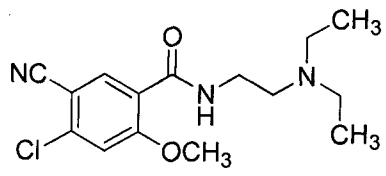
R^2 and R^4 are each independently hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, (C_1-C_{30})aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl.

22. The method of Claim 21, wherein the effective amount is about 0.1 mg/kg to about 25 mg/kg.

23. A method for treating Parkinson's disease in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a compound represented by the following structural formula:



(III),

or a pharmaceutically acceptable salt thereof.

24. The method of Claim 23, wherein the compound is the hydrochloride salt of the compound of Structural Formula (III).

25. The method of Claim 23 or Claim 24, wherein the effective amount is an effective amount to stimulate dopaminergic transmission.

26. The method of Claim 23 or Claim 24, wherein the effective amount is about 0.1 mg/kg to about 25 mg/kg.

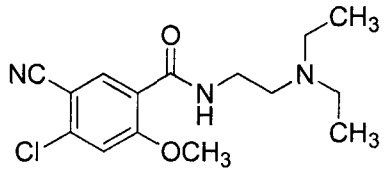
27. The method of Claim 23 or Claim 24, wherein the effective amount is an effective amount to restore dopamine homeostasis.

28. The method of any one of Claims 23-27, wherein the mammal is a human.

29. The method of any one of Claims 23-28, wherein the compound is administered in combination with a second agent for treating Parkinson's disease.

30. The method of Claim 29, wherein the second agent is or contains levodopa.

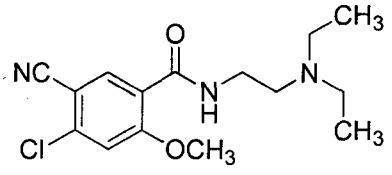
31. A compound represented by the following structural formula:



(III),

or a pharmaceutically acceptable salt thereof, for use in treating Parkinson's disease in a mammal in need thereof.

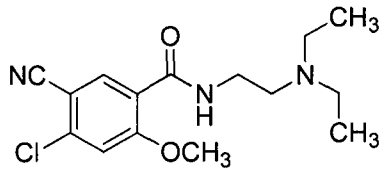
32. Use of a compound in the manufacture of a medicament for the treatment of Parkinson's disease, the compound represented by the following structural formula:



(III),

or a pharmaceutically acceptable salt thereof.

33. A method for treating Parkinson's disease in a human in need thereof, the method comprising administering to the human an effective amount of a compound represented by the following structural formula:



(III),

or a pharmaceutically acceptable salt thereof, wherein the effective amount is about 0.1 mg/kg to about 150 mg/kg.

34. The method of Claim 33, wherein the effective amount is about 0.1 mg/kg to about 25 mg/kg.

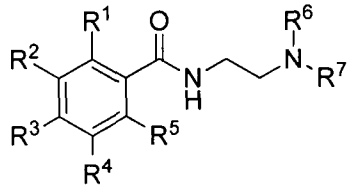
35. A pharmaceutical composition comprising:

(i) an effective amount of a compound having an affinity for a pre-synaptic dopamine D2 receptor, an affinity for a post-synaptic dopamine D2 receptor, and an averaged affinity for dopamine D2 receptors, wherein:

the averaged affinity for dopamine D2 receptors is characterized by a K_d of about 10^{-5} to about 10^{-8} M;

the affinity of the compound for a pre-synaptic dopamine D2 receptor, as characterized by K_d, is about 5 to about 100 times greater than the affinity of the compound for a post-synaptic dopamine D2 receptor, as characterized by K_d; and

the compound is represented by the following structural formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3 and R^5 are each independently hydrogen, halogen, hydroxy, (C_1-C_8)aliphatic-O-, (C_3-C_8)carbocyclyloxy, (C_3-C_8)carbocyclyl(C_1-C_4)alkoxy, (C_1-C_8)aliphatic-OC(O)-, (C_1-C_8)aliphatic-C(O)O-, (C_1-C_8)aliphatic- or $N(R^8)_2$, wherein

each R^8 is independently hydrogen or (C_1-C_8)aliphatic-; or

two R^8, together with the N to which they are bound, form a 4-8-membered heterocyclyl; and

each aliphatic, carbocyclyl, or alkyl group is optionally and independently substituted;

