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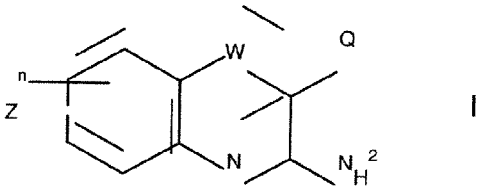
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(54) Title: AMINO-QUINOXALINE AND AMINO-QUINOLINE COMPOUNDS FOR USE AS ADENOSINE A_{2A} RECEPTOR ANTAGONISTS



I

(57) Abstract: Compounds of the Formula (I), where W represents CH or N; and Q represents -CN, -C(=NOH)NH_2, -CONHR[1] or various herein described heterocyclic radicals; as well as pharmaceutically acceptable salts, solvates, esters and prodrugs thereof are adenosine A_{2a} receptor antagonists and, therefore, are useful in the treatment of central nervous system diseases, in particular Parkinson's disease.

WO 2009/111442 A1

AMINO-QUINOXALINE AND AMINO-QUINOLINE COMPOUNDS FOR USE AS ADENOSINE A_{2a} RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to amino-quinoxaline and amino-quinoline adenosine A_{2a} receptor antagonist compounds, methods of using said compounds in the treatment of central nervous system diseases, in particular Parkinson's disease, and to pharmaceutical compositions comprising said compounds.

2. Description of Related Art

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On the central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets.

Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins. Biochemical and pharmacological studies, together with advances in molecular biology, have allowed the identification of at least four subtypes of

adenosine receptors: A_1, A_{2a}, A_{2b} and A_3. A_1 and A_3 are high-affinity, inhibiting the activity of the enzyme adenylate cyclase, and A_{2a} and A_{2b} are low-affinity, stimulating the activity of the same enzyme. Analogs of adenosine able to interact as antagonists with the A_1, A_{2a}, A_{2b} and A_3 receptors have also been identified.

Selective antagonists for the A_{2a} receptor are of pharmacological interest because of their reduced level of side effects. In the central nervous system, A_{2a} antagonists can have antidepressant properties and stimulate cognitive functions. Moreover, data has shown that A_{2a} receptors are present in high density in the basal ganglia, known to be important in the control of movement. Hence, A_{2a} antagonists can improve motor impairment due to neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin.

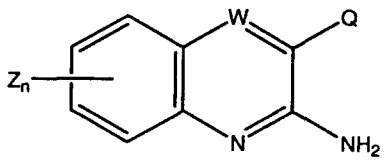
Some xanthine-related compounds have been found to be A_1 receptor selective antagonists, and xanthine and non-xanthine compounds have been found to have high A_{2a} affinity with varying degrees of A_{2a} vs. A_1 selectivity. Triazolo-pyrimidine adenosine A_{2a} receptor antagonists have been disclosed previously, for example in WO 95/01356; US 5,565,460; WO 97/05138; WO 98/52568, WO 01/92264, PCT/US02/32630, filed October 11, 2002, and US 6,897,217.

Adenosine A_{2a} receptor antagonists have been disclosed as being useful in the treatment or prevention of Extra Pyramidal Syndrome, dystonia, restless leg syndrome (RLS) or periodic limb movement in sleep (PLMS) in PCT/US03/40456, filed December 17, 2003, and have been disclosed as being

useful in the treatment of attention deficit hyperactivity disorder (ADHD) in WO 02/055083.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the structural Formula I:



I

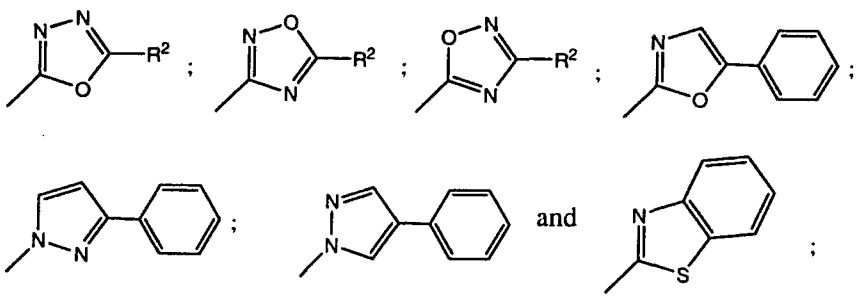
wherein:

W represents CH or N;

Z represents hydrogen, halogen or haloalkyl;

n represents an integer from 0-4;

Q represents -CN, $-C(=NOH)NH_2$ or $-CONHR^1$; or represents a heterocyclic radical selected from the group consisting of:



R^1 represents hydrogen, aralkyl, aryloxyalkyl, benzocycloalkyl or heteroarylalkyl; and

R^2 represents amino, aryl, heteroaryl, arylamino, arylalkyl or heteroarylalkyl;

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula I in a pharmaceutically acceptable carrier.

Yet another aspect of the invention is a method of treating central nervous system diseases such as depression, cognitive diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia or psychoses of organic origin, and stroke, comprising administering a therapeutically acceptable amount of at least one compound of Formula I to a mammal in need of such treatment.

The invention also relates to a method of treating attention related disorders, such as attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD), comprising administering a therapeutically acceptable amount therefor of at least one compound of Formula I to a mammal in need of such treatment.

The invention also relates to a method of treating or preventing Extra-Pyramidal Syndrome (e.g., dystonia, akathisia, pseudoparkinsonism and tardive dyskinesia), of treating primary (idiopathic) dystonia, and of treating or preventing dystonia in patients who exhibit dystonia as a result of treatment with a tricyclic antidepressant, lithium or an anticonvulsant, or who have used

cocaine, comprising administering a therapeutically acceptable amount therefor of at least one compound of Formula I to a mammal in need of such treatment.

The invention further relates to a method of treating abnormal movement disorders, such as restless leg syndrome (RLS) or periodic limb movement in sleep (PLMS), comprising administering to a patient in need thereof a therapeutically effective amount therefor of at least one compound of Formula I.

In particular, the invention is drawn to the method of treating Parkinson's disease comprising administering a therapeutically acceptable amount therefor of at least one compound of Formula I to a mammal in need of such treatment.

Still another aspect of the invention is a method of treating Parkinson's disease with a combination of a therapeutically acceptable amount therefor of at least one compound of Formula I and one or more agents useful in the treatment of Parkinson's disease, for example dopamine; a dopaminergic agonist; an inhibitor of monoamine oxidase, type B (MAO-B); a DOPA decarboxylase inhibitor (DCI); or a catechol-O-methyltransferase (COMT) inhibitor.

The invention further relates to a pharmaceutical composition comprising a therapeutically acceptable amount of at least one compound of Formula I and one or more agents known to be useful in the treatment of Parkinson's disease in a pharmaceutically acceptable carrier.

The invention also comprises a method of treating RLS or PLMS comprising administering to a patient in need thereof a therapeutically acceptable amount therefor of a combination of at least one compound of Formula I with another agent useful in treating RLS or PLMS, such as

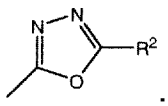
levodopa/carbidopa, levodopa/benserazide, a dopamine agonist, a benzodiazepine, an opioid, an anticonvulsant or iron.

DETAILED DESCRIPTION OF THE INVENTION

In one preferred embodiment, the compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof is one wherein W represents N.

In another preferred embodiment, the compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof is one wherein Q represents $-CONHR^1$.

In another preferred embodiment, the compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof is one wherein Q represents a heterocyclic radical of the formula:



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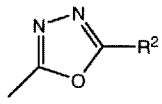
In an especially preferred embodiment, the compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof is one wherein:

W represents N;

Z represents hydrogen, halogen or haloalkyl;

n represents an integer from 0-2;

Q represents $-CONHR^1$ or represents a heterocyclic radical of the formula:



;

R^1 represents aralkyl, benzocycloalkyl or heteroarylalkyl; and

R^2 represents aryl, heteroaryl or arylalkyl.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of

suitable alkynyl groups include ethynyl, 2-propynyl, 2-butynyl and 3-methyl-1-butynyl. “Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. “Heteroaryl” may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl,

1,2,4-thiadiazolyl, , pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of

suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

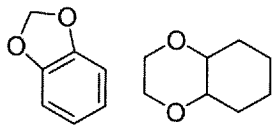
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

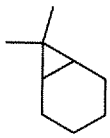
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or

different, each being independently selected from the group consisting of alkyl, haloalkyl, alkylsulfonylalkyl, haloalkoxy, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, alkoxycarbonyl, aryl, cycloalkyl, acyl, alkylsulfonyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:



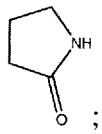
and .



"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

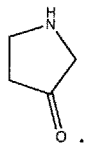
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to

about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" may also include a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Examples of such moiety are 2-pyrrolidone:



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and 3-pyrrolidone:

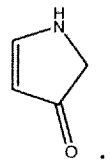


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"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

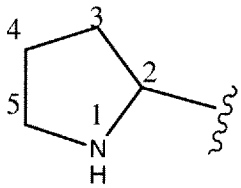
"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, , 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Heterocyclenyl" may also include a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. An example of such moiety is 1,2-dihydro-pyrrol-3-one:



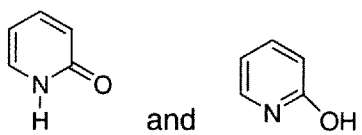
"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower

alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups

include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Arylamino" means an aryl-NH- group in which the aryl group is as previously described. Non-limiting example of a suitable arylamino group is phenylamino. The bond to the parent moiety is through the nitrogen.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and

the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "pharmaceutical composition" means a composition, as defined above, in a form and comprising active ingredients, vehicles, carriers and/or auxiliaries suitable for pharmaceutical use.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V.

Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl

(such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula I contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula I incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —CH(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$CH(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$CH(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical

techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides,

lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts

are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino alcohol). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula I as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers.

For example, if a compound of Formula I incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula I may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact

that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula I (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

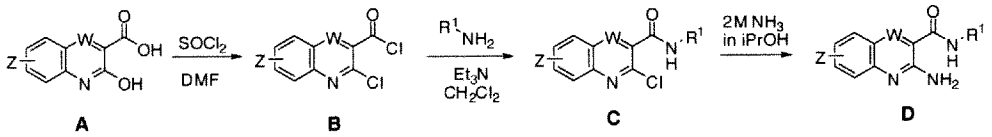
The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the

lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

In general, the compounds of this invention may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the amino-quinoxalines and related heterocyclic derivatives are set forth in the Examples below and generalized in Schemes **1-5**. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art or organic synthesis. All stereoisomers and tautomeric forms of the compounds are contemplated.

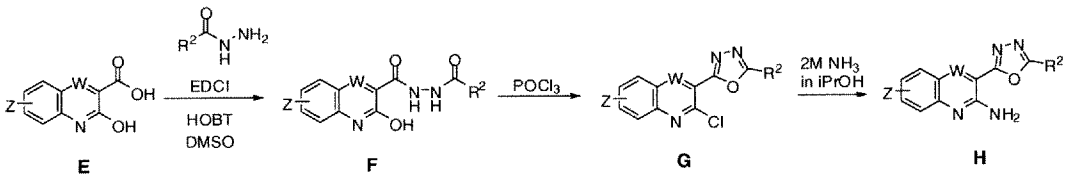
The preparation of compounds of structure **D** is illustrated in Scheme 1. Reaction of a carboxylic acid **A** with thionyl chloride yields quinoxaline **B**. Quinoxaline **B** may then be reacted with various amines to give quinoxaline **C**. Subsequent reaction of quinoxaline **C** with ammonia at elevated temperature then provides compounds **D**.

Scheme 1



Compounds of structure **H** may be prepared as illustrated in Scheme 2. Reaction of a carboxylic acid **E** with various hydrazides in the presence of EDCI and HOBt in DMSO yields quinoxaline **F**. Quinoxaline **F** may then be treated with phosphorus oxychloride to give quinoxaline **G**. Subsequent reaction of quinoxaline **G** with ammonia at elevated temperature then provides compounds **H**.

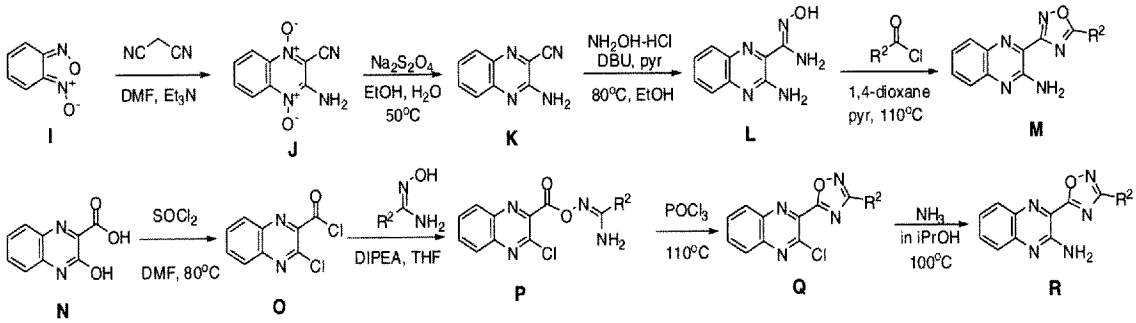
Scheme 2



Compounds of structure **M** may be prepared as illustrated in Scheme 3. Reaction of benzofuroxan **I** with malononitrile provides 2-amino-3-cyanoquinoxaline 1,4-dioxide **J**. Reduction of compound **J** with sodium hydrosulfite yields 2-amino-3-cyanoquinoxaline **K**. Treatment of quinoxaline **K** with hydroxylamine hydrochloride provides amide-oxime **L**. Reaction of compound **L** with various acid chlorides at high temperature yields compounds of type **M**.

