ALKYL AMINE DERIVATIVES OF SUBSTITUTED QUINOXALINE 2,3-DIONES AS GLUTAMATE RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

This invention is for novel glutamate receptor antagonists which are new compounds of the 5,6,7,8-substituted quinoxaline 2,3-diones type. The fused ring system is substituted at the a- or b-position by amino acid derivatives. The compounds are active as excitatory amino acid receptor antagonists acting at glutamate receptors, including either or both N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors such as the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and the kainate receptor. The invention also relates to the use of those quinoxaline-2,3-diones as neuroprotective agents for treating conditions such as cerebral ischemia or cerebral infarction resulting from a range of phenomena, such as thromboembolic or hemorrhagic stroke, cerebral vasospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma, as well as to treat chronic neurodegenerative disorders such as Alzheimer's Disease, Parkinsonism and Huntington's Disease, and as anticonvulsants. The compounds of the present invention may also be useful in the treatment of schizophrenia, epilepsy, anxiety, pain, and drug addiction. Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of the excitatory amino acids (EAA) glutamate and aspartate at the N-methyl-D-aspartate (NMDA) receptor, the α-amino-

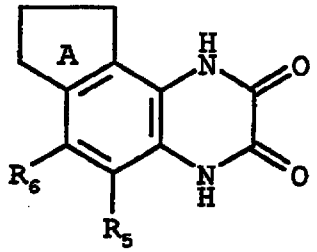
3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, and the kainate receptor. AMPA/kainate receptors may be referred to jointly as non-NMDA receptors. This excitotoxic action is considered responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma, as well as Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease.

Several classes of quinoxalinedione derivatives have been disclosed as glutamate (EAA) receptor antagonists. For example, among excitatory amino acid receptor antagonists recognized for usefulness in the treatment of disorders are those that block AMPA receptors (Bigge C.F. and Malone T.C., Curr. Opin. Ther. Pat., 1993:951; Rogawski M.A., TiPS, 1993;14:325). AMPA receptor antagonists have prevented neuronal injury in several models of global cerebral ischemia (Li H. and Buchan A.M., J. Cerebr. Blood Flow Metab., 1993;13:933; Nellgård B. and Wieloch T., J. Cerebr. Blood Flow Metab., 1992;12:2) and focal cerebral ischemia (Bullock R., Graham D.I., Swanson S., McCulloch J., J. Cerebr. Blood Flow Metab., 1994;14:466; Xue D., Huang Z.-G., Barnes K., Lesiuk H.J., Smith K.E., Buchan A.M., J. Cerebr. Blood Flow Metab., 1994;14:251). AMPA antagonists have also shown efficacy in models for analgesia (Xu X.-J., Hao J.-X, Seiger A., Wiesenfeld-Hallin Z., J. Pharmacol. Exp. Ther., 1993;267:140), and epilepsy (Namba T., Morimoto K., Sato K., Yamada N., Kuroda S., Brain Res., 1994;638:36; Brown S.E., McCulloch J., Brain Res., 1994;641:10; Yamaguchi S.I., Donevan S.D.,

Rogawski M.A., Epilepsy Res., 1993;15:179; Smith S.E., Durmuller N., Meldrum B.S., Eur. J. Pharmacol., 1991;201:179). AMPA receptor antagonists have also demonstrated promise in chronic neurodegenerative disorders such as Parkinsonism (Klockgether T., Turski L., Honoré T., Zhang Z., Gash D.M., Kurlan R., Greenamyre J.T., Ann. Neurol., 1993;34(4):585-593).

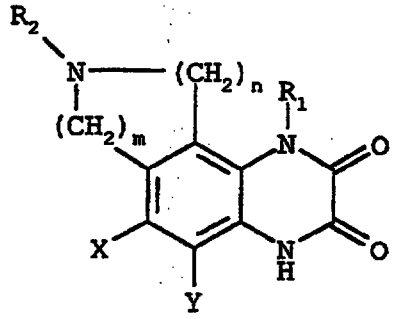
Excitatory amino acid receptor antagonists that block NMDA receptors are also recognized for usefulness in the treatment of disorders. NMDA receptors are intimately involved in the phenomenon of excitotoxicity, which may be a critical determinant of outcome of several neurological disorders. Disorders known to be responsive to blockade of the NMDA receptor include acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, neuropathic pain, and anxiety, and may be a significant causal factor in chronic neurodegenerative disorders such as Parkinson's disease (Klockgether T., Turski L., Ann. Neurol., 1993;34:585-593), human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (Francis P.T., Sims N.R., Procter A.W., Bowen D.M., J. Neurochem., 1993;60(5):1589-1604), and Huntington's disease. (See Lipton S., TINS, 1993;16(12):527-532; Lipton S.A., Rosenberg P.A., New Eng. J. Med., 1994;330(9):613-622; and Bigge C.F., Biochem. Pharmacol., 1993;45:1547-1561 and references cited therein.) NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control withdrawal symptoms from addictive drugs (Eur. Pat. Appl. 488,959A).

Copending United States Serial Number 08/124,770 discloses glutamate receptor antagonist quinoxalinedione derivatives represented by the formula:



wherein A is a 5 to 7 atom containing ring having a nitrogen which may be substituted by hydrogen, alkyl, or CH_2CH_2OH. This application does not disclose or suggest compounds having the instant amino as substituents, or the requisite methodology to prepare the same.

Copending application United States Serial Number 08/404,400 teaches glutamate receptor antagonists which are quinoxalinediones of formula



or a pharmaceutically acceptable salt thereof wherein

R_1 is hydrogen, an alkyl, or an alkylaryl;

X and Y are independently hydrogen, halogen, nitro, cyano, trifluoromethyl, COOH, $CONR_4R_5$, SO_2CF_3, SO_2R_4, $SONR_4R_5$, alkyl, alkenyl, $(CH_2)_zCONR_4R_5$, $(CH_2)_zCOOR_4$, or $NHCOR_4$, wherein R_4 and R_5 are independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl, or alkylaryl, and z is an integer from 0 to 4;

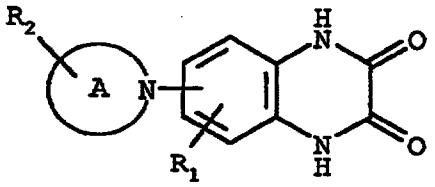
R_2 is $alkylCOOR_3$, alkylamine, alkylquanidine, aryl, alkylaryl, COalkyl, COalkylaryl, $CONR_3alkyl$, $CONR_3aryl$, $CONR_3alkylaryl$, $CSNR_3alkyl$, $CSNR_3alkylaryl$

or a common amino acid moiety joined by an amide bond, wherein R_3 is hydrogen, alkyl, or alkylaryl; and

m and n are independently 0, 1, or 2 provided that m + n is >1.

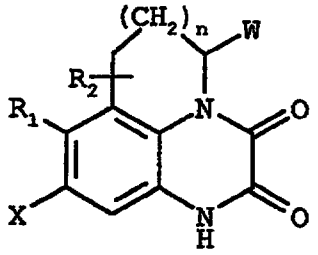
This application does not disclose or suggest the compounds of the instant invention having amines as substituents at the a- or b-positions nor the methodology to prepare them.