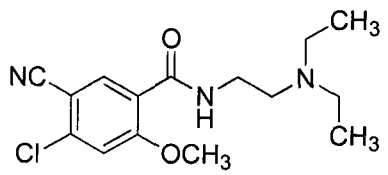
R^2 and R^4 are each independently hydrogen, cyano, nitro, (C_1-C_8)aliphatic-S(O)- or (C_1-C_8)aliphatic-S(O)O-;

R^6 and R^7 are each independently hydrogen, (C_1-C_{30})aliphatic-, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl, or alkylaryl, wherein at least one C in each aliphatic or alkyl group is optionally and independently replaced by a heteroatom selected from oxygen, sulfur and nitrogen, and wherein each aliphatic, carbocyclyl, heterocyclyl, aryl, heteroaryl, aralkyl and alkylaryl is optionally and independently substituted; or

R^6 and R^7, together with the N to which they are bound, form a 4-8-membered, optionally substituted heterocyclyl or a 5-12-membered, optionally substituted heteroaryl; and

ii) an effective amount of a second therapeutic agent for treating Parkinson's disease.

36. The pharmaceutical composition of Claim 35, wherein the compound is represented by structural formula III:



(III),

or a pharmaceutically acceptable salt thereof.

37. The pharmaceutical composition of Claim 35 or 36, wherein the second therapeutic agent is or contains levodopa.

38. The pharmaceutical composition of any of Claims 35-37, wherein the effective amount of the compound represented by Structural Formula I, or the pharmaceutically acceptable salt thereof, is about 0.1 mg/kg to about 25 mg/kg.

39. The pharmaceutical composition of any of Claims 35-37, wherein the effective amount of the compound represented by Structural Formula I, or the pharmaceutically acceptable salt thereof, is an effective amount to stimulate dopaminergic transmission.

40. The pharmaceutical composition of any of Claims 35-37, wherein the effective amount of the compound represented by Structural Formula I, or the pharmaceutically acceptable salt thereof, is an effective amount to restore dopamine homeostasis.