Compounds of structure **R** may be prepared as illustrated in Scheme 3. Reaction of quinoxaline carboxylic acid **N** with thionyl chloride at high temperature provides dichloride **O**. Treatment of dichloride **O** with various amide-oximes yields chloride **P**. Cyclization of compound **P** is accomplished using $POCl_3$ at high temperature to provide oxadiazole **Q**. Compounds of type **R** are produced by reaction of oxadiazole **Q** with 2M NH_3 in isopropanol.

Scheme 3

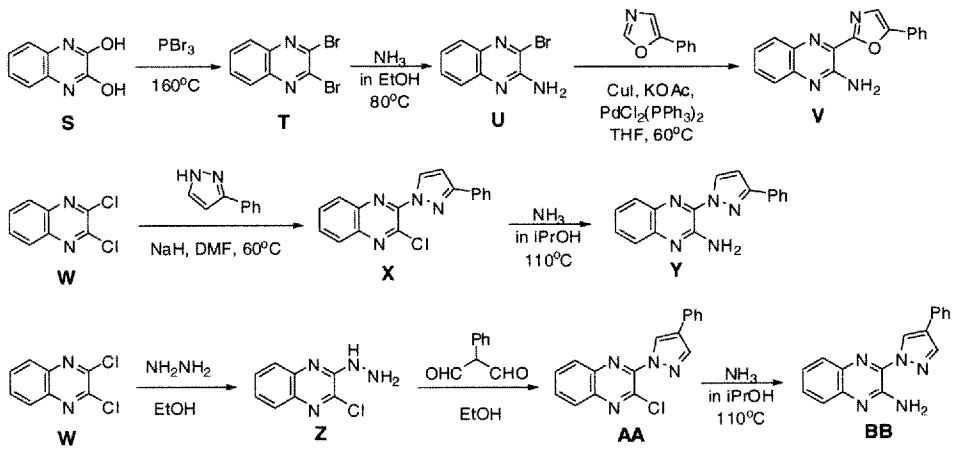


Compounds of structure **V** may be prepared as illustrated in Scheme 4. Reaction of quinoxaline-2,3-diol **S** with phosphorus tribromide at elevated temperature provides 2,3-dibromoquinoxaline **T**. Treatment of quinoxaline **T** with ammonia in ethanol yields 2-amino-3-bromoquinoxaline **U**. Coupling of compound **U** with 5-phenyloxazole provides compounds of type **V**.

Compounds of structure **Y** may be prepared as illustrated in Scheme 4. Treatment of 3-phenyl-1H-pyrazole with sodium hydride and reaction with 2,3-dichloroquinoxaline **W** yields quinoxaline **X**. Chloride displacement of compound **X** with 2M ammonia in isopropanol provides compounds of type **Y**.

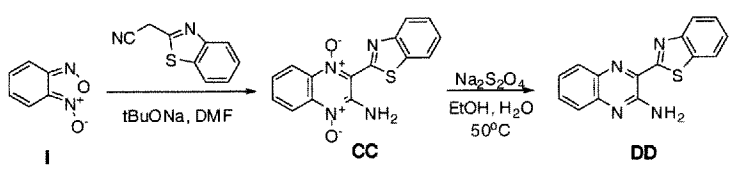
Compounds of structure **BB** may be prepared as illustrated in Scheme 4. Treatment of 2,3-dichloroquinoxaline **W** with hydrazine hydrate provides hydrazine **Z**. Condensation of hydrazine **Z** with 2-phenylmalonaldehyde provides quinoxaline **AA**. Chloride displacement of compound **AA** with 2M ammonia in isopropanol provides compounds of type **BB**.

Scheme 4



Compounds of structure **DD** may be prepared as illustrated in Scheme 5. Treatment of benzofuroxan **I** with 2-(benzo[d]thiazol-2-yl)acetonitrile and sodium *tert*-butoxide in DMF yields 2-amino-3-(benzo[d]thiazol-2-yl)quinoxaline 1,4-dioxide **CC**. Reduction of compound **CC** with sodium hydrosulfite provides compounds of type **DD**.

Scheme 5



The starting materials and reagents depicted in Schemes **1-5** are either available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ), or can be prepared using methods well-known to those of skill in the art of organic synthesis.

One skilled in the art will recognize that the synthesis of compounds of Formula I may require protection of certain functional groups (*i.e.*, derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of the compounds of Formula I and methods for their installation and removal may be found in Greene *et. al., Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

Examples

The following examples constitute illustrative examples of compounds of the present invention and are not to be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

General Methods

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner described below. Microwave reactions were performed using the Biotage Initiator microwave. ^{1}H NMR spectra were obtained on a Gemini AS-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in

Hertz indicated parenthetically. Where LC/MS data are presented, analyses were performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0min – 10% CH_3CN, 5min – 95% CH_3CN, 7min – 95% CH_3CN, 7.5min – 10% CH_3CN, 9min – stop. The observed parent ion is given.

The following solvents and reagents may be referred to by their abbreviations:

Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; Ph = phenyl, and Ac = acetyl

µl = microliters

EtOAc = ethyl acetate

AcOH or HOAc = acetic acid

Atm = atmosphere

BINAP = rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc or BOC = *tert*-butoxycarbonyl

BSA = *N,O*-(bistrimethylsilyl)acetamide

CH_2Cl_2 = dichloromethane

DIPEA = diisoproylethylamine

DMAP = 4-dimethylaminopyridine

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

EDTA = ethylenediaminetetraacetic acid

EtOH = ethanol

g = grams

h = hour

HOBt = 1-hydroxybenzotriazole

LAH = lithium aluminum hydride

LCMS or LC/MS = liquid chromatography mass spectrometry

min = minute

mg = milligrams

mL = milliliters

mmol = millimoles

mCPBA = 3-chloroperoxybenzoic acid

MeOH = methanol

MS = mass spectrometry

NMR = nuclear magnetic resonance spectrometry

RT or rt = room temperature (ambient, about 25°C)

TEA or Et_3N = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TMS = trimethylsilyl

TMSOTf = trimethylsilyl trifluoromethanesulfonate

TBS = *tert*-butyldimethylsilyl

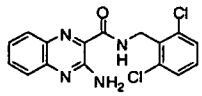
X-Phos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

In general, the compounds of this invention may be prepared from known or readily prepared starting materials, following methods known to one

skilled in the art or organic synthesis. All stereoisomers and tautomeric forms of the compounds are contemplated.

Example 1

Preparation of Compound 1

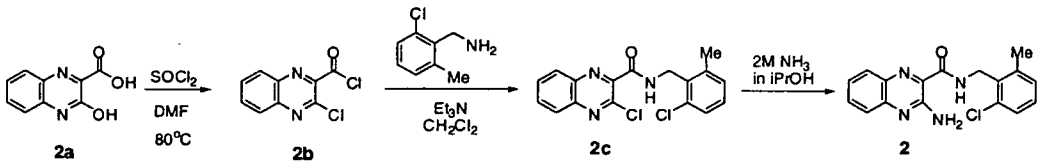


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Using Steps B and C described in Example 2, compound 1 was prepared substituting 2,6-dichlorobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 2

Preparation of Compound 2



2a 2b 2c 2

Step A – Synthesis of Compound 2b

To 3-hydroxy-2-quinoxalinecarboxylic acid (1.0g, 5.3mmol) was added thionyl chloride (10mL) and DMF (5 drops) and the solution was stirred and heated to 80°C for 24h. Allowed to cool and concentrated under vacuum to give compound 2b (1.2g, 99%)

Step B – Synthesis of Compound 2c

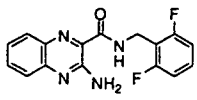
To compound 2b (100mg, 0.44mmol) was added CH_2Cl_2 (6mL), Et_3N (0.09mL, 0.66mmol) and 2-chloro-6-methylbenzylamine (78mg, 0.48mmol) and the solution was stirred for 1h. Transferred to sep. funnel, washed with H_2O, washed with brine, dried ($MgSO_4$), filtered, and concentrated to give compound 2c (152mg, 100%).

Step C – Synthesis of Compound 2

To compound 2c (152mg, 0.44mmol) was added 2M NH_3 in isopropanol (8mL), (or 2M NH_3 in ethanol), the tube sealed and the solution was stirred and heated to 100°C for 20h. Allowed to cool and concentrated under vacuum. Crude material was purified by preparative TLC (5%MeOH/CH_2Cl_2) to yield compound 2 (140mg, 98%).

Example 3

Preparation of Compound 3

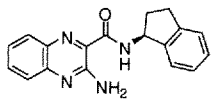


3

Using Steps B and C described in Example 2, compound 3 was prepared substituting 2,6-difluorobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 4

Preparation of Compound 4

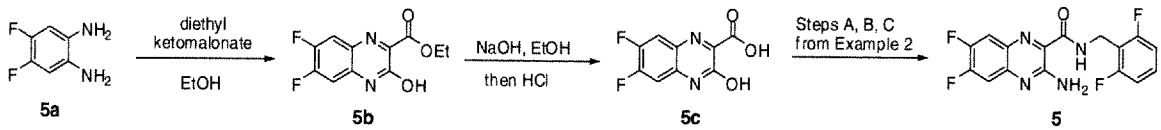


4

Using Steps B and C described in Example 2, compound 4 was prepared substituting (S)-2,3-dihydro-1H-inden-1-amine for 2-chloro-6-methylbenzylamine in Step B.

Example 5

Preparation of Compound 5



5a 5b 5c 5

Step A – Synthesis of Compound 5b

To compound 5a (2.2g, 15.3mmol) was added EtOH (40mL), and diethyl ketomalonate (2.83mL, 18.3mmol) and the solution was stirred and heated to reflux for 16h. Allowed to cool and concentrated under vacuum. Purified by flash column chromatography using silica gel (30%EtOAc/hexanes) to yield compound 5b (3.2g, 82%).

Step B – Synthesis of Compound 5c

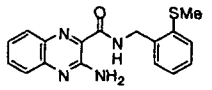
To compound 5b (2.0g, 7.9mmol) was added 1N NaOH (23.6mL, 23.6mmol) and EtOH (20mL) and the solution was heated to reflux for 2h. Allowed to cool, added 1N HCl (25mL) and the solution was stirred for 30min. Filtered solid and dried to yield compound 5c (1.3g, 73%).

Step C – Synthesis of Compound 5

Using Steps A, B, and C from Example 2, substituting compound 5c for compound 2a and substituting 2,6-difluorobenzylamine for 2-chloro-6-methylbenzylamine, compound 5 was prepared.

Example 6

Preparation of Compound 6

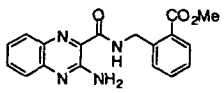


6

Using Steps B and C described in Example 2, compound 6 was prepared substituting 2-methylthiobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 7

Preparation of Compound 7

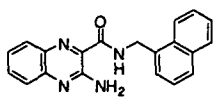


7

Using Steps B and C described in Example 2, compound 7 was prepared substituting methyl 2-(aminomethyl)benzoate for 2-chloro-6-methylbenzylamine in Step B.

Example 8

Preparation of Compound 8

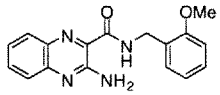


8

Using Steps B and C described in Example 2, compound 8 was prepared substituting 1-naphthalenemethylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 9

Preparation of Compound 9

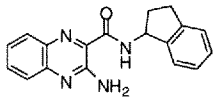


9

Using Steps B and C described in Example 2, compound 9 was prepared substituting 2-methoxybenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 10

Preparation of Compound 10

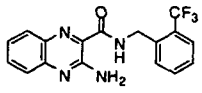


10

Using Steps B and C described in Example 2, compound 10 was prepared substituting 2,3-dihydro-1H-inden-1-amine for 2-chloro-6-methylbenzylamine in Step B.