JP06228112-A discloses glutamate receptor antagonists which are quinoxaline-2,3(1H,4H)-dione derivatives of formula



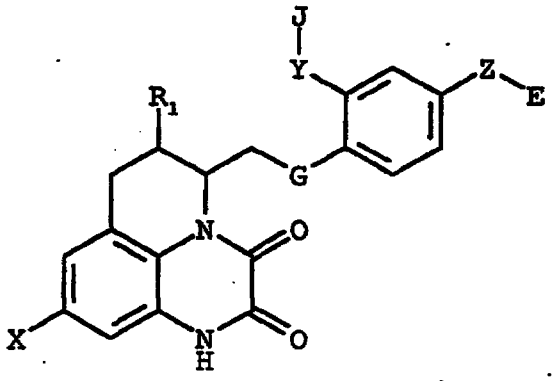
wherein R_1 is H, NO_2, or CF_3;
Ring A is a nitrogen-containing saturated heterocyclic group which may contain sulfur or oxygen;
R_2 is H, OH, lower alkoxy, COOH, lower alkoxy carbonyl, NH_2, or lower alkoxy carbonyl-amino. This reference does not teach or suggest the instant compounds which must be attached to the quinoxaline dione fused ring system by an alkylene.

WO 93/08188 covers a tricyclic quinoxalinedione of formula



as useful or selective antagonists of glutamate receptors.

European Patent Application 0627434 covers tricyclic quinoxalinedione of Formula I below which are selective antagonists of glycine binding site of the NMDA receptor



wherein X represents hydrogen, alkyl, halogen, cyano, trifluoromethyl, or nitro;

R_1 represents hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl;

G represents $-CONR_2-$ or $-NR_2CO-$, wherein R_2 represents hydrogen or alkyl;

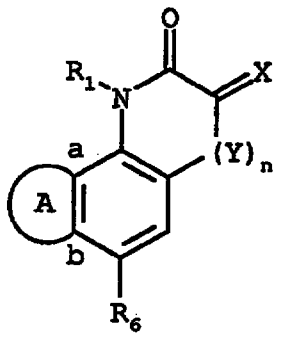
J represents an acidic group or a group which is convertible thereto in vivo;

E represents a basic group or a group which is convertible thereto in vivo;

Y represents a single bond, alkylene, alkenylene, substituted alkylene, or Y_1-Q-Y_2, wherein Y_1 represents a single bond or alkylene, Y_2 represents alkylene, and Q represents a heteroatom selected from oxygen or sulfur; and

Z represents alkylene.

WO 94/26747 discloses compounds of Formula I below as useful in the treatment of cerebrovascular disorder



wherein R_1 is hydrogen, alkyl or benzyl;

X is O or NOR_2, wherein R_2 is hydrogen, alkyl, or benzyl;

Y is N-R_4, wherein R_4 is hydrogen, OH, or alkyl;

n is 0 or 1;

R_6 is phenyl, naphthyl, thienyl, pyridyl, all of which may be substituted one or more times with substituents selected from the group consisting of halogen;

CF_3, NO_2, amino, alkyl, alkoxy, and phenyl; and

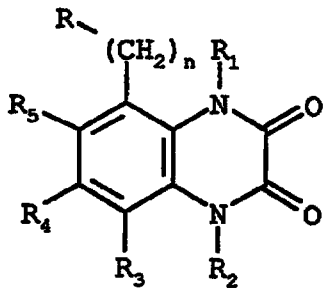
A is a ring of 5 to 7 atoms fused with the benzo ring at the positions marked a and b.

The compounds of the instant invention differ from the art in that they provide noncoplanar compounds with greater solubility and, therefore, better ability to penetrate the blood-brain barrier. These are important attributes in pharmaceuticals.

An object of this invention is to provide novel quinoxalinediones with amines at the a- or b-positions which function as antagonists.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by Formula I:



I

or a pharmaceutically acceptable salt thereof wherein R, R_1, R_2, R_3, R_4, R_5, R_{11}, R_{12}, and n are as described below.

The instant invention is also related to a pharmaceutical composition containing the compound defined by Formula I in an amount effective to treat cerebrovascular disorders responsive to the blockade of glutamate receptors (such as the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and the kainate receptor), and a pharmaceutically acceptable carrier. Exemplary disorders responsive to such treatment include cerebral ischemia caused by cerebral trauma, stroke, hypoglycemia, heart attack, and surgery; anxiety and schizophrenia; and chronic neurodegenerative disorders such as Huntington's disease, ALS, Parkinsonism, and Alzheimer's disease. The pharmaceutical composition of this invention may also be employed as an analgesic or the treatment of epilepsy.

The invention further relates to a method of treating cerebrovascular disorders responsive to antagonism of glutamate receptors NMDA by administering a compound of above-defined Formula I in a unit dosage form.

Another object of this invention is to provide a method of treating disorders responsive to the antagonism of glutamate or aspartate receptors in a

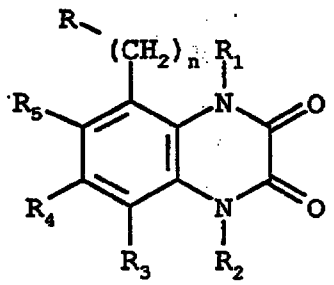
human by administering a pharmaceutically effective amount of the 2,3-quinoxalinediones of this invention.

Another object of this invention is to provide novel methods of preparing the 2,3-quinoxalinediones.

A further object of this invention is directed to novel intermediates useful in the preparation of the 2,3-quinoxalinediones of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The substituted quinoxaline-2,3-diones of the instant invention are those of Formula I



I

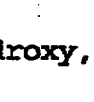
or a pharmaceutically acceptable salt thereof wherein R is a secondary or tertiary amine;

R_1 is hydrogen,
alkyl,
aralkyl,
carboxyalkyl,
phosphoroalkyl, or
phosphonoalkyl;

R_2 is hydrogen, hydroxy, or amino;

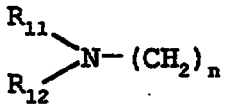
R_3 and R_4 are each independently
hydrogen,
alkyl,
alkenyl,
cycloalkyl,

halogen,
haloalkyl,
nitro,
cyano,
SO_2CF_3,
$C(O)R_6$,
$CH_2SO_2R_6$,
$(CH_2)_mCO_2R_9$ wherein R_9 is hydrogen, alkyl, aralkyl, or cycloalkyl,
$(CH_2)_mCONR_7R_8$,
$(CH_2)_mSO_2NR_7R_8$, or
$NHCOR_6$ wherein m is an integer of from 0 to 4,

R_6 is hydroxy, alkoxy, , alkyl, haloalkyl, aryl, aralkyl, and R_7 and R_8 are each independently selected from hydrogen, alkyl, cycloalkyl, aralkyl, or aryl;

R_5 is hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
halogen,
haloalkyl,
aryl,
aralkyl,
heteroaryl,
nitro,
cyano,
$-SO_2CF_3$,
$C(O)R_6$,
$(CH_2)_mCO_2R_9$,
$(CH_2)_mCONR_7R_8$,
$SONR_7R_8$, or

$NHCOR_6$ wherein m, R_7, and R_8 are as defined above;

R_5 may be at the a-position and  at the b-position on the ring; and

R_{11} and R_{12} are each independently

hydrogen,

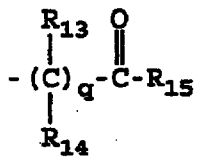
alkyl,

alkenyl,

alkynyl,

cycloalkyl,

heterocycloalkyl,



wherein q is an integer of from 0 to 3 and R_{13} and R_{14} are each independently selected from hydrogen, alkyl, aralkyl, cycloalkyl, and heteroalkyl and R_{15} is hydrogen, alkyl, aryl, aralkyl, heteroaralkyl, heteroaryl and $NR_{16}R_{17}$ wherein R_{16} and R_{17} are each independently selected from hydrogen, alkyl, and aryl,