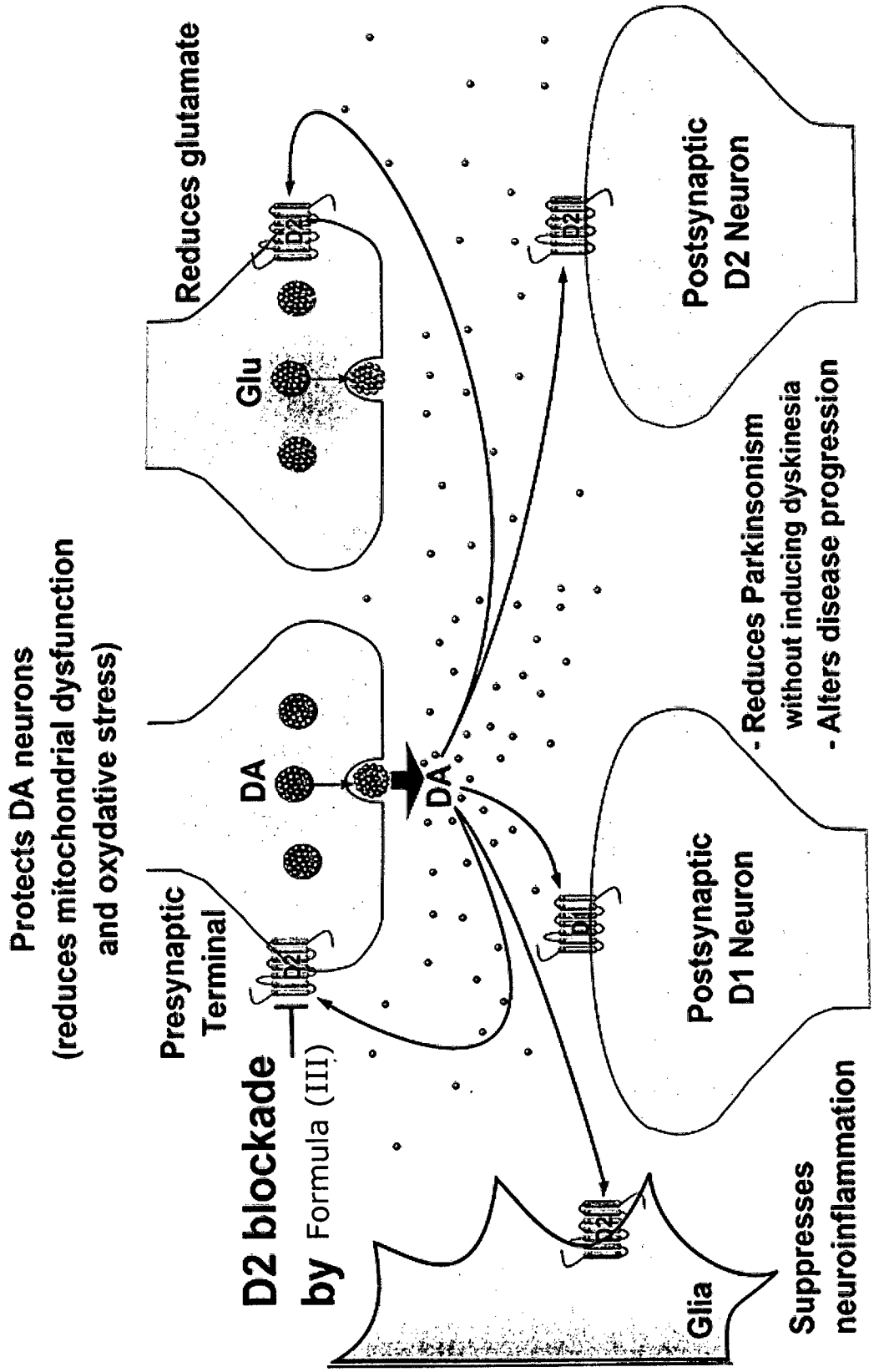

Protects DA neurons
(reduces mitochondrial dysfunction
and oxydative stress)
Reduces glutamate
Glu
Postsynaptic
D2 Neuron
Presynaptic
Terminal
DA
DA
D2 blockade
by Formula (III)
Postsynaptic
D1 Neuron
- Reduces Parkinsonism
without inducing dyskinesia
- Alters disease progression
Glia
Suppresses
neuroinflammation