Example 11

Preparation of Compound 11

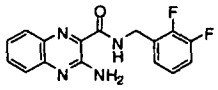


11

Using Steps B and C described in Example 2, compound 11 was prepared substituting 2-trifluoromethylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 12

Preparation of Compound 12

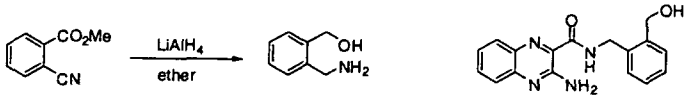


12

Using Steps B and C described in Example 2, compound 12 was prepared substituting 2,3-difluorobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 13

Preparation of Compounds 13b and 13



13a 13b 13

Step A – Synthesis of Compound 13b

To a solution of $LiAlH_4$ (5.6g, 147mmol) in ether (45mL) was added methyl 2-cyanobenzoate (4.8g, 30mmol) in ether (75mL) and the solution was stirred for 5h at reflux. Cooled solution in an ice bath, added water drop wise, white solid was removed by filtration and rinsed with ether. The ether layer was dried ($MgSO_4$), filtered, concentrated, added 4N HCl in dioxane, filtered salt,

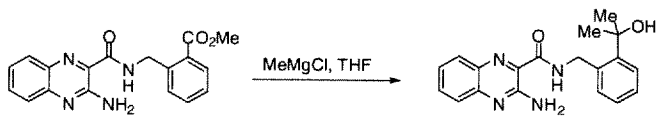
and recrystallized from ethyl acetate to give compound 13b as the HCl salt (2.26g, 43%).

Step B – Synthesis of Compound 13

Using Steps B and C described in Example 2, compound 13 was prepared substituting compound 13b for 2-chloro-6-methylbenzylamine in Step B.

Example 14

Preparation of Compound 14



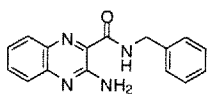
7 14

Step A – Synthesis of Compound 14

To compound 7 (57mg, 0.17mmol) was added THF (6mL), and MeMgCl (3.0M in THF, 0.17mL, 0.51mmol) and the solution was stirred 5h. The reaction was concentrated under vacuum and purified by preparative TLC (5%CH_3OH/CH_2Cl_2) to yield compound 14 (8mg, 14%).

Example 15

Preparation of Compound 15

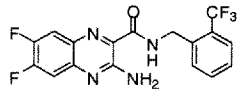


15

Using Steps B and C described in Example 2, compound 15 was prepared substituting benzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 16

Preparation of Compound 16

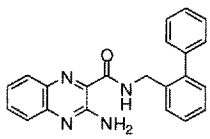


16

Using Step C described in Example 5, substituting 2-trifluoromethylbenzylamine for 2,6-difluorobenzylamine, compound 16 was prepared.

Example 17

Preparation of Compound 17

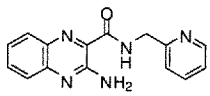


17

Using Steps B and C described in Example 2, compound 17 was prepared substituting 2-phenylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 18

Preparation of Compound 18

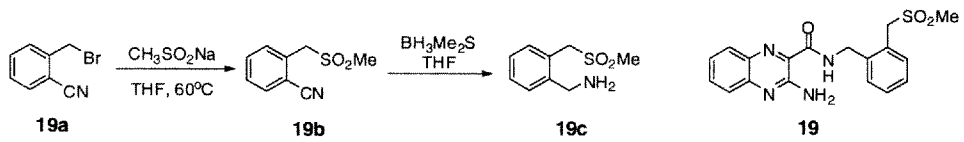


18

Using Steps B and C described in Example 2, compound 18 was prepared substituting 2-aminomethylpyridine for 2-chloro-6-methylbenzylamine in Step B.

Example 19

Preparation of Compounds 19c and 19



19a 19b 19c 19

Step A – Synthesis of Compound 19b

To compound 19a (3.0g, 15.3mmol) was added THF (25mL), and methanesulfinic acid sodium salt (1.77g, 16.8mmol) and the solution was stirred and heated to reflux for 31h. Removed solid precipitate and concentrated filtrate to yield compound 19b (2.73g, 91%).

Step B – Synthesis of Compound 19c

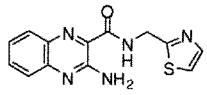
To compound 19b (200mg, 1.02mmol) was added THF (6mL), cooled in an ice bath, and added BH_3•Me_2S complex (2M in THF, 3.1mL, 3.06mmol). The solution was stirred at 0°C for 30min and room temperature for 17h. To the solution was added MeOH, concentrated under vacuum, and purified by flash column chromatography to yield compound 19c (128mg, 62%).

Step C – Synthesis of Compound 19

Using Steps B and C described in Example 2, compound 19 was prepared substituting compound 19c for 2-chloro-6-methylbenzylamine in Step B.

Example 20

Preparation of Compound 20

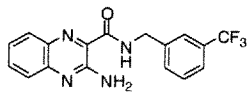


20

Using Steps B and C described in Example 2, compound 20 was prepared substituting 2-aminomethylthiazole for 2-chloro-6-methylbenzylamine in Step B.

Example 21

Preparation of Compound 21

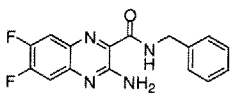


21

Using Steps B and C described in Example 2, compound 21 was prepared substituting 3-trifluoromethylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 22

Preparation of Compound 22

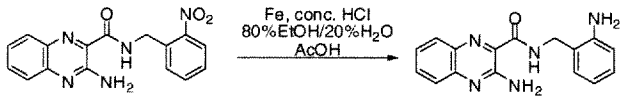


22

Using Step C described in Example 5, substituting benzylamine for 2,6-difluorobenzylamine, compound 22 was prepared.

Example 23

Preparation of Compound 23



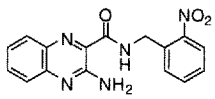
24 23

Step A – Synthesis of Compound 23

To compound 24 (225mg, 0.70mmol) was added EtOH (8mL), H_2O (2mL), AcOH (10mL), Fe powder (292mg, 5.2mmol), and conc. HCl (5 drops) and the solution was stirred for 30 min at 100°C. Allowed to cool, filtered through a plug of celite, and concentrated under vacuum. Purified by preparative TLC (10%MeOH/CH_2Cl_2) to give compound 23 (39mg, 19%).

Example 24

Preparation of Compound 24

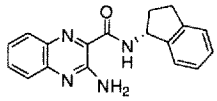


24

Using Steps B and C described in Example 2, compound 24 was prepared substituting 2-nitrobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 25

Preparation of Compound 25

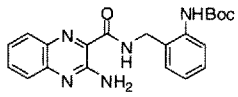


25

Using Steps B and C described in Example 2, compound 25 was prepared substituting (R)-2,3-dihydro-1H-inden-1-amine for 2-chloro-6-methylbenzylamine in Step B.

Example 26

Preparation of Compound 26

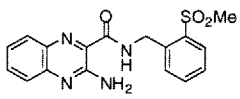


26

Using Steps B and C described in Example 2, compound 26 was prepared substituting tert-butyl 2-(aminomethyl)phenylcarbamate for 2-chloro-6-methylbenzylamine in Step B.

Example 27

Preparation of Compound 27

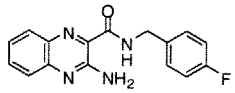


27

Using Steps B and C described in Example 2, compound 27 was prepared substituting 2-(methanesulfonyl)benzylamine hydrochloride for 2-chloro-6-methylbenzylamine in Step B.

Example 28

Preparation of Compound 28

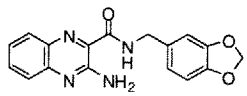


28

Using Steps B and C described in Example 2, compound 28 was prepared substituting 4-fluorobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 29

Preparation of Compound 29

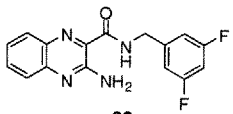


29

Using Steps B and C described in Example 2, compound 29 was prepared substituting 3,4-methylenedioxybenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 30

Preparation of Compound 30

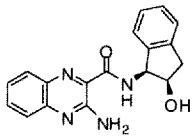


30

Using Steps B and C described in Example 2, compound 30 was prepared substituting 3,5-difluorobenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 31

Preparation of Compound 31

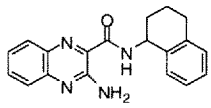


31

Using Steps B and C described in Example 2, compound 31 was prepared substituting (1S,2R)-(-)-cis-1-amino-2-indanol for 2-chloro-6-methylbenzylamine in Step B.

Example 32

Preparation of Compound 32

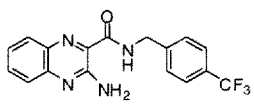


32

Using Steps B and C described in Example 2, compound 32 was prepared substituting 1,2,3,4-tetrahydro-1-naphthylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 33

Preparation of Compound 33

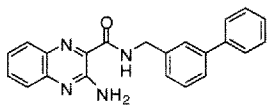


33

Using Steps B and C described in Example 2, compound 33 was prepared substituting 4-trifluoromethylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 34

Preparation of Compound 34

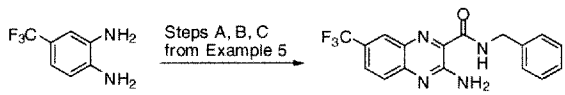


34

Using Steps B and C described in Example 2, compound 34 was prepared substituting 3-phenylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 35

Preparation of Compound 35

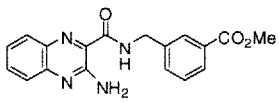


35a 35

Using Steps A, B, and C from Example 5, substituting compound 35a for 5a and substituting benzylamine for 2-chloro-6-methylbenzylamine, compound 35 was prepared.

Example 36

Preparation of Compound 36

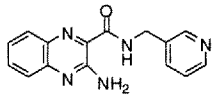


36

Using Steps B and C described in Example 2, compound 36 was prepared substituting methyl 3-(aminomethyl)benzoate for 2-chloro-6-methylbenzylamine in Step B.

Example 37

Preparation of Compound 37

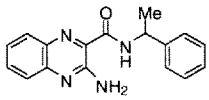


37

Using Steps B and C described in Example 2, compound 37 was prepared substituting 3-aminomethylpyridine for 2-chloro-6-methylbenzylamine in Step B.

Example 38

Preparation of Compound 38

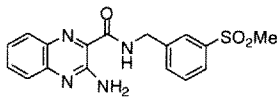


38

Using Steps B and C described in Example 2, compound 38 was prepared substituting DL-α-methylbenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 39

Preparation of Compound 39

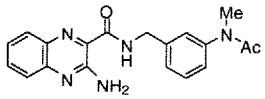


39

Using Steps B and C described in Example 2, compound 39 was prepared substituting 3-(methanesulfonyl)benzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 40

Preparation of Compound 40

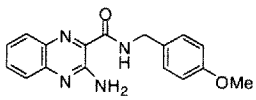


40

Using Steps B and C described in Example 2, compound 40 was prepared substituting *N*-[3-(aminomethyl)phenyl]-*N*-methylacetamide hydrochloride for 2-chloro-6-methylbenzylamine in Step B.

Example 41

Preparation of Compound 41

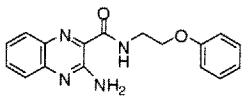


41

Using Steps B and C described in Example 2, compound 41 was prepared substituting 4-methoxybenzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 42

Preparation of Compound 42

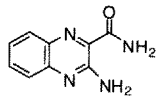


42

Using Steps B and C described in Example 2, compound 42 was prepared substituting 2-phenoxyethanamine for 2-chloro-6-methylbenzylamine in Step B.

Example 43

Preparation of Compound 43

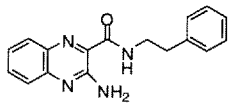


43

Using Step C described in Example 2, compound 43 was prepared substituting compound 2b for compound 2c.

Example 44

Preparation of Compound 44



44

Using Steps B and C described in Example 2, compound 44 was prepared substituting 2-phenethylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 45

Preparation of Compound 45



45a 45b 45

Step A – Synthesis of Compound 45b

To benzofuroxan (20g, 147mmol) was added DMF (100mL), Et_3N (3.0mL, 21.5mmol), and malononitrile (10g, 156mmol) and the solution was

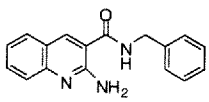
stirred at 0°C for 3h. The solution was filtered, rinsed with ether, and dried to yield compound 45b (23g, 77%).

Step B – Synthesis of Compound 45

To compound 45b (2.0g, 9.9mmol) was added MeOH (20mL) and the solution was heated to 50°C. A solution of $Na_2S_2O_4$ (4.8g, 28mmol) in H_2O (20mL) was added and the solution was stirred for 6h. To the solution was added a solution of $Na_2S_2O_4$ (4.8g, 28mmol) in H_2O (20mL) and the solution was stirred for 12h. Allowed to cool to room temperature, filtered yellow solid and dried to yield compound 45 (1.3g, 78%).

Example 46

Preparation of Compound 46

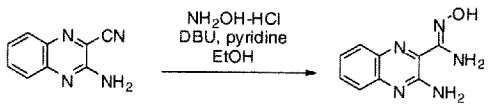


46

Using Steps A, B, and C described in Example 2, compound 46 was prepared substituting 2-chloro-3-quinolinecarboxylic acid for compound 2a in Step A and substituting benzylamine for 2-chloro-6-methylbenzylamine in Step B.