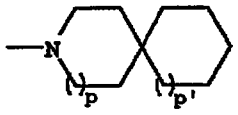
hydroxyalkyl,

aminoalkyl,

alkylaminoalkyl,

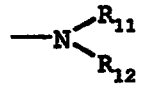
thioalkyl,

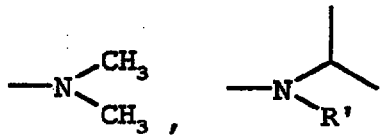




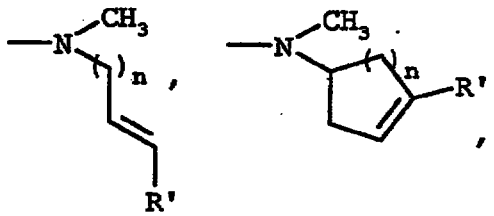
, wherein p and p' are each independently an integer selected from 0 and 1 and wherein in the second ring 1 or 2 carbon atoms can

be replaced by 1 or 2 heteroatoms selected from N, O, or S.

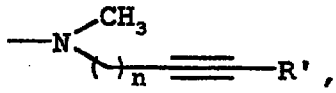
In  the R_{11} and R_{12} are not joined and are not amino acids. The group is a secondary or tertiary amine bearing substituted alkyl groups. These include hydrogen, alkyl, for example, the group can be



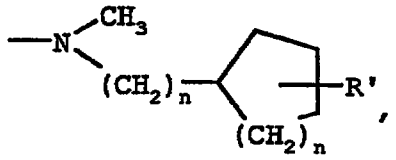
alkenylalkyl, alkylalkenylalkyl,



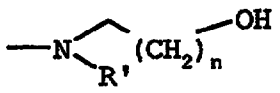
alkynylalkyl, alkylalkynylalkyl,

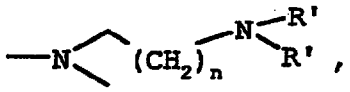


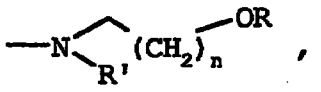
cycloalkyl,
nonaromatic heterocycloalkyl,



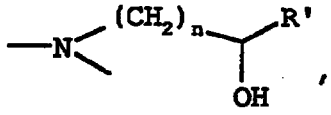
hydroxyalkyl,
alkylhydroxyalkyl,

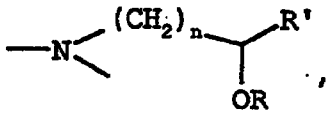


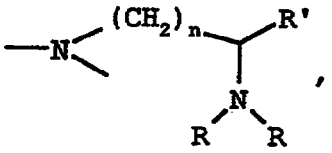




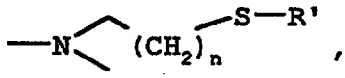
aminoalkyl,
alkylaminoalkyl,

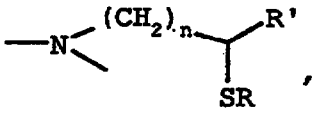


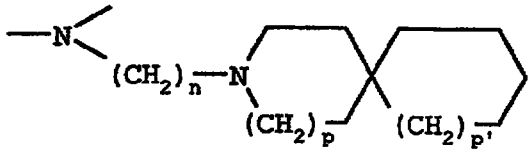


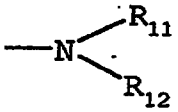


thioalkyl,
alkylthioalkyl,




, and



Preferred compounds are those of Formula I wherein R is  wherein R_{11} and R_{12} are each

independently
hydrogen,
alkyl,
cycloalkyl,
nonaromatic heterocycloalkyl,
R_{13} and R_{14} = independently hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl,



or
wherein q is an integer of from 0 to 3 and R_{15} is
hydrogen,
alkyl,
aralkyl,
aryl,
heteroaryl,
$NR_{16}R_{17}$ wherein R_{16} and R_{17} are each independently selected from
hydrogen,
alkyl, and
aryl.
More preferred compounds are those of Formula I wherein
R_{11} and R_{12} are each independently
hydrogen,
methyl,
ethyl,
propyl,
butyl,
cycloalkyl,
heterocycloalkyl,
alkylaminoalkyl,
aminoalkyl,
hydroxyalkyl, and
alkoxyalkyl.

Still more preferred compounds are those of Formula I wherein

R_{11} and R_{12} are each independently

hydrogen,

methyl,

ethyl,

propyl,

butyl, or

cyclohexyl;

R_1 is hydrogen;

R_2 is hydrogen;

R_3 and R_4 are each independently hydrogen or nitro; and

R_5 is methyl.

The most preferred compounds are selected from:

5-Diethylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;

5-Dipropylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;

5-Dibutylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;

5-Cyclohexylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;

5-[(Cyclohexyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione; and

5-Dimethylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione.

The compounds of Formula I are capable of forming pharmaceutically acceptable acid addition salts.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids,

aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention may exist as a mixture of cis and trans isomers or R- and S- isomers, or as the individual cis and trans

isomers or R- and S- isomers. The mixture of isomers as well as the individual isomers are intended to be encompassed within the scope of the present invention.

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

The term "carboxyalkyl" means alkyl as above and attached to a carboxy group.

The term "phosphoroalkyl" means alkyl as above and attached to a phosphoro group.

The term "phosphonoalkyl" means alkyl as above and attached to a phosphoro group.

The term "alkenyl" means a straight or branched unsaturated hydrocarbon radical having from 3 to 6 carbon atoms and includes, for example, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, and the like.

The term "alkynyl" means a straight or branched chain alkynyl group of 2 to 6 carbon atoms, for example, but not limited to ethynyl, 2,3-propynyl, 2,3- or 3,4-butylnyl.

"Alkoxy" is O-alkyl of from 1 to 6 carbon atoms as defined above for "alkyl".

The term "aryl" means an aromatic radical which is a phenyl group, a phenyl group substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, halogen, trifluoromethyl, amino, alkylamino as defined above for alkyl, dialkylamino as defined for alkyl, or 1,3-benzodioxol-5-yl.

The term "aralkyl" means aryl and alkyl as defined above and includes but is not limited to benzyl,

2-phenylethyl, 3-phenylpropyl; a preferred group is benzyl.

The term "heteroaryl" means a heteroaromatic radical which is 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-pyrimidinyl, or 2-, or 3-thienyl.

"Halogen" is fluorine, chlorine, bromine, or iodine.

The term "haloalkyl" is halogen and alkyl as defined above such as, but not limited to, trifluoromethyl and trichloromethyl.

"Alkylaryl" means aryl as defined above and alkyl as defined above, for example, but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl; a preferred group is benzyl.

The term "heterocycloalkyl" means an alicyclic ring with one or more atoms substituted by a heteroatom, i.e., N, O, and S.

Spiro rings include but are not limited to 5- or 6-membered rings are replaced by a heteroatom selected from N, O, and S.

The second ring may also be a gemdialkyl group instead of a ring.

The compounds of the invention exhibit valuable biological properties because of their strong excitatory amino acid (EAA) antagonizing properties at one of several binding sites on glutamate receptors: the AMPA ((RS)--amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (or kainic acid) binding site on AMPA (non-NMDA) receptors) or the glycine site of NMDA receptors.

