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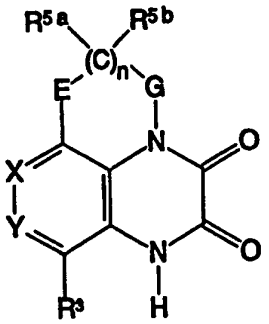
(54) Title: 4,5-BRIDGED QUINOXALINEDIONES AND QUINOLONES AND THE USE THEREOF AS EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

(57) Abstract

The present invention provides tricyclic quinoxalinediones that have high binding to the glycine receptor. Many of the compounds have structure (1), wherein each of the variables is defined in the specification. Methods of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia, and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, treating or preventing the adverse consequences of the hyperactivity of the excitatory amino acids, as well as treating anxiety, chronic pain, convulsions, and inducing anesthesia are disclosed by administering to an animal in need of such treatment a compound of formula (I) or a pharmaceutically acceptable salt thereof.



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4,5-Bridged Quinoxalinediones and Quinolones and the Use Thereof as Excitatory Amino Acid Receptor Antagonists

Background of the Invention

Field of the Invention

The present invention is in the field of medicinal chemistry and relates to compounds that exhibit high affinity for the strychnine-insensitive glycine binding site and that do not exhibit PCP side effects. In particular, the present invention relates to novel 4,5-bridged tricyclic quinoxaline-2,3-diones and pyridine (N-oxide) analogs thereof, and their use to treat or prevent neuronal degeneration associated with ischemia, pathophysiologic conditions associated with neuronal degeneration, convulsions, anxiety, chronic pain, and to induce anesthesia.

Description of the Related Art

Cells of the central and peripheral nervous system (neurons), are irreplaceable. Neuronal cell death caused by injury or disease can result in tragic consequences. Excitotoxicity refers to an excess concentration of excitatory amino acids (EAAs) which kills neurons. Excitotoxicity is involved in both acute neurological disorders, such as stroke, epilepsy and head and spinal cord trauma, and chronic neurodegenerative disorders, such as Parkinsonism, Huntington's Disease and amyotrophic lateral sclerosis (ALS). (Bigge & Boxer, *Ann. Rep. Med. Chem. 29*:13-22 (1994)). An excess concentration of EAAs leads to an overstimulation of ligand-gated calcium ion channels (the N-methyl-D-aspartate (NMDA) receptors). The resulting massive influx of calcium ions leads to neuronal cell death. A strategy for

combatting neuronal cell death is to interrupt early physiological events brought about by either an acute insult or chronic stress. One such strategy is to employ an antagonist of an excitatory amino acid receptor.

Glutamate is thought to be the major excitatory amino acid in the brain. There are three major subtypes of glutamate receptors in the CNS. These are commonly referred to as kainate, AMPA, and N-methyl-D-aspartate (NMDA) receptors (Watkins and Olverman, *Trends in Neurosci. 7*:265-272 (1987)). NMDA receptors are found in the membranes of virtually every neuron in the brain. NMDA receptors are ligand-gated cation channels that allow Na^+, K^+, and Ca^{++} to permeate when they are activated by glutamate or aspartate (non-selective, endogenous agonists) or by NMDA (a selective, synthetic agonist) (Wong and Kemp, *Ann. Rev. Pharmacol. Toxicol. 31*:401-425 (1991)).

Glutamate alone cannot activate the NMDA receptor. In order to become activated by glutamate, the NMDA receptor channel must first bind glycine at a specific, high affinity, glycine binding site that is separate from the glutamate/NMDA binding site on the receptor protein (Johnson and Ascher, *Nature 325*:329-331 (1987)). Glycine is therefore an obligatory co-agonist at the NMDA receptor/channel complex (Kemp, J.A., *et al.*, *Proc. Natl. Acad. Sci. USA 85*:6547-6550 (1988)).

In addition to the binding sites for glutamate/NMDA and glycine, the NMDA receptor carries a number of other functionally important binding sites. These include binding sites for Mg^{++}, Zn^{++}, polyamines, arachidonic acid, and phencyclidine (PCP) (Reynolds and Miller, *Adv. in Pharmacol. 21*:101-126 (1990); Miller, B., *et al.*, *Nature 355*:722-725 (1992)). The PCP binding site--now commonly referred to as the PCP receptor--is located inside the pore of the ionophore of the NMDA receptor/channel complex (Wong, E.H.F., *et al.*, *Proc. Natl. Acad. Sci. USA 83*:7104-7108 (1986); Huettner and Bean, *Proc. Natl. Acad. Sci. USA 85*:1307-1311 (1988); MacDonald, J.F., *et al.*, *Neurophysiol. 58*:251-266 (1987)). In order for PCP to gain access to the PCP receptor, the channel must first be opened by glutamate and

glycine. In the absence of glutamate and glycine, PCP cannot bind to the PCP receptor although some studies have suggested that a small amount of PCP binding can occur even in the absence of glutamate and glycine (Sircar and Zukin, *Brain Res. 556*:280-284 (1991)). Once PCP binds to the PCP receptor, it blocks ion flux through the open channel. Therefore, PCP is an open channel blocker and a non-competitive glutamate antagonist at the NMDA receptor/channel complex.

One of the most potent and selective drugs that bind to the PCP receptor is the anticonvulsant drug MK801. This drug has a K_d of approximately 3nM at the PCP receptor (Wong, E.H.F., *et al.*, *Proc. Natl. Acad. Sci. USA 83*:7104-7108 (1986)).