Example 47

Preparation of Compound 47



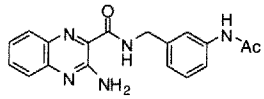
45 47

Step A – Synthesis of Compound 47

To compound 45 (1.0g, 5.9mmol) were added EtOH (30mL), pyridine (5mL, 62mmol), DBU (0.1mL, 0.7mmol), and hydroxylamine hydrochloride (0.8g, 12mmol). The solution was heated to reflux for 5h. Allowed to cool and sit for 16h. Solid was collected by filtration to yield compound 47 (1.1g, 92%).

Example 48

Preparation of Compound 48

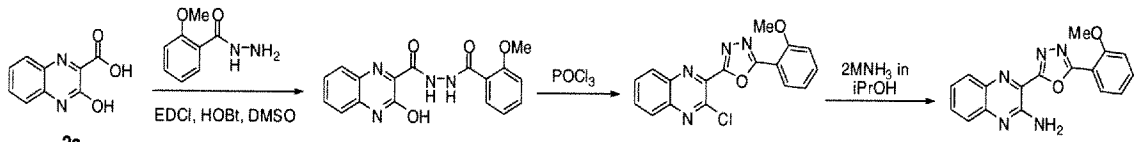


48

Using Steps B and C described in Example 2, compound 48 was prepared substituting *N*-[3-(aminomethyl)phenyl]acetamide hydrochloride for 2-chloro-6-methylbenzylamine in Step B.

Example 49

Preparation of Compound 49



2a 49b 49c 49

Step A – Synthesis of Compound 49b

To compound 2a (150mg, 0.79mmol) was added 2-methoxybenzohydrazide (171mg, 1.0mmol), EDCI (228mg, 1.19mmol), HOBt (161mg, 1.19mmol), and DMSO (6mL) and the solution was stirred for 16h. To the solution was added H_2O (150mL), stirred for 20min, filtered solid, and dried to yield compound 49b (255mg, 95%).

Step B – Synthesis of Compound 49c

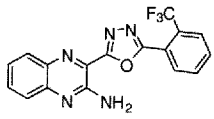
To compound 49b (255mg, 0.77mmol) was added $POCl_3$ (20mL) and the solution was stirred and heated to 105°C for 16h. Allowed to cool, concentrated under vacuum, added H_2O (100mL), stirred for 30min, filtered solid and dried to yield compound 49c (245mg, 96%).

Step C – Synthesis of Compound 49

To compound 49c (245mg, 0.72mmol) was added 2M NH_3 in isopropanol (15mL), the tube sealed, stirred, and heated to 80°C for 24h. Allowed to cool, filtered solid, rinsed with MeOH, and dried to yield compound 49 (190mg, 83%).

Example 50

Preparation of Compound 50

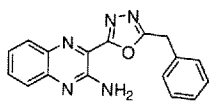


50

Using Steps A, B, and C from Example 49, substituting 2-trifluoromethylbenzohydrazide for 2-methoxybenzohydrazide, compound 50 was prepared.

Example 51

Preparation of Compound 51

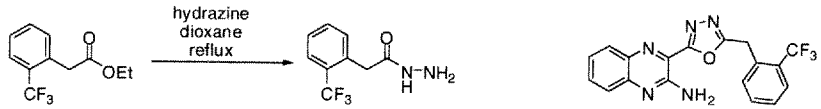


51

Using Steps A, B, and C from Example 49, substituting 2-phenylacetohydrazide for 2-methoxybenzohydrazide, compound 51 was prepared.

Example 52

Preparation of Compounds 52b and 52



52a 52b 52

Step A – Synthesis of Compound 52b

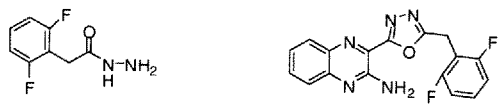
To compound 52a (1.0g, 4.3mmol) was added 1,4-dioxane (10mL), and hydrazine (1.35mL, 43mmol), and the solution was stirred at reflux for 16h. Allowed to cool and concentrated under vacuum to yield compound 52b (0.94g, 100%).

Step B – Synthesis of Compound 52

Using Steps A, B, and C from Example 49, substituting compound 52b for 2-methoxybenzohydrazide, compound 52 was prepared.

Example 53

Preparation of Compounds 53a and 53



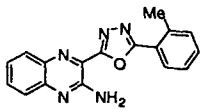
53a 53

Using Steps A, B, and C from Example 49, substituting compound 53a (prepared using Step A from Example 52 substituting ethyl 2-(2,6-

difluorophenyl)acetate for compound 52a) for 2-methoxybenzohydrazide, compound 53 was prepared.

Example 54

Preparation of Compound 54

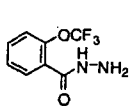


54

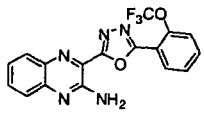
Using Steps A, B, and C from Example 49, substituting 2-methylbenzohydrazide for 2-methoxybenzohydrazide, compound 54 was prepared.

Example 55

Preparation of Compounds 55a and 55



55a

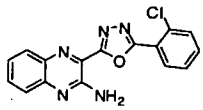


55

Using Steps A, B, and C from Example 49, substituting compound 55a (prepared using Step A from Example 52 substituting ethyl 2-(trifluoromethoxy)benzoate for compound 52a) for 2-methoxybenzohydrazide, compound 55 was prepared.

Example 56

Preparation of Compound 56

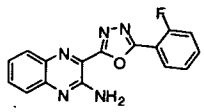


56

Using Steps A, B, and C from Example 49, substituting 2-chlorobenzohydrazide for 2-methoxybenzohydrazide, compound 56 was prepared.

Example 57

Preparation of Compound 57

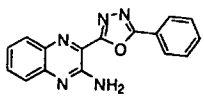


57

Using Steps A, B, and C from Example 49, substituting 2-fluorobenzohydrazide for 2-methoxybenzohydrazide, compound 57 was prepared.

Example 58

Preparation of Compound 58

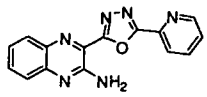


58

Using Steps A, B, and C from Example 49, substituting benzohydrazide for 2-methoxybenzohydrazide, compound 58 was prepared.

Example 59

Preparation of Compound 59

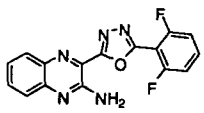


59

Using Steps A, B, and C from Example 49, substituting 2-picolinohydrazide for 2-methoxybenzohydrazide, compound 59 was prepared.

Example 60

Preparation of Compound 60

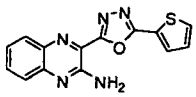


60

Using Steps A, B, and C from Example 49, substituting 2,6-difluorobenzohydrazide for 2-methoxybenzohydrazide, compound 60 was prepared.

Example 61

Preparation of Compound 61

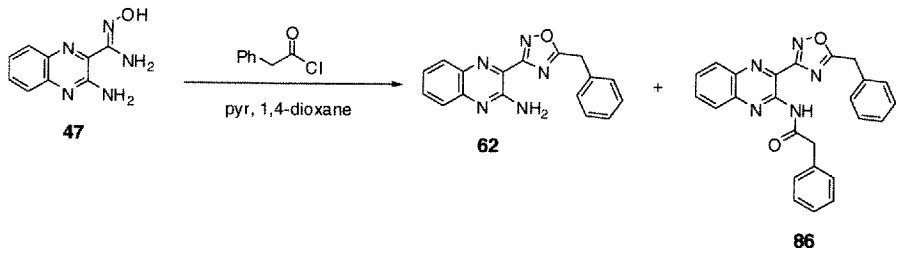


61

Using Steps A, B, and C from Example 49, substituting thiophene-2-carbohydrazide for 2-methoxybenzohydrazide, compound 61 was prepared.

Example 62

Preparation of Compounds 62 and 86

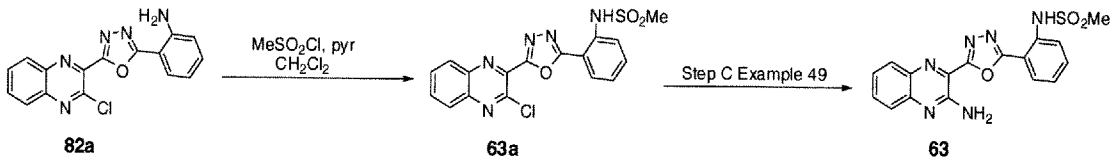


Step A – Synthesis of Compound 62 and 86

To compound 47 (300mg, 1.48mmol) was added 1,4-dioxane (10mL), pyridine (1.0mL, 12.5mmol), and phenylacetyl chloride (0.236mL, 1.78mmol). The solution was stirred for 16h. Purified reaction by preparative TLC (30%EtOAc/hexanes) to yield compound 62 (50mg, 11%) and compound 86 (13mg, 3%).

Example 63

Preparation of Compound 63



Step A – Synthesis of Compound 63a

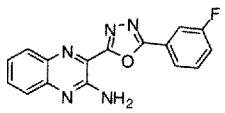
To compound 82a (prepared in Example 82, 150mg, 0.39mmol) were added CH_2Cl_2 (10mL), pyridine (0.065mL, 0.79mmol), and methanesulfonylchloride (0.061mL, 0.79mmol) and the solution was stirred for 14h. Purified the reaction by preparative TLC (25%EtOAc/hexanes) to yield compound 63a (130mg, 83%).

Step B – Synthesis of Compound 63

Using Step C from Example 49, substituting compound 63a for compound 49c, compound 63 was prepared.

Example 64

Preparation of Compound 64

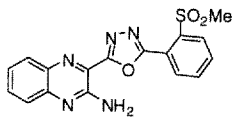


64

Using Steps A, B, and C from Example 49, substituting 2-fluorobenzohydrazide for 2-methoxybenzohydrazide, compound 64 was prepared.

Example 65

Preparation of Compound 65

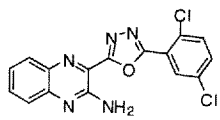


65

Using Steps A, B, and C from Example 49, substituting 2-(methylsulfonyl)benzohydrazide for 2-methoxybenzohydrazide, compound 65 was prepared.

Example 66

Preparation of Compound 66

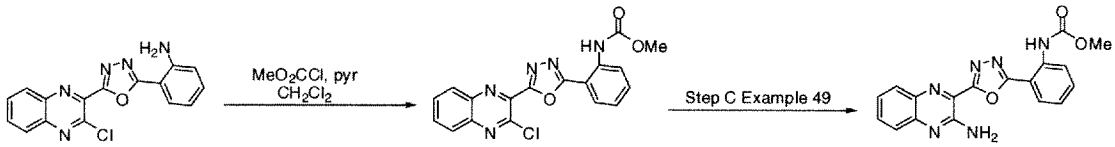


66

Using Steps A, B, and C from Example 49, substituting 2,5-dichlorobenzohydrazide for 2-methoxybenzohydrazide, compound 66 was prepared.

Example 67

Preparation of Compound 67



82a 67a 67

Step A – Synthesis of Compound 67a

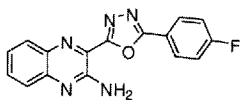
To compound 82a (prepared in Example 82, 200mg, 0.62mmol) were added CH_2Cl_2 (6mL), pyridine (0.10mL, 1.24mmol), and methyl chloroformate (0.062mL, 0.79mmol) and the solution was stirred for 1h. Transferred solution to sep. funnel, added H_2O (50mL), added CH_2Cl_2 (50mL), mixed, separated, dried ($MgSO_4$), filtered, and concentrated to yield compound 67a.

Step B – Synthesis of Compound 67

Using Step C from Example 49, substituting compound 67a for compound 49c, compound 67 was prepared.

Example 68

Preparation of Compound 68

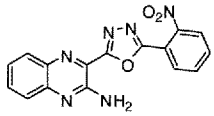


68

Using Steps A, B, and C from Example 49, substituting 4-fluorobenzohydrazide for 2-methoxybenzohydrazide, compound 68 was prepared.

Example 69

Preparation of Compound 69

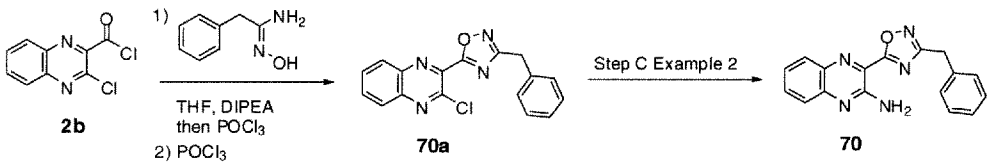


69

Using Steps A, B, and C from Example 49, substituting 2-nitrobenzohydrazide for 2-methoxybenzohydrazide, compound 69 was prepared.