The compounds of the present invention exhibit binding affinity for the AMPA receptors as described by Honoré T., et al., Neuroscience Letters, 1985;54:27-32. Preferred compounds demonstrate IC_{50} values <100 μM in this assay. The compounds of the present invention exhibit binding affinity for the kainate site (non-NMDA

receptor) as described by London E.D. and Coyle J., Mol. Pharmacol., 1979;15:492. The compounds of the present invention exhibit binding affinity for the glycine site of the NMDA receptor as described by Jones S.M., et al., Pharmacol. Methods, 1989;21:161. To measure functional AMPA antagonist activity, the effects of the agent on AMPA-induced neuronal damage in primary cortical neuronal cultures was examined using techniques similar to those outlined by Koh J.-Y., et al., J. Neurosci., 1990;10:693. In addition, the neuronal damage produced by long-term exposure to 100 μM AMPA may be measured by the release of the cytosolic enzyme lactate dehydrogenase (LDH).

Selected compounds of the present invention were tested by one or more of the above-described assays. The data obtained in these assays is set forth in Table 1. The IC_{50} values set forth in Table 1 are a measure of the concentration (μM) of the test substance which inhibits 50% of an induced release from the tested receptors.

TABLE 1. Quinoxalinediones

Compound Number	IC_{50} μM	
	AMPA	KA
1	1.501	4.483
2	0.689	6.647
3	1.631	24.93
4	4.643	20.50
5	1.264	5.128
6	3.226	5.331
7	1.15	8.23

Additionally, a preliminary indicator of in vivo CNS activity related to anticonvulsant activity and potential neuroprotection, is a maximal electroshock

(MES) assay in CF-1 strain mice (20-25 g) performed with corneal electrodes by conventional methods as described previously (Krall, et al., Epilepsia, 1988;19:409-428). The compounds of this invention generally demonstrate ED_{50} values of <50 mg/kg.

MES (IV) Data for Compound 1 from Table 1

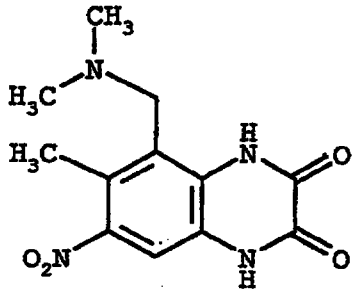


TABLE 2. Compound 1; MES Data

Time (min)	Dose (mg/kg)	Protected (%)	Ataxic (%)
3	10	40	0
	30	60	20
30	10	60	40
	30	80	40

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable

solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprises conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing 10 mg of active ingredients or, more broadly, 0.1 to 100 mg per tablet, and accordingly suitable representative unit dosage forms.

Solid forms of pharmaceutical compositions for PO administration and injectable solutions are preferred.

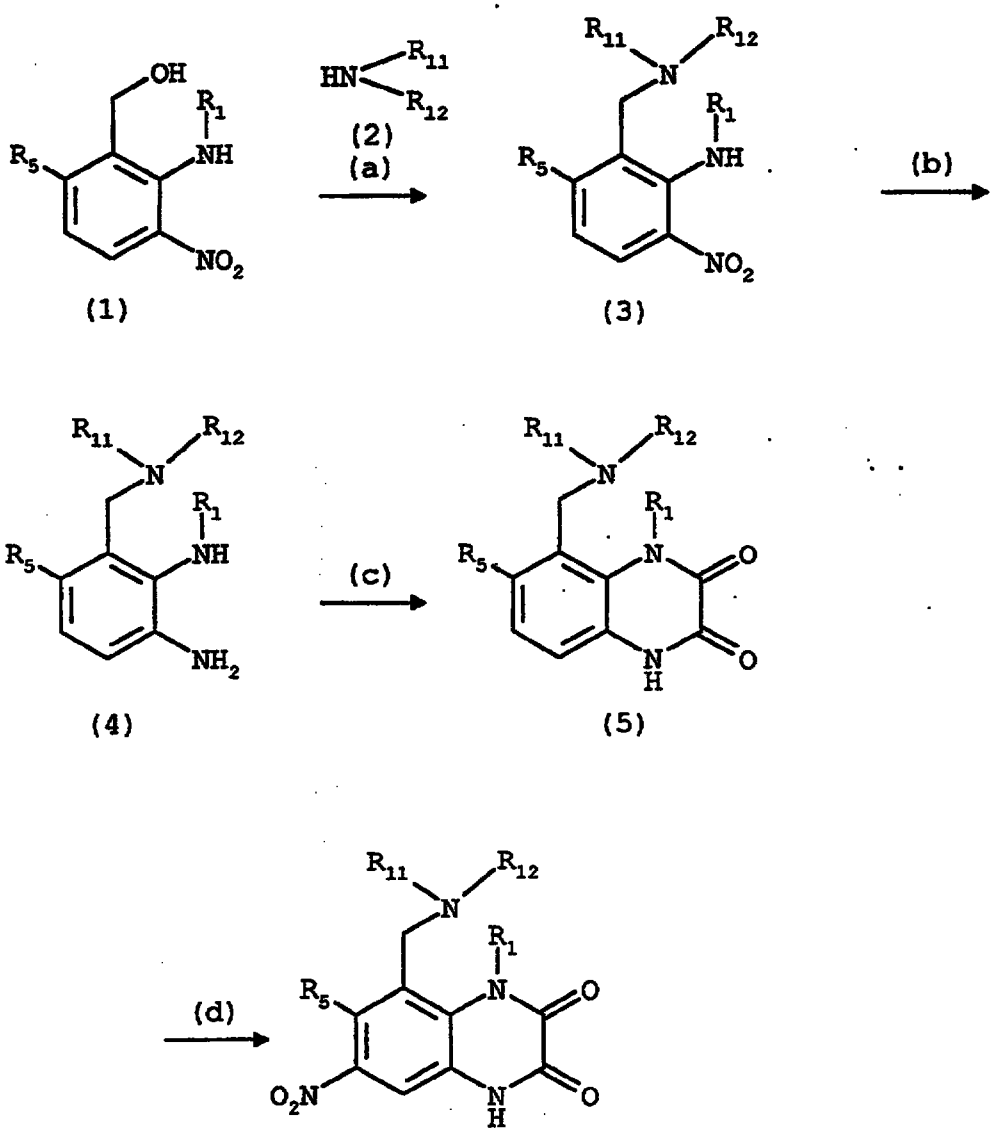
The compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the biological activity of the compounds. This includes especially excitatory amino-acid-dependent psychosis, excitatory amino-acid-dependent anoxia, excitatory amino-acid-dependent ischemia, excitatory amino-acid-dependent Parkinsonism, excitatory amino-acid-dependent convulsions, and excitatory amino-acid-dependent migraine. Suitable dosage ranges are 0.1 to 1000 mg daily, 10 to 50 mg daily, and especially 30 to 100 mg daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved, and the body weight of the subject involved, and further, the preference and experience of the physician or veterinarian in charge.

The schemes and examples which follow are intended as an illustration of certain preferred embodiments of

the invention, and no limitation of the invention is implied.

General Schemes I and II illustrate the preparation of compounds when R_4 is nitro; however, nitration step can be substituted by other electrophiles for aromatic electrophilic substitution.

General Scheme I



Step (a) of Scheme I above involves reacting nitroaniline derivative of Formula (1) with amine as depicted in Formula (2) in the presence of triarylphosphine, preferably triphenylphosphine and diester of diazodicarboxylate, preferably diethyldiazodicarboxylate in a solution of a hydrocarbon solvent like benzene or ether solvent like THF, preferably benzene at temperatures around 5°C.