FIG. 1

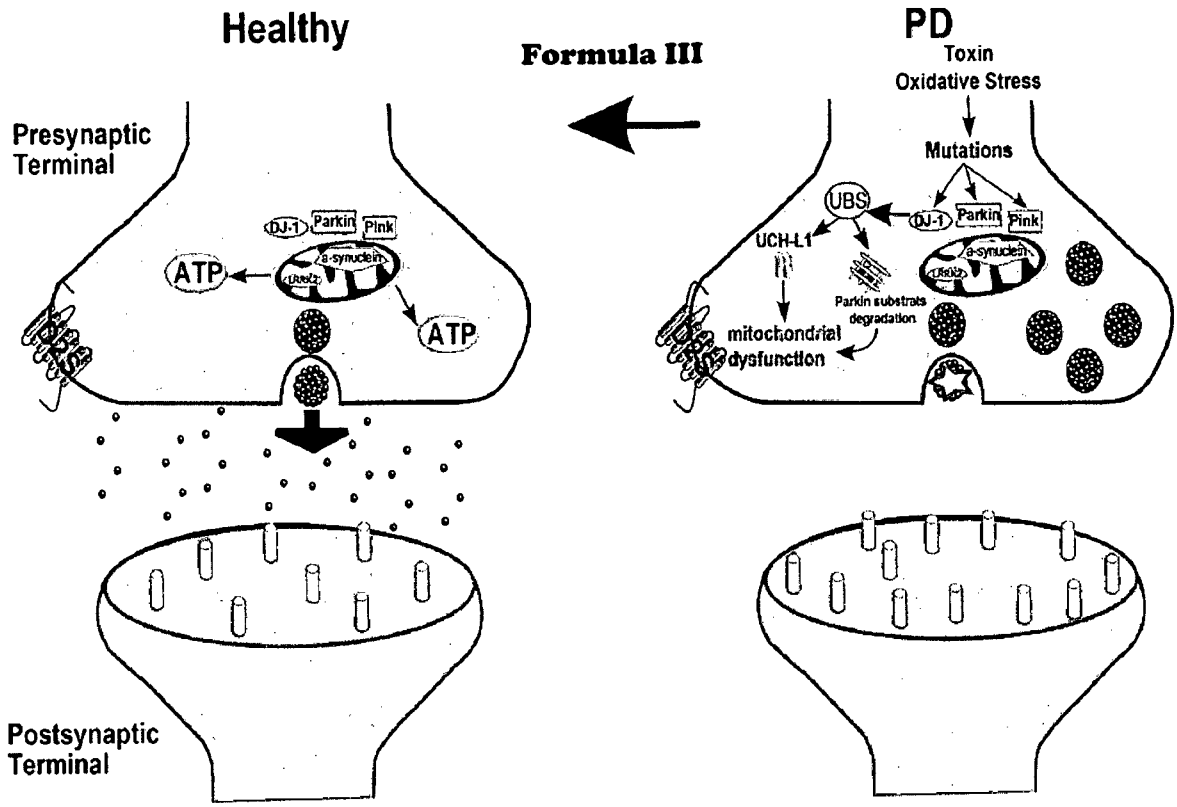

Healthy
Formula III
PD
Toxin
Oxidative Stress
Presynaptic Terminal
Mutations
UBS
DJ-1
Parkin
Pink
UCH-L1
α-synuclein
ATP
ATP
Parkin substrate degradation
mitochondrial dysfunction
Postsynaptic Terminal