Example 70

Preparation of Compound 70



2b 70a 70

Step A – Synthesis of Compound 70a

To compound 2b (477mg, 2.10mmol) were added THF (20mL), DIPEA (0.55mL, 3.15mmol), *N*'-hydroxy-2-phenylacetimidamide (316mg, 2.10mmol) and the solution was stirred for 16h. Reaction was concentrated and $POCl_3$ (10mL) was added and the solution was stirred and heated to 100°C for 16h. Allowed to cool, concentrated under vacuum, added ice water, extracted with

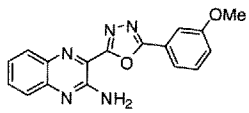
CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated. Purified by preparative TLC (30%EtOAc/hexanes) to yield compound 70a (200mg, 30%).

Step B – Synthesis of Compound 70

Using Step C from Example 2, substituting compound 70a for compound 2c, compound 70 was prepared.

Example 71

Preparation of Compound 71

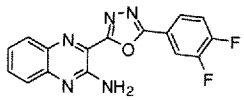


71

Using Steps A, B, and C from Example 49, substituting 3-methoxybenzohydrazide for 2-methoxybenzohydrazide, compound 71 was prepared.

Example 72

Preparation of Compound 72

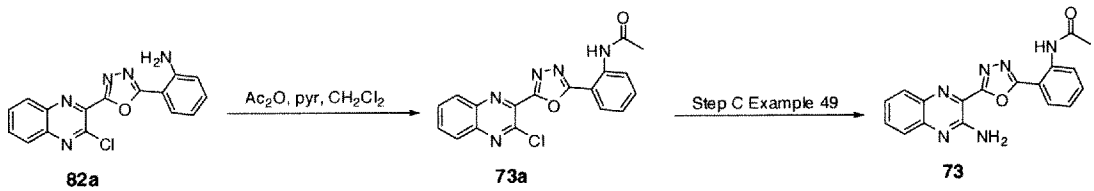


72

Using Steps A, B, and C from Example 49, substituting 3,4-difluorobenzohydrazide for 2-methoxybenzohydrazide, compound 72 was prepared.

Example 73

Preparation of Compound 73



82a 73a 73

Step A – Synthesis of Compound 73a

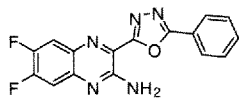
To compound 82a (prepared in Example 82, 150mg, 0.39mmol) were added CH_2Cl_2 (8mL), pyridine (0.065mL, 0.79mmol), and acetic anhydride (0.07mL, 0.79mmol) and the solution was stirred for 16h. Purified the reaction by preparative TLC (30%EtOAc/hexanes) to yield compound 73a (140mg, 98%).

Step B – Synthesis of Compound 73

Using Step C from Example 49, substituting compound 73a for compound 49c, compound 73 was prepared.

Example 74

Preparation of Compound 74

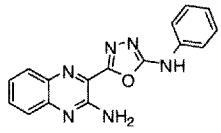


74

Using Steps A, B, and C from Example 49, substituting compound 5c for compound 2a and substituting benzohydrazide for 2-methoxybenzohydrazide, compound 74 was prepared.

Example 75

Preparation of Compound 75

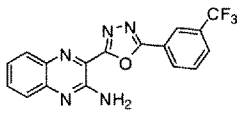


75

Using Steps A, B, and C from Example 49, substituting *N*-phenylhydrazinecarboxamide for 2-methoxybenzohydrazide, compound 75 was prepared.

Example 76

Preparation of Compound 76

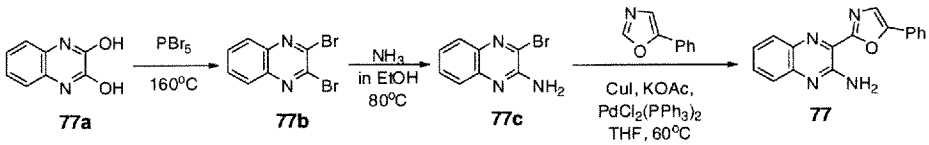


76

Using Steps A, B, and C from Example 49, substituting 3-trifluoromethylbenzohydrazide for 2-methoxybenzohydrazide, compound 76 was prepared.

Example 77

Preparation of Compound 77



77a 77b 77c 77

Step A – Synthesis of Compound 77b

To compound 77a (3.0g, 18.5mmol) were added PBr_5 (17g) and the solution was heated to 160°C for 2h. Cooled to 0°C and added ice and stirred for 30min. The solution was extracted with CH_2Cl_2, washed with 1N NaOH, dried ($MgSO_4$), filtered, and concentrated to give compound 77b (5.2g, 98%).

Step B – Synthesis of Compound 77c

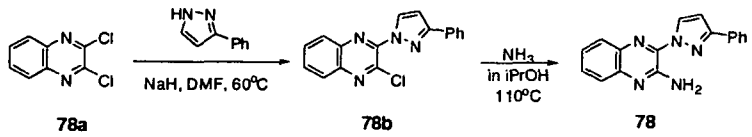
Using Step C from Example 2, substituting compound 77b for compound 2c, compound 77c was prepared.

Step C – Synthesis of Compound 77

To compound 77c (150mg, 0.67mmol) was added KOAc (131mg, 1.3mmol), CuI (19mg, 0.066mmol), $PdCl_2(PPh_3)_2$ (35mg, 0.066mmol), THF (3mL), and 5-phenyloxazole (97mg, 0.67mmol). The solution was stirred and heated to 60°C for 48h. The reaction was purified by preparative TLC (30%EtOAc/hexanes) to yield compound 77 (20mg, 10%).

Example 78

Preparation of Compound 78



Step A – Synthesis of Compound 78b

To 3-phenyl-1H-pyrazole (188mg, 1.3mmol) in DMF (8mL) was added NaH (60% in oil, 60mg, 1.5mmol) and the solution was stirred for 5min. To the solution was added compound 78a (200mg, 1.0mmol) and the solution was heated to 60°C for 1h. Allowed to cool, concentrated under vacuum, and

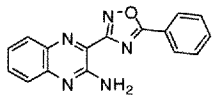
purified by preparative TLC (30%EtOAc/hexanes) to yield compound 78b (61mg, 20%).

Step B – Synthesis of Compound 78

Using Step C from Example 2, substituting compound 78b for compound 2c, compound 78 was prepared.

Example 79

Preparation of Compound 79

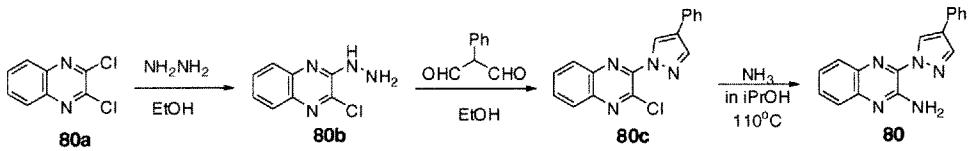


79

Using Step A from Example 62, substituting benzoyl chloride for phenylacetyl chloride, compound 79 was prepared.

Example 80

Preparation of Compound 80



80a 80b 80c 80

Step A – Synthesis of Compound 80b

To compound 80a (7.6g, 38mmol) were added EtOH (125mL) and hydrazine hydrate (5.6mL, 114mmol) and the solution was stirred for 24h. Filtered solid, rinsed with EtOH, and dried to yield compound 80b (3.7g, 50%).

Step B – Synthesis of Compound 80c

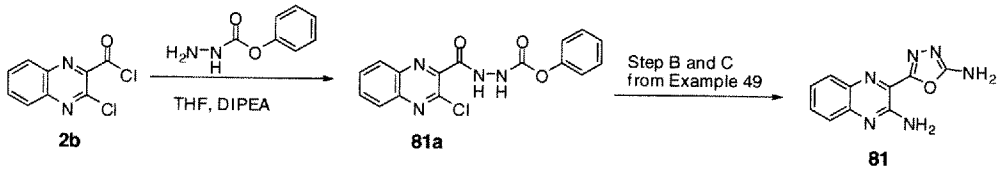
To compound 80b (100mg, 0.52mmol) were added EtOH (6mL) and 2-phenylmalondialdehyde (76mg, 0.52mmol) and the solution was stirred for 1h. The reaction was concentrated and triturated with MeOH to yield compound 80c (90mg, 57%).

Step C – Synthesis of Compound 80

Using Step C from Example 2, substituting compound 80c for compound 2c, compound 80 was prepared.

Example 81

Preparation of Compound 81



2b 81a 81

Step A – Synthesis of Compound 81a

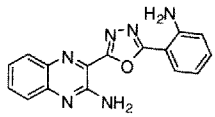
To a solution of hydrazine (0.83mL, 26mmol) in ether was added phenyl chloroformate (0.92mL, 7.4mmol) at -20°C. The solution was stirred for 1h, removed solid by filtration, and filtrate was concentrated to give phenyl hydrazinecarboxylate. To phenyl hydrazinecarboxylate was added compound 2b (1.2g, 5.2mmol), THF (20mL), and DIPEA (1.5mL) and the solution was stirred for 1h. Partitioned reaction between sat. aq. $NaHCO_3$ and CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated to yield compound 81a (400mg, 22%).

Step B – Synthesis of Compound 81

Using Steps B and C from Example 49, substituting compound 81a for compound 49b, compound 81 was prepared.

Example 82

Preparation of Compound 82

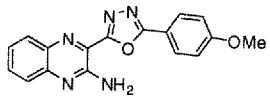


82

Using Steps A, B, and C from Example 49, substituting 2-aminobenzohydrazide for 2-methoxybenzohydrazide, compound 82 was prepared.

Example 83

Preparation of Compound 83

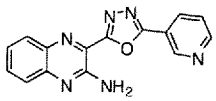


83

Using Steps A, B, and C from Example 49, substituting 4-methoxybenzohydrazide for 2-methoxybenzohydrazide, compound 83 was prepared.

Example 84

Preparation of Compound 84

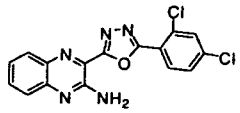


84

Using Steps A, B, and C from Example 49, substituting nicotinohydrazide for 2-methoxybenzohydrazide, compound 84 was prepared.

Example 85

Preparation of Compound 85



85

Using Steps A, B, and C from Example 49, substituting 2,4-dichlorobenzohydrazide for 2-methoxybenzohydrazide, compound 85 was prepared.

Example 86

Preparation of Compound 87



45a 87a 87

Using Step A from Example 45, substituting benzothiazole-2-acetonitrile for malononitrile and substituting NaOtBu for Et_3N, compound 87a was prepared. Using Step B from Example 45, substituting compound 87a for compound 45b, compound 87 was prepared.

Example 87

LC/MS Data For Selected Compounds

LC/MS data for selected Amino-Quinoxalines and Related Heterocyclic derivatives is provided below in Table 1, wherein the compound numbers correspond to the compound numbering set forth in the above specification.

Table 1

LC/MS Data For Selected Amino-Quinoxalines and Related Heterocyclic Derivatives

Compound No.	Compound Name	LCMS Calculated M+1	LCMS Observed M+1
1	3-AMINO-N-[(2,6-DICHLOROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	347	347.2
2	3-AMINO-N-[(2-CHLORO-6-METHYLPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	327.1	327.1
3	3-AMINO-N-[(2,6-DIFLUOROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	315.1	315.2
4	3-AMINO-N-(2,3-DIHYDRO-1H-INDEN-1(R)-YL)-2-QUINOXALINECARBOXAMIDE	305.3	305.2
5	3-AMINO-N-[(2,6-DIFLUOROPHENYL)METHYL]-6,7-DIFLUORO-2-QUINOXALINECARBOXAMIDE	351	351
6	3-AMINO-N-[[2-(METHYLTHIO)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	325.1	325.2
7	METHYL 2-[[[(3-AMINO-2-QUINOXALINYL)CARBONYL]AMINO]METHYL]BENZOATE	337.1	337.2
8	3-AMINO-N-(1-NAPHTHALENYLMETHYL)-2-QUINOXALINECARBOXAMIDE	329.4	329.2
9	3-AMINO-N-[(2-METHOXYPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	309.3	309.2
10	3-AMINO-N-(2,3-DIHYDRO-1H-INDEN-1-YL)-2-QUINOXALINECARBOXAMIDE	305.3	305.2
11	3-AMINO-N-[[2-(TRIFLUOROMETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	347.1	347.2
12	3-AMINO-N-[(2,3-DIFLUOROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	315.1	315.2
13	3-AMINO-N-[[2-(HYDROXYMETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	309.3	309.2
14	3-AMINO-N-[[2-(1-HYDROXY-1-METHYLETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	337.4	337.2
15	3-AMINO-N-(PHENYLMETHYL)-2-QUINOXALINECARBOXAMIDE	279.1	279.2
16	3-AMINO-6,7-DIFLUORO-N-[[2-(TRIFLUOROMETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	383	383
17	3-AMINO-N-[[1,1'-BIPHENYL]-2-YLMETHYL]-2-QUINOXALINECARBOXAMIDE	355.2	355.2
18	3-AMINO-N-(2-PYRIDINYLMETHYL)-2-QUINOXALINECARBOXAMIDE	280.1	280.2