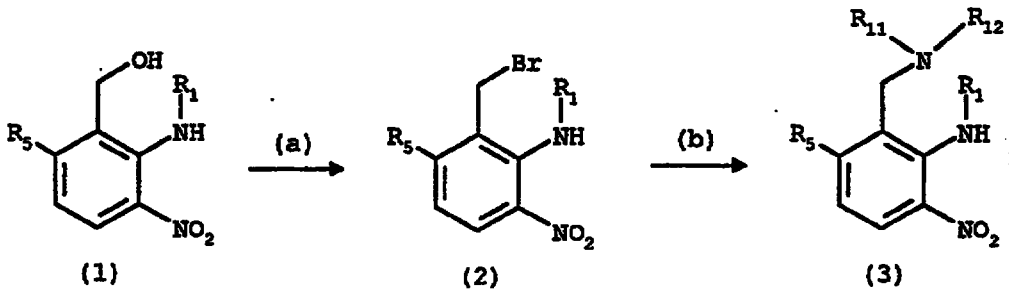
The reaction mixture is stirred for 2 to 16 hours and monitored by TLC (SiO_2, pet. ether:EtOAc, 1:1). Solvent is evaporated under reduced pressure and product isolated by column chromatography (SiO_2, mixture of pet. ether and EtOAc).

Step (b) involves reducing the nitroaniline derivative of Formula (3) via hydrogenolysis (H_2, around 50 psi) in the presence of a catalyst like Ra Ni or Pd/C, preferably Ra Ni in a hydroxylated solvent like methanol. The catalyst is filtered off and the filtrate evaporated to give the o-phenylenediamine derivative, which is used in the next step without additional purification.

Step (c) involves reacting the o-phenylenediamine derivative as shown in Formula (4) with oxalic acid derivative like dimethyl oxalate in a hydroxylated solvent like methanol at refluxing temperatures for 12 to 24 hours. The reaction mixture is partially evaporated to give crude product, which is purified by crystallization.

Step (d) involves reacting the quinoxaline-2,3-dione derivative shown in Formula (5) with a nitrating mixture, preferably KNO_3 and sulfuric acid or TFA at temperatures ranging from 0°C to room temperature. The reaction mixture is poured over ice, and the solid obtained is purified by crystallization or column chromatography (SiO_2, pet. ether:EtOAc mixture).

Scheme II



(1) (2) (3)

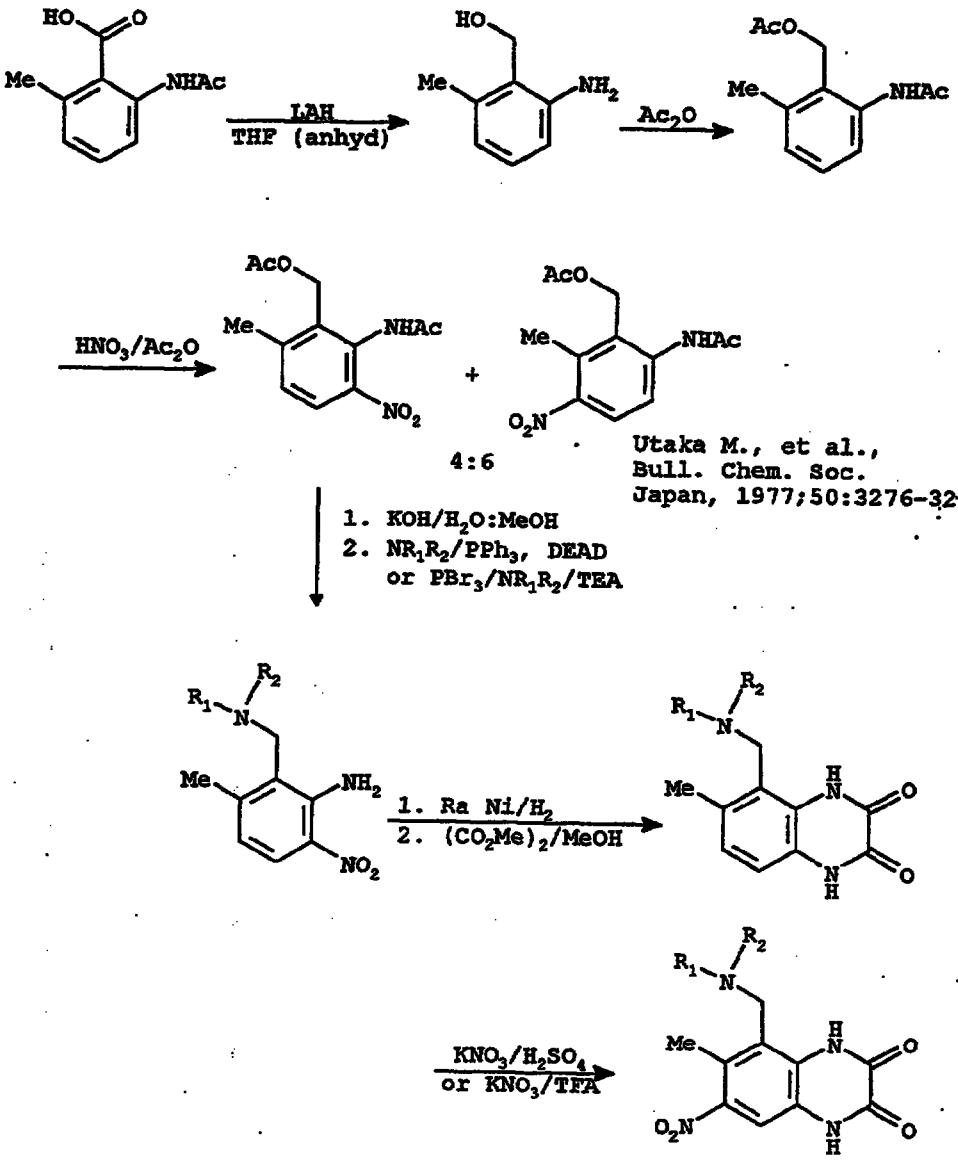
Step (a) in Scheme II above involves bromination of the nitroaniline derivative shown in Formula (1) with brominating agents like CBr_4/PPh_3 or PBr_3 in a solvent like ether. The volatile materials are evaporated under reduced pressure and the crude product is used directly in Step (b) or purified by column chromatography (SiO_2, pet. ether:EtOAc mixture).

Step (b) involves reacting the benzyl bromide derivative shown in Formula (2) with appropriate amino compound shown in Structure (3) in the presence of a base like triethylamine in an ether solvent like THF at temperatures ranging from 10-60°C. The reaction mixture is evaporated to under reduced pressure and quenched with water. Product extracted with a solvent like EtOAc. Final product is purified by column chromatography (SiO_2, pet. ether:EtOAc).

Formula (3) in Scheme II cannot be further derivatized to 4, 5, and 6 in Scheme I.

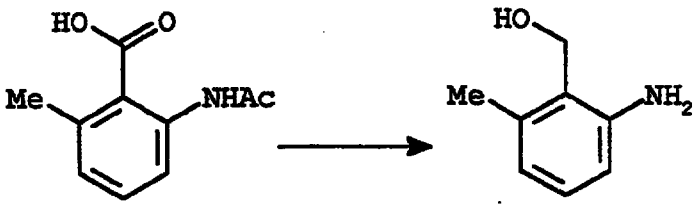
These general experimental schemes cover most of the final products of the invention. Others are made by known experimental procedures.