FIG. 2A

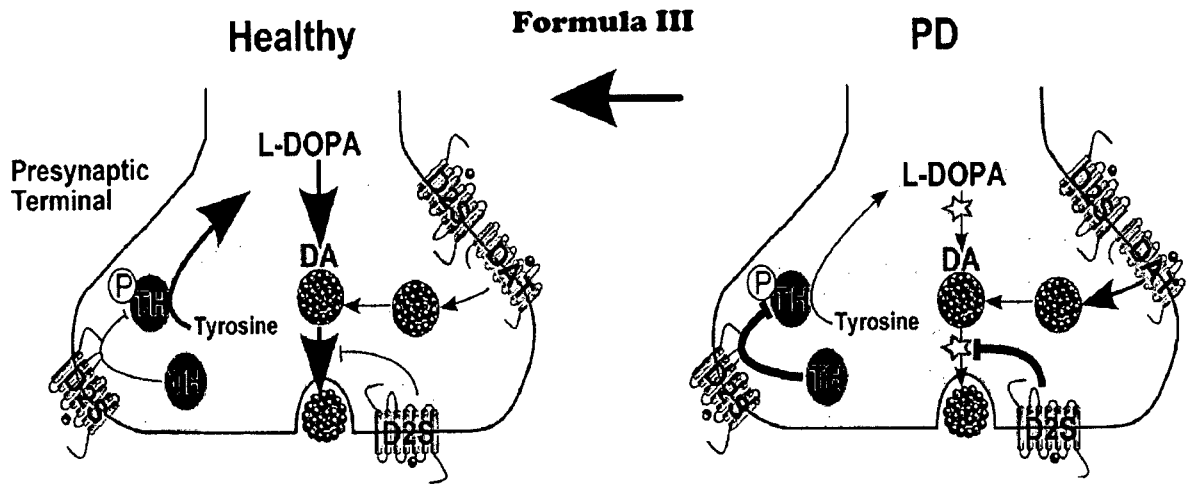

Healthy
Formula III
PD
L-DOPA
L-DOPA
Presynaptic Terminal
DA
DA
P
TH
Tyrosine
Tyrosine
D2S
D2S

FIG. 2B

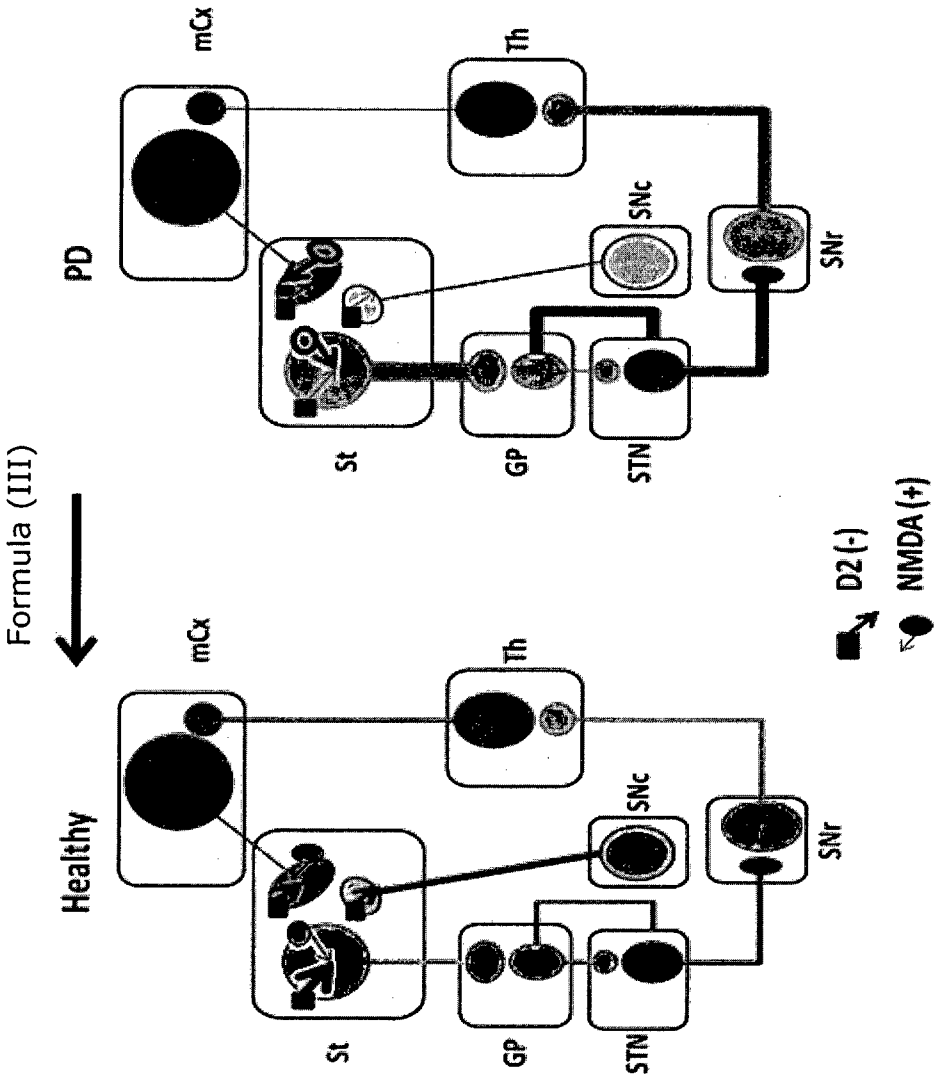

PD
mCx
Th
SNc
SNr
St
GP
STN
Formula (III)
Healthy
mCx
Th
SNc
SNr
St
GP
STN
D2(-)
NMDA(+)