19	3-AMINO-N-[[2-[(METHYLSULFONYL)METHYL]PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	371.4	371.2
20	3-AMINO-N-(2-THIAZOLYLMETHYL)-2-QUINOXALINECARBOXAMIDE	286.1	286.2
21	3-AMINO-N-[[3-(TRIFLUOROMETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	347.1	347.2
22	3-AMINO-6,7-DIFLUORO-N-(PHENYLMETHYL)-2-QUINOXALINECARBOXAMIDE	315	315
23	3-AMINO-N-[(2-AMINOPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	294.1	294.2
24	3-AMINO-N-[(2-NITROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	324.1	324.2
25	3-AMINO-N-(2,3-DIHYDRO-1H-INDEN-1(S)-YL)-2-QUINOXALINECARBOXAMIDE	305.3	305.2
26	1,1-DIMETHYLETHYL [2-[[[(3-AMINO-2-QUINOXALINYL)CARBONYL]AMINO]METHYL]PHENYL]CARBAMATE	394.2	394.2
27	3-AMINO-N-[[2-(METHYLSULFONYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	357.4	357.2
28	3-AMINO-N-[(4-FLUOROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	297.1	297.2
29	3-AMINO-N-(1,3-BENZODIOXOL-5-YLMETHYL)-2-QUINOXALINECARBOXAMIDE	323.1	323.2
30	3-AMINO-N-[(3,5-DIFLUOROPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	315.1	315.2
31	3-AMINO-N-(2,3-DIHYDRO-2(R)-HYDROXY-1H-INDEN-1(S)-YL)-2-QUINOXALINECARBOXAMIDE	321.3	321.2
32	3-AMINO-N-(1,2,3,4-TETRAHYDRO-1-NAPHTHALENYL)-2-QUINOXALINECARBOXAMIDE	319.4	319.2
33	3-AMINO-N-[[4-(TRIFLUOROMETHYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	347.1	347.2
34	3-AMINO-N-[[1,1'-BIPHENYL]-3-YLMETHYL]-2-QUINOXALINECARBOXAMIDE	355.2	355.2
35	3-AMINO-N-(PHENYLMETHYL)-6-(TRIFLUOROMETHYL)-2-QUINOXALINECARBOXAMIDE	347	347
36	METHYL 3-[[[(3-AMINO-2-QUINOXALINYL)CARBONYL]AMINO]METHYL]BENZOATE	337.1	337.2
37	3-AMINO-N-(3-PYRIDINYLMETHYL)-2-QUINOXALINECARBOXAMIDE	280.1	280.2
38	3-AMINO-N-(1-PHENYLETHYL)-2-QUINOXALINECARBOXAMIDE	293.3	293.2
39	3-AMINO-N-[[3-(METHYLSULFONYL)PHENYL]METHYL]-2-QUINOXALINECARBOXAMIDE	357.1	357.2

40	N-[[3-[ACETYL(METHYL)AMINO]PHENYL]METHYL]-3-AMINO-2-QUINOXALINECARBOXAMIDE	350.2	350.2
41	3-AMINO-N-[(4-METHOXYPHENYL)METHYL]-2-QUINOXALINECARBOXAMIDE	309.1	309.2
42	3-AMINO-N-(2-PHENOXYETHYL)-2-QUINOXALINECARBOXAMIDE	309.1	309.2
43	3-AMINO-2-QUINOXALINECARBOXAMIDE	189.1	189.1
44	3-AMINO-N-(2-PHENYLETHYL)-2-QUINOXALINECARBOXAMIDE	292.1	293.2
45	3-AMINO-2-QUINOXALINECARBONITRILE	171.1	171.1
46	2-AMINO-N-(PHENYLMETHYL)-3-QUINOLINECARBOXAMIDE	278.3	278.1
47	3-AMINO-N'-HYDROXY-2-QUINOXALINECARBOXIMIDAMIDE	204	204
48	N-[[3-(ACETYLAMINO)PHENYL]METHYL]-3-AMINO-2-QUINOXALINECARBOXAMIDE	336.1	336.2
49	3-[5-(2-METHOXYPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	320.1	320.2
50	3-[5-[2-(TRIFLUOROMETHYL)PHENYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	358.1	358.2
51	3-[5-(PHENYLMETHYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	304.1	304.1
52	3-[5-[[2-(TRIFLUOROMETHYL)PHENYL]METHYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	372	372
53	3-[5-[(2,6-DIFLUOROPHENYL)METHYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	340	340
54	3-[5-(2-METHYLPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	304.1	304.2
55	3-[5-[2-(TRIFLUOROMETHOXY)PHENYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	374	374
56	3-[5-(2-CHLOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	324.1	324.2
57	3-[5-(2-FLUOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	308.1	308.2
58	3-(5-PHENYL-1,3,4-OXADIAZOL-2-YL)-2-QUINOXALINAMINE	290.1	290.2
59	3-[5-(2-PYRIDINYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	291.1	291.2
60	3-[5-(2,6-DIFLUOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	326.1	326.2
61	3-[5-(2-THIENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	296.1	296.2
62	3-[5-(PHENYLMETHYL)-1,2,4-OXADIAZOL-3-YL]-2-QUINOXALINAMINE	304	304
63	N-[2-[5-(3-AMINO-2-QUINOXALINYL)-1,3,4-OXADIAZOL-2-YL]PHENYL]METHANESULFONAMIDE	383.1	383.2
64	3-[5-(3-FLUOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	308.1	308.2
65	3-[5-[2-(METHYLSULFONYL)PHENYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	368.1	368.2
66	3-[5-(2,5-DICHLOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	358	358.2
67	METHYL [2-[5-(3-AMINO-2-QUINOXALINYL)-1,3,4-OXADIAZOL-2-YL]PHENYL]CARBAMATE	363.1	363.2

68	3-[5-(4-FLUOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	308.1	308.2
69	3-[5-(2-NITROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	335.1	335.2
70	3-[3-(PHENYLMETHYL)-1,2,4-OXADIAZOL-5-YL]-2-QUINOXALINAMINE	304	304
71	3-[5-(3-METHOXYPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	320.1	320.2
72	3-[5-(3,4-DIFLUOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	326.1	326.2
73	N-[2-[5-(3-AMINO-2-QUINOXALINYL)-1,3,4-OXADIAZOL-2-YL]PHENYL]ACETAMIDE	347.1	347.2
74	6,7-DIFLUORO-3-(5-PHENYL-1,3,4-OXADIAZOL-2-YL)-2-QUINOXALINAMINE	326.3	326.2
75	3-[5-(PHENYLAMINO)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	305.1	305.2
76	3-[5-[3-(TRIFLUOROMETHYL)PHENYL]-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	358.1	358.2
77	3-(5-PHENYL-2-OXAZOLYL)-2-QUINOXALINAMINE	289	289
78	3-(3-PHENYL-1H-PYRAZOL-1-YL)-2-QUINOXALINAMINE	288.3	288.2
79	3-(5-PHENYL-1,2,4-OXADIAZOL-3-YL)-2-QUINOXALINAMINE	290	290
80	3-(4-PHENYL-1H-PYRAZOL-1-YL)-2-QUINOXALINAMINE	288.3	288.2
81	3-(5-AMINO-1,3,4-OXADIAZOL-2-YL)-2-QUINOXALINAMINE	229.1	229.1
82	3-[5-(2-AMINOPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	305.1	305.2
83	3-[5-(4-METHOXYPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	320.2	320.2
84	3-[5-(3-PYRIDINYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	291.1	291.2
85	3-[5-(2,4-DICHLOROPHENYL)-1,3,4-OXADIAZOL-2-YL]-2-QUINOXALINAMINE	358	358.2
86	N-[3-[5-(PHENYLMETHYL)-1,2,4-OXADIAZOL-3-YL]-2-QUINOXALINYL]BENZENEACETAMIDE	422	422
87	3-(2-BENZOTHIAZOLYL)-2-QUINOXALINAMINE	279	279

Because of their adenosine A_{2a} receptor antagonist activity, compounds of the present invention are useful in the treatment of depression, cognitive function diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, psychoses of organic origin, attention deficit disorders, EPS, dystonia, RLS and PLMS. In particular, the compounds of the present invention can improve motor-impairment due to neurodegenerative diseases such as Parkinson's disease.

The other agents known to be useful in the treatment of Parkinson's disease that can be administered in combination with the compounds of Formula I include: L-DOPA; dopaminergic agonists such as quinpirole, ropinirole, pramipexole, pergolide and bromocriptine; MAO-B inhibitors such as deprenyl and selegiline; DOPA decarboxylase inhibitors such as carbidopa and benserazide; and COMT inhibitors such as tolcapone and entacapone.

In this specification, the term "at least one compound of Formula I" (or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof) means that one to three different compounds of Formula I (or pharmaceutically acceptable salt, solvate, ester or prodrug thereof) may be used in a pharmaceutical composition or method of treatment. Preferably one compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof is used. Similarly, "one or more agents useful in the treatment of Parkinson's disease" means that one to three different agents, preferably one agent, may be used in a pharmaceutical composition or method of treatment. Preferably, one agent is used in combination with one compound of Formula I or pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

The pharmacological activity of the compounds of the invention was determined by the following *in vitro* assays to measure A_{2a} receptor activity.

Human Adenosine A_{2a} and A_1 Receptor Competition Binding Assay Protocol

Membrane sources:

A_{2a}: Human A_{2a} Adenosine Receptor membranes, Catalog #RB-HA2a, Receptor Biology, Inc., Beltsville, MD. Dilute to 17 µg/100 µl in membrane dilution buffer (see below).

Assay Buffers:

Membrane dilution buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM $MgCl_2$.

Compound Dilution Buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) +
10 mM $MgCl_2$ supplemented with 1.6 mg/ml methyl cellulose and 16% DMSO. Prepared fresh daily.

Ligands:

A_{2a}: [3H]-SCH 58261, custom synthesis, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 1 nM in membrane dilution buffer. Final assay concentration is 0.5 nM.

A_1: [3H]- DPCPX, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 2 nM in membrane dilution buffer. Final assay concentration is 1 nM.

Non-specific Binding:

A_{2a}: To determine non-specific binding, add 100 nM CGS 15923 (RBI, Natick, MA). Working stock is prepared at 400 nM in compound dilution buffer.

A_1: To determine non-specific binding, add 100 μM NECA (RBI, Natick, MA). Working stock is prepared at 400 μM in compound dilution buffer.

Compound Dilution:

Prepare 1 mM stock solutions of compounds in 100% DMSO. Dilute in compound dilution buffer. Test at 10 concentrations ranging from 3 μM to 30 pM. Prepare working solutions at 4X final concentration in compound dilution buffer.

Assay procedure:

Perform assays in deep well 96 well plates. Total assay volume is 200 μl. Add 50 μl compound dilution buffer (total ligand binding) or 50 μl CGS 15923 working solution (A_{2a} non-specific binding) or 50 μl NECA working solution (A_1 non-specific binding) or 50 μl of drug working solution. Add 50 μl ligand stock ([3H]-SCH 58261 for A_{2a}, [3H]-DPCPX for A_1). Add 100 μl of diluted membranes containing the appropriate receptor. Mix. Incubate at room temperature for 90 minutes. Harvest using a Brandel cell harvester onto Packard GF/B filter plates. Add 45 μl Microscint 20 (Packard), and count using the Packard TopCount Microscintillation Counter. Determine IC_{50} values by fitting the displacement curves using an iterative curve fitting program (Excel). Determine K_i values using the Cheng-Prusoff equation.

Using the above test procedures, the following results were obtained for preferred and/or representative compounds of the invention.

Results of the binding assay on compounds of the invention showed A_{2a} K_i values of 0.2 to 97.2 nM, with preferred compounds showing K_i values between 0.2 and 5.0 nM. Selectivity is determined by dividing K_i for A_1 receptor by K_i for A_2 receptor. Preferred compounds of the invention have a selectivity ranging from about 100 to about 1500.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

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

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound of formula I in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased

by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

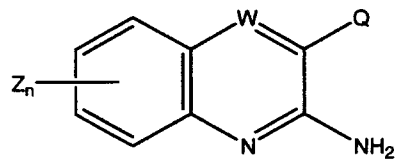
The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for compounds of formula I is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from central nervous system diseases such as Parkinson's disease or the other disease or conditions listed above.