SCHEME 1



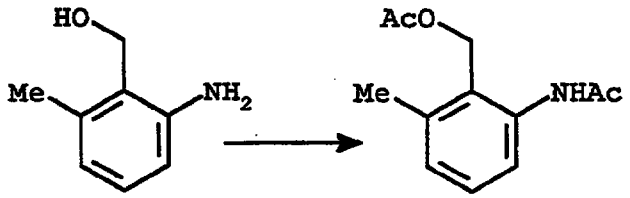
Utaka M., et al., Bull. Chem. Soc. Japan, 1977;50:3276-3280.

Scheme 1



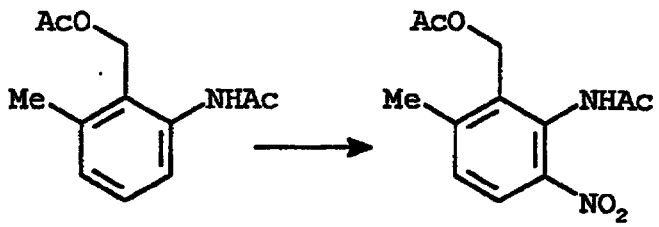
(2-Amino-6-methyl-phenyl)-methanol

2-Amino-6-methyl-benzoic acid (45 g, 300 mmol) was suspended in ether and LAH (13.26 g, 350 mmol), was added portionwise. The reaction mixture was stirred at room temperature for 4 hours and quenched with aqueous NH_4Cl. Reaction mixture was filtered, and the filtrate was extracted with ether (3 x 200 mL). The wet cake was also washed with ether (200 mL), and the ether solutions were pooled together and washed with water (200 mL) and dried over $MgSO_4$. Solvent was evaporated to give a crystalline product (19.04 g, 46%), mp 78-81°C; MS (CI): M+1 = 138.



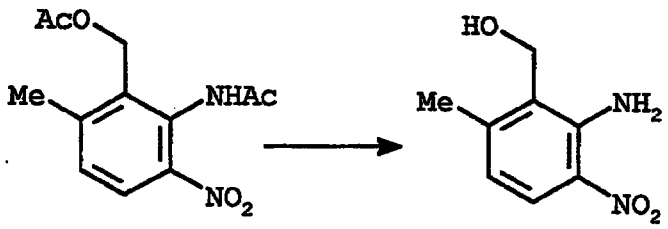
Acetic acid 2-acetylamino-6-methyl-benzyl ester

A solution of 2-amino-6-methyl-phenyl)-methanol (19.04 g, 138.9 mmol) in acetic anhydride (100 mL) was heated to 50°C for 2 hours. Excess acetic anhydride removed under vacuum to give a pale brown solid, crystallized from CCl_4 (29.8 g, 97%), mp 118-119°C (rep. 118-118.5°C); MS (CI): M+1 = 222.



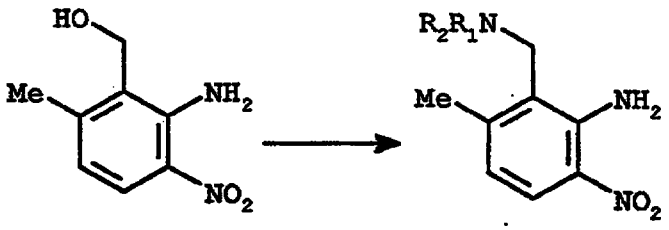
Acetic acid 2-acetylamino-6-methyl-3-nitro-benzyl ester

To a solution of acetic acid 2-acetylamino-6-methyl-benzyl ester in acetic acid (400 mL) nitric acid (60%, 16 mL) was added dropwise keeping temperature below 5°C, under stirring. Reaction mixture was stirred for additional 2 hours at room temperature and poured in ice water and stirred for 0.5 hours. Brown oil separated which on treatment with ethyl acetate (50 mL) gave buff needles, (7.65 g, 18.5%), mp 148-149°C (rep. 147-148°C); MS (CI): M+1 = 267.



(2-Amino-6-methyl-3-nitro-phenyl)-methanol

Acetic acid 2-acetylamino-6-methyl-3-nitro-benzyl ester (7 g, 26.2 mmol) was dissolved in methanolic KOH (0.5N). The solution was evaporated after 1 hour of stirring at room temperature. Product was extracted in EtOAc (150 mL), washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent gave orange needles (4.45 g, 93.4%), mp 134-136°C (rep. 135-136°C).



General method for the preparation of 2-(disubstituted aminomethyl-3-methyl-6-nitro-phenylamine

To a suspension of (2-amino-6-methyl-3-nitro-phenyl)-methanol (1 eq.) and PPh_3 (1.5 eq.) in benzene (10 mL), diethyl azodicarboxylate (DEAD) (1.5 eq.) was added under nitrogen and 5°C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The dark reaction mixture was concentrated under vacuum, and the residue was chromatographed over silica gel (hexanes:ethyl acetate, 95:5 to 75:25) to give the desired product. Various derivatives synthesized are listed in Table 1 below.

TABLE 1

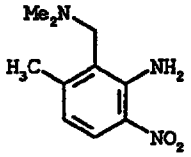
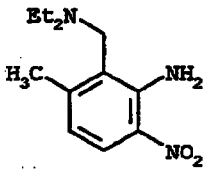
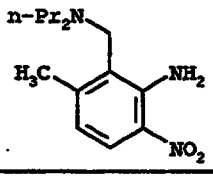
Compound	Structure	Yield (%)	MS (CI, M+1)
2-Dimethylaminomethyl-3-methyl-6-nitro-phenylamine		86	210
2-Diethylaminomethyl-3-methyl-6-nitro-phenylamine		45	238
2-Dipropylaminomethyl-3-methyl-6-nitro-phenylamine		56	266

TABLE 1 (cont'd)

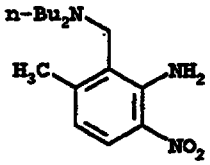
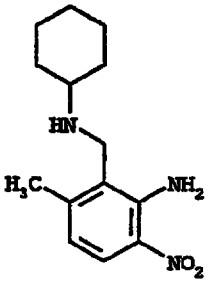
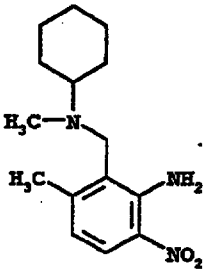
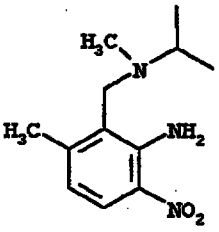
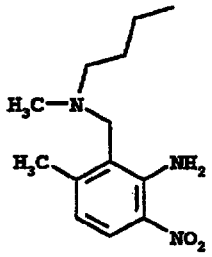
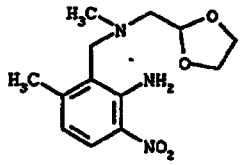
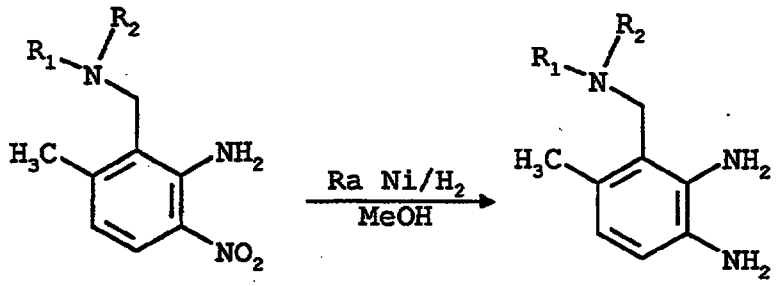
Compound	Structure	Yield (%)	MS (CI, M+1)
2-Dibutylaminomethyl-3-methyl-6-nitro-phenylamine		51	294
2-Cyclohexylamino methyl-3-methyl-6-nitro-phenylamine		50	264
2-[(Cyclohexyl-methyl-amino)-methyl]-3-methyl-6-nitro-phenylamine		60	278
2-[(Isopropyl-methyl-amino)-methyl]-3-methyl-6-nitro-phenylamine		43	238