FIG. 3

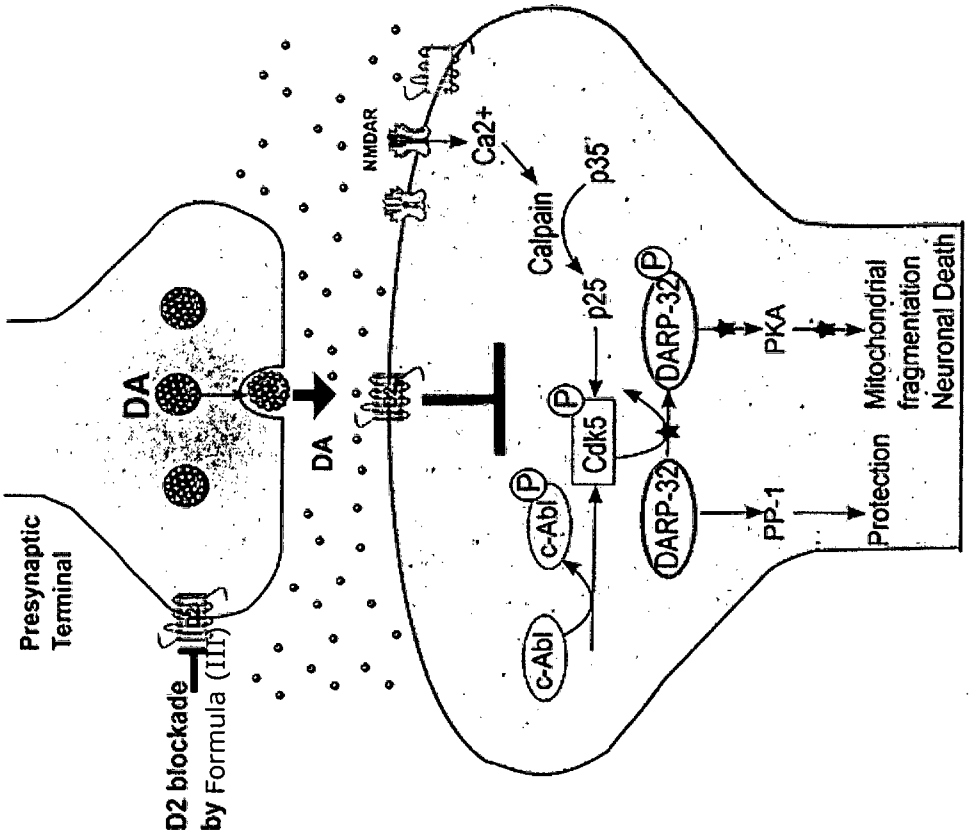

Presynaptic Terminal
DA
D2 blockade by Formula (III)
DA
NMDAR
Ca2+
Calpain
p35
p25
Cdk5
P
c-Abl
P
c-Abl
DARP-32
P
DARP-32
PKA
PP-1
Mitochondrial fragmentation
Neuronal Death
Protection

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000433

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/166 A61K31/198 A61P25/16 A61K31/277
ADD.

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)
A61K

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)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	the whole document	1-40

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X Further documents are listed in the continuation of Box C.

X See patent family annex.

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"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

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"&" 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 June 2014	24/06/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Madalinska, K

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000433

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 96/31462 A1 (CENTAUR PHARMACEUTICALS INC [US]; FLITTER WILLIAM DAVID [GB]; GARLAND) 10 October 1996 (1996-10-10) abstract; claims 90-92	1-40

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International application No
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