The doses and dosage regimen of the dopaminergic agents will be determined by the attending clinician in view of the approved doses and dosage regimen in the package insert, taking into consideration the age, sex and condition of the patient and the severity of the disease. It is expected that when the combination of a compound of Formula I and a dopaminergic agent is administered, lower doses of the components will be effective compared to the doses of the components administered as monotherapy.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound represented by the structural Formula I:



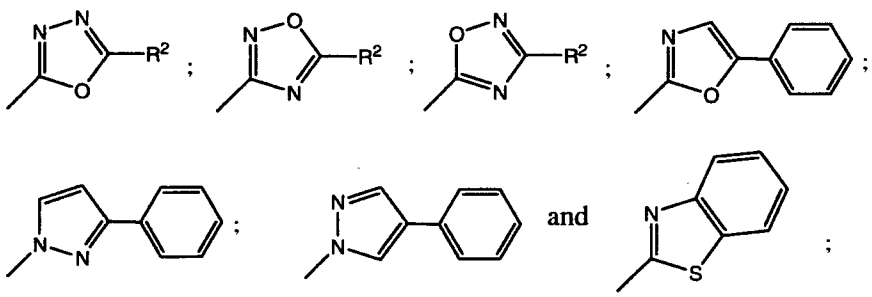
I

wherein:

W represents CH or N;

Z represents hydrogen, halogen or haloalkyl;

Q represents -CN, $-C(=NOH)NH_2$ or $-CONHR^1$; or represents a heterocyclic radical selected from the group consisting of:



and

;

R^1 represents hydrogen, aralkyl, aryloxyalkyl, benzocycloalkyl or heteroarylalkyl; and

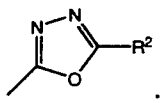
R^2 represents amino, aryl, heteroaryl, arylamino, arylalkyl or heteroarylalkyl;

or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound of Formula I.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein W represents N.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein Q represents –$CONHR^1$.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein Q represents a heterocyclic radical of the formula:



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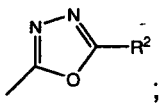
5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

W represents N;

Z represents hydrogen, halogen or haloalkyl;

n represents an integer from 0-2;

Q represents –$CONHR^1$ or represents a heterocyclic radical of the formula:

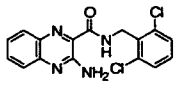
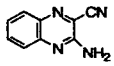


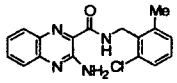
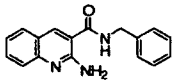
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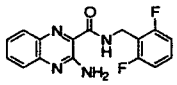
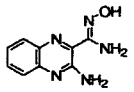
R^1 represents aralkyl, benzocycloalkyl or heteroarylalkyl; and

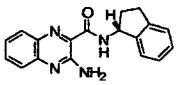
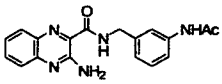
R^2 represents aryl, heteroaryl or arylalkyl.

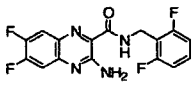
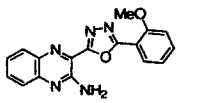
6. A compound selected from the group consisting of:

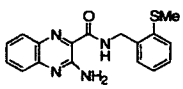
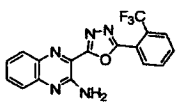

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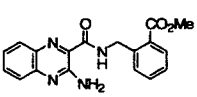
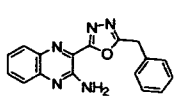

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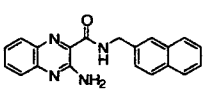
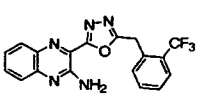

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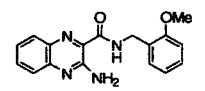
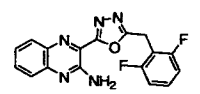

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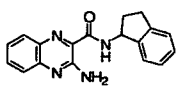
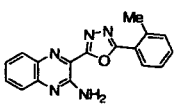

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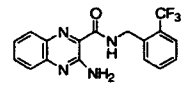
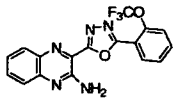

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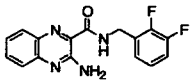
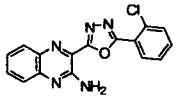

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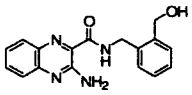
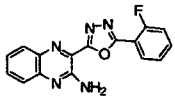

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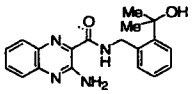
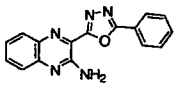

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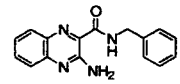
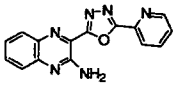

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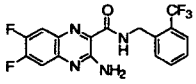
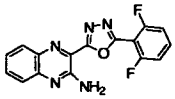

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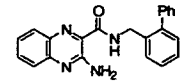
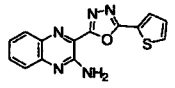

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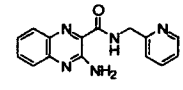
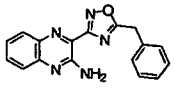

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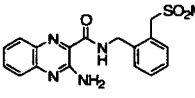
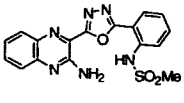

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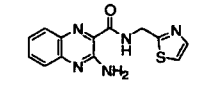
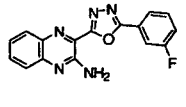

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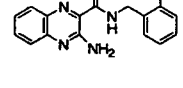
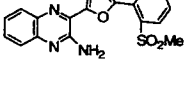

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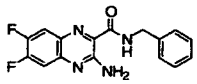

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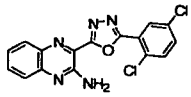

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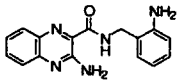

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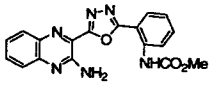
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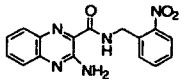
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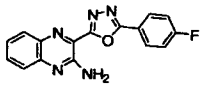
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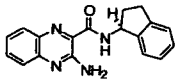
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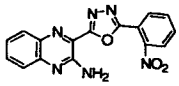
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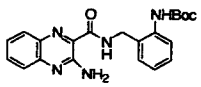
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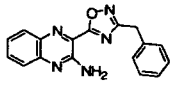
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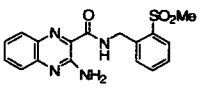
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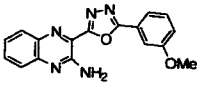
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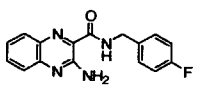
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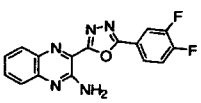
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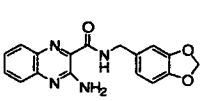
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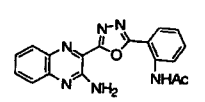
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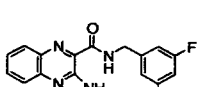
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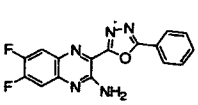
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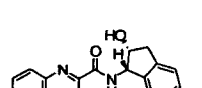
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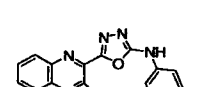
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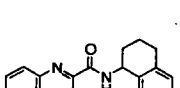
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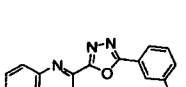
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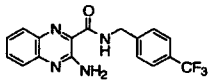
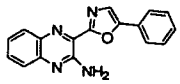
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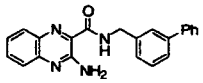
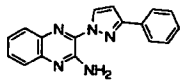
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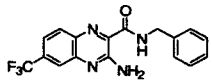
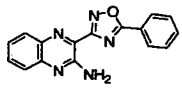
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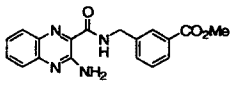
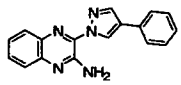
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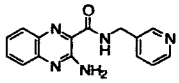
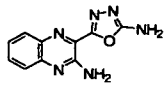
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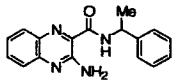
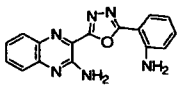

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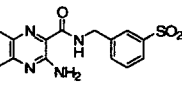
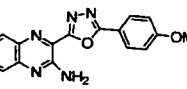

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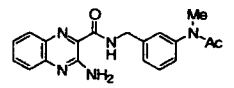
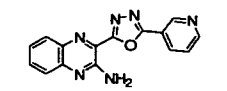

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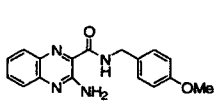
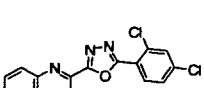

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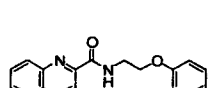
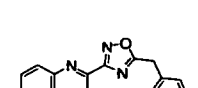

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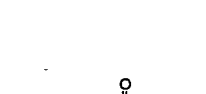
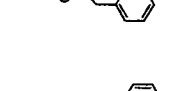

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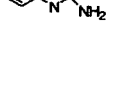
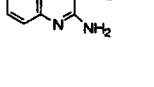

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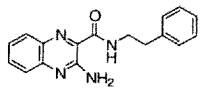

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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

7. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

8. A pharmaceutical composition comprising at least one compound of claim 6, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

9. The pharmaceutical composition of claim 7, further comprising one or more additional therapeutic agents.

10. The pharmaceutical composition of claim 8, further comprising one or more additional therapeutic agents.

11. The pharmaceutical composition of claim 9, wherein the one or more additional therapeutic agents are one or more therapeutic agents useful for the treatment of Parkinson's Disease.

12. The pharmaceutical composition of claim 10, wherein the one or more additional therapeutic agents are one or more therapeutic agents useful for the treatment of Parkinson's disease.

13. The pharmaceutical composition of claim 11, wherein the one or more therapeutic agents useful for the treatment of Parkinson's disease are one or more therapeutic agents selected from the group consisting of L-DOPA, dopaminergic agonists, MAO-B inhibitors, DOPA decarboxylase inhibitors and COMT inhibitors.

14. The pharmaceutical composition of claim 12, wherein the one or more therapeutic agents useful for the treatment of Parkinson's disease are one or more therapeutic agents selected from the group consisting of L-DOPA, dopaminergic agonists, MAO-B inhibitors, DOPA decarboxylase inhibitors and COMT inhibitors.

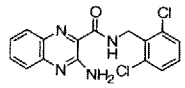
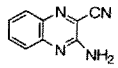
15. A method of treating a disease of the central nervous system or stroke, comprising administering an effective amount therefor of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof to a mammal in need of such treatment.

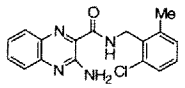
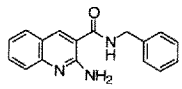
16. The method of claim 15, wherein the disease of the central nervous system is depression, a cognitive disease or a neurodegenerative disease.

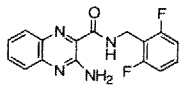
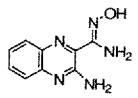
17. The method of claim 15, wherein the disease of the central nervous system is Parkinson's disease, senile dementia, a psychosis of organic origin, attention deficit disorder, Extra Pyramidal Syndrome, dystonia, restless leg syndrome or periodic limb movement in sleep.

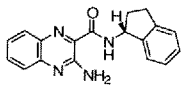
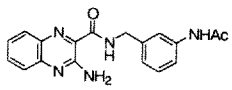
18. A method of treating Parkinson's disease comprising administering an effective amount therefor of a pharmaceutical composition according to claim 7 to a mammal in need thereof.