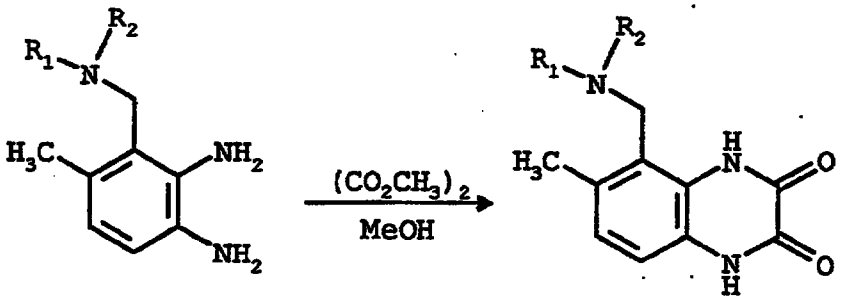
TABLE 1 (cont'd)

Compound	Structure	Yield (%)	MS (CI, M+1)
2-[(Butyl-methyl-amino)-methyl]-3-methyl-6-nitro-phenylamine		64	252
2-[([1,3]Dioxolan-2-ylmethyl-methyl-amino)-methyl]-3-methyl-6-nitro-phenylamine		53	282



General method for preparation of 3-dialkylamino-methyl-4-methyl-benzene-1,2-diamine

A solution of 2-(disubstituted aminomethyl-3-methyl-6-nitro-phenylamine (1 eq., approx. 5 mmol) in methanol (75 mL) was hydrogenated (CH_2, 50 psi) in a Parr apparatus. The reaction was monitored by TLC (SiO_2, pet. ether:EtOAc, 1:1) and filtered on completion. The filtrate was concentrated, and the product obtained was used further without additional purification.



General method for the preparation of 5-dialkylamino methyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione

A solution of 3-dialkylaminomethyl-4-methyl-benzene-1,2-diamine (1 eq.) and dimethyl oxalate (1.5 eq.) in methanol (35 mL) was heated to reflux for 16 hours. The reaction mixture was partially evaporated to give the product as a solid, which was used further without additional purification. The compounds synthesized are listed in Table 2 below.

TABLE 2

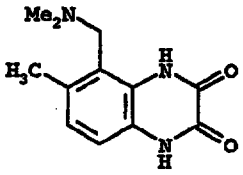
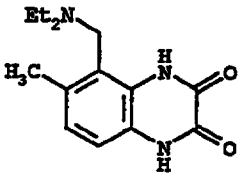
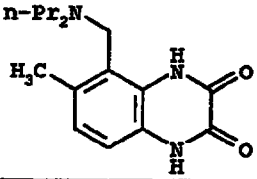
Compound	Structure	Yield (%)	MS (CI M+1)
5-Dimethylaminomethyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		39	234
5-Diethylaminomethyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		66	262
5-Dipropylaminomethyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		38	290

TABLE 2 (cont'd)

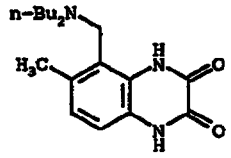
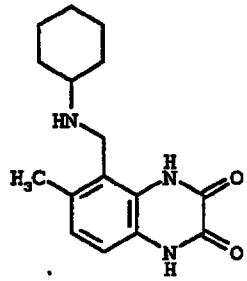
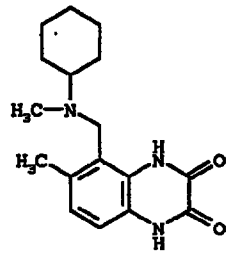
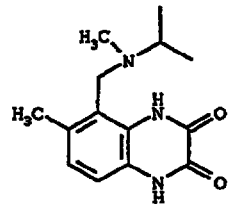
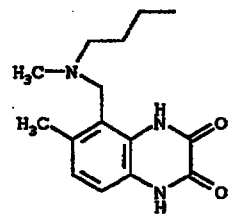
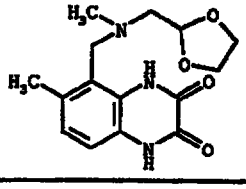
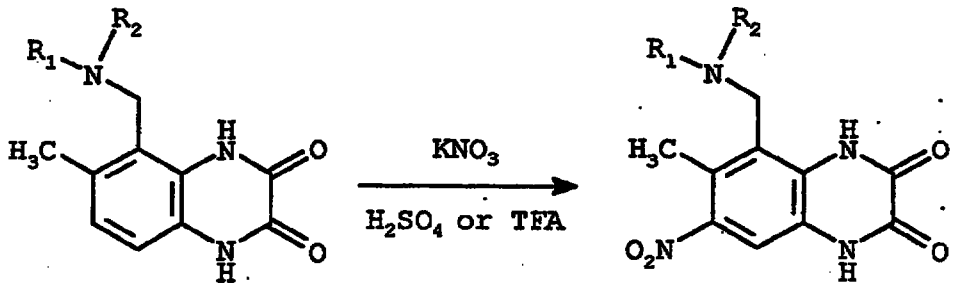
Compound	Structure	Yield (%)	MS (CI M+1)
5-Dibutylaminomethyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		18	318
5-Cyclohexylamino methyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		62	288
5-[(Cyclohexyl-methyl-amino)-methyl]-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		75	302
5-[(Isopropyl-methyl-amino)-methyl]-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		95	202
5-[(Butyl-methyl-amino)-methyl]-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		45	276

TABLE 2 (cont'd)

Compound	Structure	Yield (%)	MS (CI M+1)
5-[([1,3]Dioxolan-2-ylmethyl-methyl-amino)-methyl]-6-methyl-1,4-dihydro-quinoxaline-2,3-dione		38	306



General method for the preparation of 5-dialkylamino methyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione

To a solution of 5-dialkylaminomethyl-6-methyl-1,4-dihydro-quinoxaline-2,3-dione (1 eq., approx. 2-5 mmol) in concentrated H_2SO_4 (5 mL) or TFA (5 mL), KNO_3 was added at 0°C under stirring. In case of H_2SO_4 as a solvent, reaction mixture was poured over ice and the solid obtained crystallized or passed through a column (SiO_2, $CHCl_3$, and $CHCl_3$:MeOH 95:5) to give pure product. With TFA as a solvent, excess TFA was evaporated (<35°C) and solid obtained purified as mentioned above after neutralization with NH_3.

The compounds synthesized are listed in Table 3 below.

TABLE 3

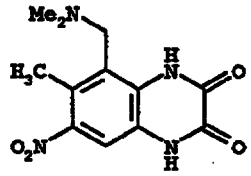
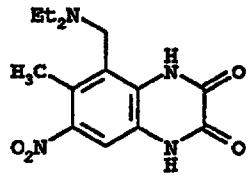
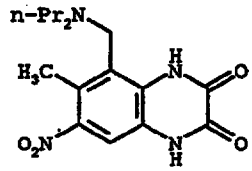
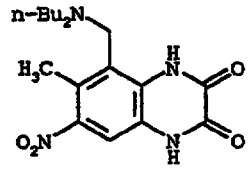
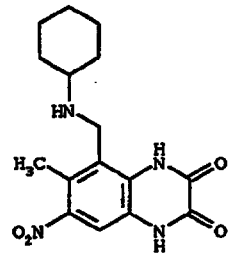
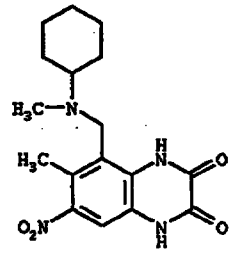
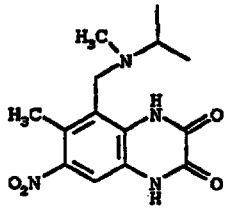
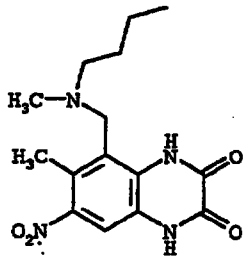
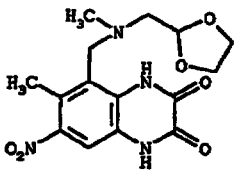
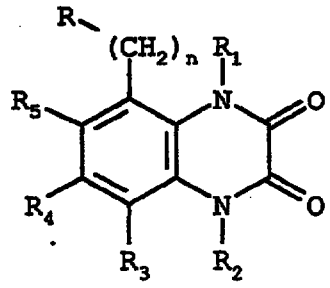
Compound	Structure	Yield (%)	MS (CI, M+1)
5-Dimethylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		55	279
5-Diethylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		33	307
5-Dipropylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		60	335
5-Dibutylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		39	363
5-Cyclohexylamino methyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		37	333
5-[(Cyclohexyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		63	347

TABLE 3 (cont'd)

Compound	Structure	Yield (%)	MS (CI, M+1)
5-[(Isopropyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		82	307
5-[(Butyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		85	321
5-[([1,3]Dioxolan-2-ylmethyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione		52	351

CLAIMS

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein

R is a secondary or tertiary amine;

R_1 is hydrogen,
alkyl,
aralkyl,
carboxyalkyl,
phosphoroalkyl, or
phosphonoalkyl;

R_2 is hydrogen, hydroxy, or amino;

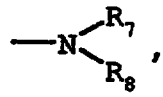
R_3 and R_4 are each independently
hydrogen,
alkyl,
alkenyl,
cycloalkyl,
halogen,
haloalkyl,
nitro,
cyano,
SO_2CF_3,
$C(O)R_6$,
$CH_2SO_2R_6$,

* C L M S *

$(CH_2)_mCO_2R_9$ wherein R_9 is hydrogen, alkyl, aralkyl, or cycloalkyl,

$(CH_2)_mCONR_7R_8$,

$(CH_2)_mSO_2NR_7R_8$, or

$NHCOR_6$ wherein m is an integer of from 0 to 4, R_6 is hydroxy, alkoxy, , alkyl, haloalkyl, aryl, aralkyl, and R_7 and R_8 are each independently selected from hydrogen, alkyl, cycloalkyl, aralkyl, or aryl;

R_5 is hydrogen,

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

halogen,

haloalkyl,

aryl,

aralkyl,

heteroaryl,

nitro,

cyano,

SO_2CF_3,

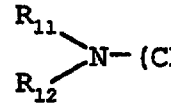
$C(O)R_6$,

$(CH_2)_mCO_2R_9$,

$(CH_2)_mCONR_7R_8$,

$SONR_7R_8$, or

$NHCOR_6$ wherein m, R_7, and R_8 are as defined above;

R_5 may be at the a-position and  at the b-position on the ring; and

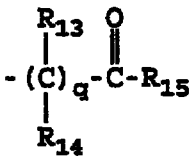
R_{11} and R_{12} are each independently

hydrogen,

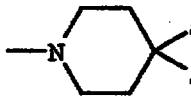
alkyl,

* C L M S *

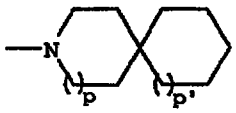
alkenyl,
alkynyl,
cycloalkyl,
heterocycloalkyl,



wherein q is an integer of from 0 to 3 and R_{13} and R_{14} are each independently selected from hydrogen, alkyl, aralkyl, cycloalkyl, and heteroalkyl and R_{15} is hydrogen, alkyl, aryl, aralkyl, heteroaralkyl, heteroaryl and $NR_{16}R_{17}$ wherein R_{16} and R_{17} are each independently selected from hydrogen, alkyl, and aryl,
hydroxyalkyl,
aminoalkyl,
alkylaminoalkyl,
thioalkyl,

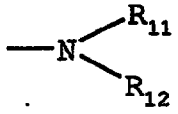


,



, wherein p and p' are each independently an integer selected from 0 and 1 and wherein in the second ring 1 or 2 carbon atoms can be replaced by 1 or 2 heteroatoms selected from N, O, or S.

2. A compound according to Claim 1 wherein

R is  wherein R_{11} and R_{12} are each

independently
hydrogen,
alkyl,
cycloalkyl,
nonaromatic heterocycloalkyl,
R_{13} and R_{14} = independently hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl,



or
wherein q is an integer of from 0 to 3 and
R_{15} is
hydrogen,
alkyl,
aralkyl,
aryl,
heteroaryl,
$NR_{16}R_{17}$ wherein R_{16} and R_{17} are each independently selected from
hydrogen,
alkyl, and
aryl.

3. A compound according to Claim 2 wherein R_{11} and R_{12} are each independently
hydrogen,
methyl,
ethyl,
propyl,
butyl, or
cycloalkyl,
heterocycloalkyl,
alkylaminoalkyl,
aminoalkyl,
hydroxyalkyl, and
alkoxyalkyl.

* C L M S *

4. A compound according to Claim 2 wherein R_{11} and R_{12} are each independently
hydrogen,
methyl,
ethyl,
propyl,
butyl, or
cyclohexyl;
R_1 is hydrogen;
R_2 is hydrogen;
R_3 and R_4 are each independently hydrogen or nitro; and
R_5 is methyl.

5. A compound according to Claim 2, selected from
5-Diethylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;
5-Dipropylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;
5-Dibutylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;
5-Cyclohexylaminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione;
5-[(Cyclohexyl-methyl-amino)-methyl]-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione.

6. A compound according to Claim 2 named 5-Dimethyl aminomethyl-6-methyl-7-nitro-1,4-dihydro-quinoxaline-2,3-dione.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 together with a pharmaceutically acceptable carrier in unit dosage form.

* C L M S *

8. A method for treating disorders responsive to the blockade of glutamate receptors in a patient suffering therefrom which comprises administering a composition according to Claim 1.

9. A method for treating stroke which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

10. A method for treating cerebral hypoxia/ischemia which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

11. A method for treating Alzheimer's disease which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

12. A method for treating Parkinsonism which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

13. A method for treating Huntington's disease which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

14. A method for treating disorders responsive to anticonvulsants which comprises administering a therapeutically effective amount of a compound according to Claim 1 to a patient in need of said treatment.

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(57) Abstract

A novel series of substituted quinoxaline 2,3-diones useful as neuroprotective agents are taught. Novel intermediates, processes of preparation, and pharmaceutical compositions containing the compounds are also taught. The compounds are glutamate antagonists and are useful in the treatment of stroke, cerebral ischemia, or cerebral infarction resulting from thromboembolic or hemorrhagic stroke, cerebral vasospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia, Alzheimer's, Parkinson's, and Huntington's diseases.