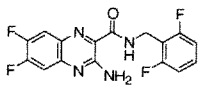
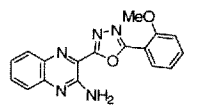
19. The method of claim 18, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound selected from the group consisting of:

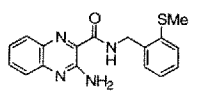
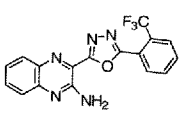

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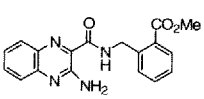
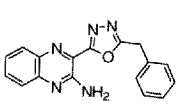

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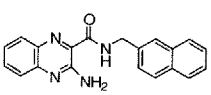
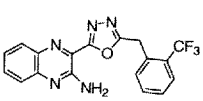

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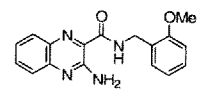
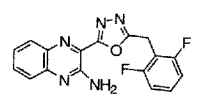

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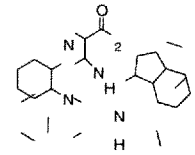

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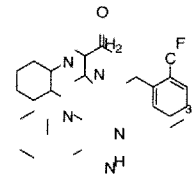

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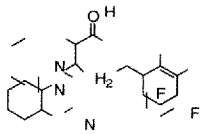

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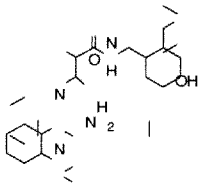
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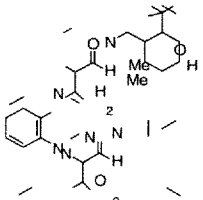
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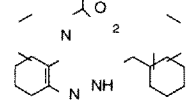

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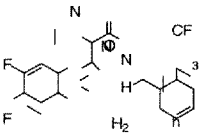

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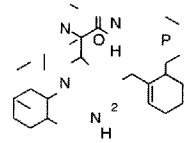

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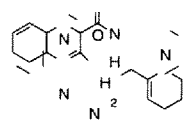

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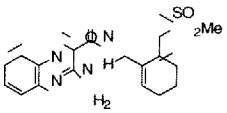

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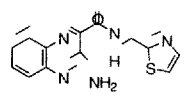

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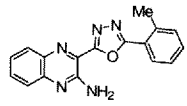

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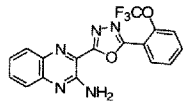

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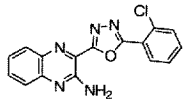

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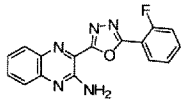

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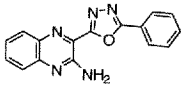

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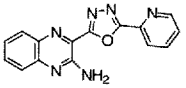

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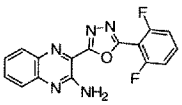

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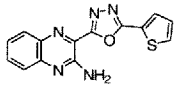

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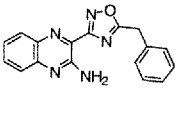

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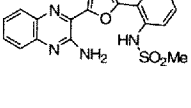

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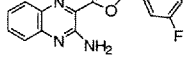

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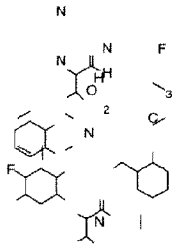

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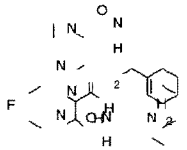

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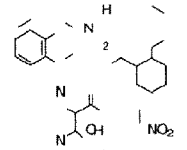

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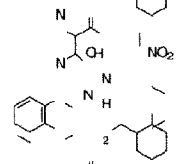

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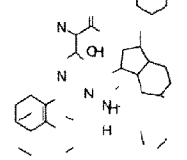

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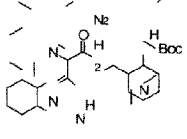


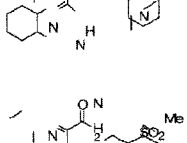


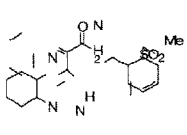


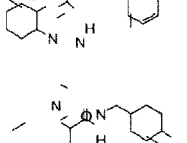


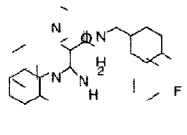


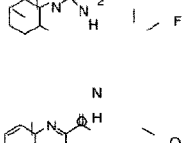


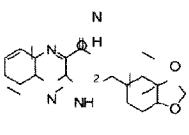


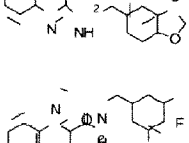


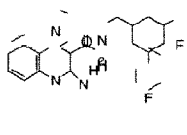


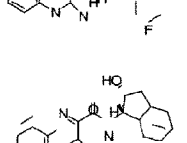


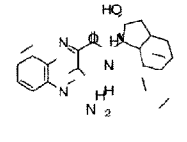


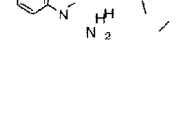


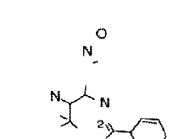


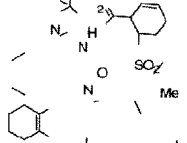


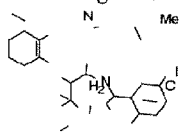


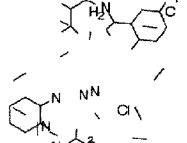


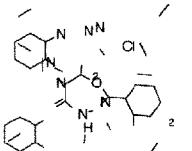


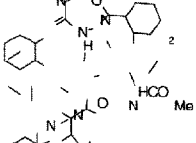


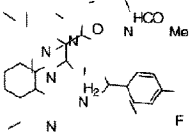


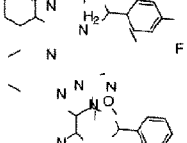


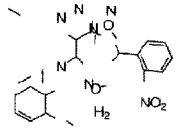


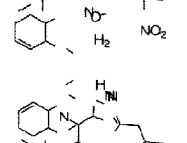


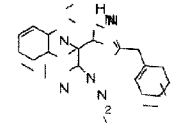


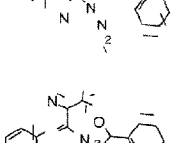


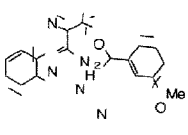


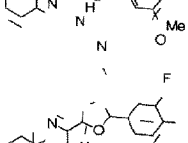


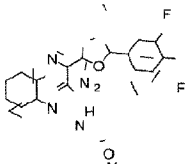


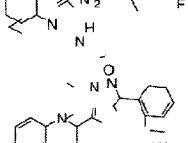


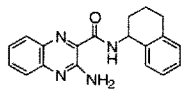
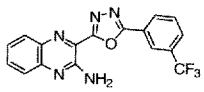


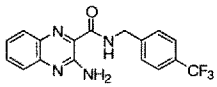
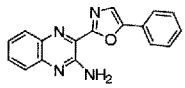


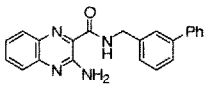
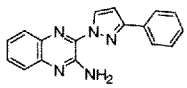


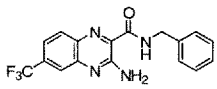
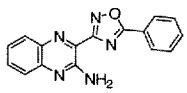


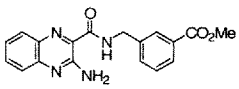
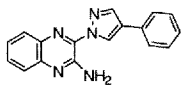


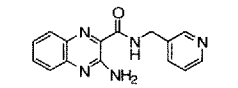
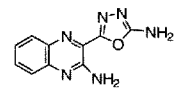

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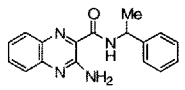
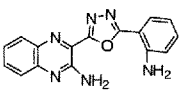

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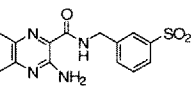
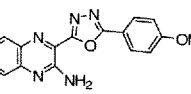

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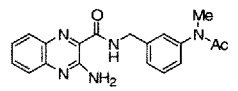
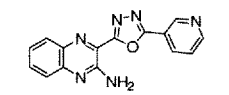

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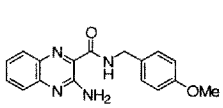
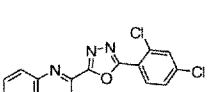

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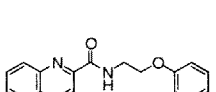
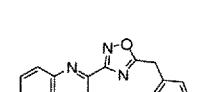

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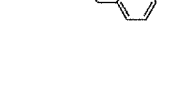

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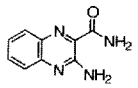

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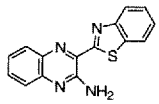

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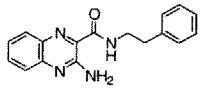

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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

20. The method of claim 18, wherein the pharmaceutical composition additionally comprises one or more additional therapeutic agents are one or more therapeutic agents useful for the treatment of Parkinson's disease.

21. The method of claim 20, wherein the one or more therapeutic agents useful for the treatment of Parkinson's disease are one or more therapeutic agents selected from the group consisting of L-DOPA, dopaminergic agonists, MAO-B inhibitors, DOPA decarboxylase inhibitors and COMT inhibitors.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/035828

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D241/44 C07D401/12 C07D403/04 C07D405/12 C07D413/04
C07D417/04 C07D417/12 A61K31/498 A61P25/00 A61P25/16

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)
C07D A61K A61P

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 practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOBLIA P ET AL: "Novel vanadyl complexes with quinoxaline N<1>,N<4>-dioxide derivatives as potent in vitro insulin-mimetic compounds" JOURNAL OF INORGANIC BIOCHEMISTRY, ELSEVIER, vol. 100, no. 2, 1 February 2006 (2006-02-01), pages 281-287, XP025038346 ISSN: 0162-0134 [retrieved on 2006-02-01] page 282	1-3,5,6

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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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

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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
17 July 2009	07/08/2009

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	Fazzi, Raffaella

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/035828

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VIEITES M ET AL: "Selective hypoxia-cytotoxins based on vanadyl complexes with 3-aminoquinoxaline-2-carbonitrile-N<1>,N<4>-dioxide derivatives" JOURNAL OF INORGANIC BIOCHEMISTRY, ELSEVIER, vol. 100, no. 8, 1 August 2006 (2006-08-01), pages 1358-1367, XP025038291 ISSN: 0162-0134 [retrieved on 2006-08-01] page 1359	1-3,5,6
X	KIRAN ET AL.: "Rediscovered synthesis of 3-cyanoquinoline derivatives" HETEROCYCLIC COMMUNICATIONS, vol. 12, no. 6, 2006, pages 481-484, XP009120139 page 482; examples 4-6	1-3,5,6
X	CHARUSHIN ET AL: "Pyrido[2,3-b]- and pyrimido[4,5-b]quinoxalines: the first fluorine-containing derivatives" MENDELEEV COMMUNICATIONS, INSTITUTE OF PHYSICS PUBLISHING, BRISTOL, GB, vol. 11, no. 2, 1 January 2001 (2001-01-01), pages 54-55, XP022533183 ISSN: 0959-9436 examples 2,4	1-3,5
X	SHARMA ET AL.: "A facile synthesis of annelated pyridines from beta-formyl enamides under microwave irradiation" TETRAHEDRON LETTERS, vol. 41, no. 18, 2000, pages 3493-3496, XP002537625 example 10; table 1	1-3,5,6
X	MONTOYA ET AL.: "Synthesis and antituberculosis activity of some new 2-quinoxalinecarbonitriles" IL FARMACO, vol. 53, no. 8-9, 1998, pages 570-573, XP002537626 page 571	1-3,5,6
X	MONGE ET AL.: "New Quinoxaline and Pyrimido[4,5-b]quinoxaline Derivatives. potential Antihypertensive and Blood Platelet Antiaggregating Agents" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 26, 1989, pages 1623-1626, XP002537627 examples 2,8	1-3,5,6

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/035828

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	UKHOV ET AL.: "Synthesis of substituted 2-aminoquinoline-3-carboxylic acid amides" CHEMISTRY OF HETEROCYCLIC COMPOUNDS, vol. 24, no. 11, 1988, pages 1256-1258, XP002537628 page 1257; example IIf	1-3,5,6
X	ALTHUIS ET AL.: "Structure-Activity Relationship in a Series of Novel 3,4-Dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylic Acid Antiallergy Agents" J. MED. CHEM., vol. 23, no. 3, 1980, pages 262-269, XP002537629 page 267; table VII	1-3,5,6
X	MILCENT R.: "Contribution à létude des oxadiazoles 1,3,4: synthèses de quelques composés polyhétérocycliques dérivés de l'acide (phényl-5 oxadiazol-1,3,4 YL2) acétique" ANNALES DE CHIMIE, vol. 2, no. 14, 1967, pages 221-226, XP009120140 page 16; example VI	1-6
X	TAYLOR ET AL.: "The Synthesis of Pyrimido[4,5-b]quinolines" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 78, 1956, pages 5108-5115, XP002537630 page 5110 - page 5111; examples III,XVIII	1-3,5,6
X	GOWENLOCK A ET AL: "Synthesis of Alloxazine from 2-Aminoquinoxaline-3-carboxyammide" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY, LETCHWORTH., GB, 1 January 1948 (1948-01-01), pages 517-519, XP009120144 ISSN: 0368-1769 page 518; example I	1-3,5,6
A	WO 02/055083 A (VERNALIS RES LTD [GB]; GILLESPIE ROGER JOHN [GB]; LERPINIERE JOANNE [G) 18 July 2002 (2002-07-18) cited in the application the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/035828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02055083 A	18-07-2002	AT 424207 T	15-03-2009
		AU 2002219355 B2	24-11-2005
		BR 0206559 A	22-06-2004
		CA 2433453 A1	18-07-2002
		CN 1496262 A	12-05-2004
		CN 101214248 A	09-07-2008
		CZ 20031955 A3	14-01-2004
		DK 1392312 T3	15-06-2009
		EP 1392312 A1	03-03-2004
		ES 2323301 T3	13-07-2009
		HR 20030533 A2	30-06-2005
		HU 0401047 A2	28-09-2004
		JP 2004517862 T	17-06-2004
		JP 2009102337 A	14-05-2009
		MX PA03006165 A	16-09-2003
		NO 20033146 A	09-09-2003
		NZ 527248 A	28-05-2004
		PL 363101 A1	15-11-2004
		RU 2317084 C2	20-02-2008
		US 2008234296 A1	25-09-2008
		US 2004097526 A1	20-05-2004
		US 2007049607 A1	01-03-2007
		YU 55503 A	25-05-2006
		ZA 200305087 A	12-07-2004