Both PCP and MK801 as well as other PCP receptor ligands, *e.g.*, dextromethorphan, ketamine, and N,N'-disubstituted guanidines, have neuroprotective efficacy both *in vitro* and *in vivo* (Gill, R., *et al.*, *J. Neurosci. 7*:3343-3349 (1987); Keana, J.F.W., *et al.*, *Proc. Natl. Acad. Sci. USA 86*:5631-5635 (1989); Steinberg, G.K., *et al.*, *Neuroscience Lett. 89*: 193-197 (1988); Church, J., *et al.*, In: *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*, Domino and Kamenka, eds., Ann Arbor: NPP Books, pp. 747-756 (1988)). The well-characterized neuroprotective efficacy of these drugs is largely due to their capacity to block excessive Ca^{++} influx into neurons through NMDA receptor channels, which become over activated by excessive glutamate release in conditions of brain ischemia (*e.g.* in stroke, cardiac arrest ischemia etc.) (Collins, R.C., *Metabol. Br. Dis. 1*:231-240 (1986); Collins, R.C., *et al.*, *Annals Int. Med. 110*:992-1000 (1989)).

However, the therapeutic potential of these PCP receptor drugs as ischemia rescue agents in stroke has been severely hampered by the fact that these drugs have strong PCP-like behavioral side effects (psychotomimetic behavioral effects) which appear to be due to the interaction of these drugs with the PCP receptor (Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989); Koek, W., *et al.*, *J. Pharmacol. Exp. Ther. 245*:969 (1989); Willets and Balster, *Neuropharmacology 27*:1249 (1988)). These

PCP-like behavioral side effects appear to have caused the withdrawal of MK801 from clinical development as an ischemia rescue agent. Furthermore, these PCP receptor ligands appear to have considerable abuse potential as demonstrated by the abuse liability of PCP itself.

The PCP-like behavioral effects of the PCP receptor ligands can be demonstrated in animal models: PCP and related PCP receptor ligands cause a behavioral excitation (hyperlocomotion) in rodents (Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989)) and a characteristic catalepsy in pigeons (Koek, W., *et al.*, *J. Pharmacol. Exp. Ther. 245*:969 (1989); Willets and Balster, *Neuropharmacology 27*:1249 (1988)); in drug discrimination paradigms, there is a strong correlation between the PCP receptor affinity of these drugs and their potency to induce a PCP-appropriate response behavior (Zukin, S.R., *et al.*, *Brain Res. 294*:174 (1984); Brady, K.T., *et al.*, *Science 215*:178 (1982); Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 141*:497 (1987)).

Drugs acting as competitive antagonists at the glutamate binding site of the NMDA receptor, such as, CGS 19755 and LY274614, also have neuroprotective efficacy because these drugs--like the PCP receptor ligands--can prevent excessive Ca^{++} flux through NMDA receptor/channels in ischemia (Boast, C.A., *et al.*, *Brain Res. 442*:345-348 (1988); Schoepp, D.D., *et al.*, *J. Neural. Trans. 85*:131-143 (1991)). However, competitive NMDA receptor antagonists also have PCP-like behavioral side-effects in animal models (behavioral excitation, activity in PCP drug discrimination tests) although not as potently as MK801 and PCP (Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989)).

An alternate way of inhibiting NMDA receptor channel activation is by using antagonists at the glycine binding site of the NMDA receptor. Since glycine must bind to the glycine site in order for glutamate to effect channel opening (Johnson and Ascher, *Nature 325*:329-331 (1987); Kemp, J.A., *et al.*, *Proc. Natl. Acad. Sci. USA 85*:6547-6550 (1988)), a glycine antagonist

can completely prevent ion flux through the NMDA receptor channel--even in the presence of a large amount of glutamate.

Recent *in vivo* microdialysis studies have demonstrated that, in the rat focal ischemia model, there is a large increase in glutamate release in the ischemic brain region with no significant increase in glycine release (Globus, M.Y.T., *et al.*, *J. Neurochem. 57*:470-478 (1991)). Thus, theoretically, glycine antagonists should be very powerful neuroprotective agents because they can prevent the opening of NMDA channels by glutamate non-competitively and, therefore, unlike competitive NMDA antagonists, do not have to overcome the large concentrations of endogenous glutamate that are released in the ischemic brain region.

Furthermore, because glycine antagonists act at neither the glutamate/NMDA nor the PCP binding sites to prevent NMDA channel opening, these drugs might not cause the PCP-like behavioral side effect seen with both PCP receptor ligands and competitive NMDA receptor antagonists (Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989); Koek, W., *et al.*, *J. Pharmacol. Exp. Ther. 245*:969 (1989); Willets and Balster, *Neuropharmacology 27*:1249 (1988); Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989); Zukin, S.R., *et al.*, *Brain Res. 294*:174 (1984); Brady, K.T., *et al.*, *Science 215*:178 (1982); Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 141*:497 (1987)). That glycine antagonists may indeed be devoid of PCP-like behavioral side effects has been suggested by recent studies in which available glycine antagonists were injected directly into the brains of rodents without resulting in PCP-like behaviors (Tricklebank, M.D., *et al.*, *Eur. J. Pharmacol. 167*:127-135 (1989)).

However, there have been two major problems that have prevented the development of glycine antagonists as clinically useful neuroprotective agents:

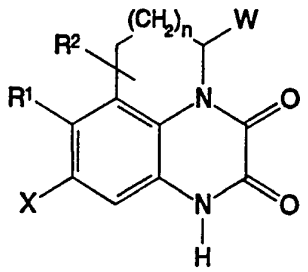
A. Most available glycine antagonists with relatively high receptor binding affinity *in vitro* such as 7-Cl-kynurenic acid (Kemp, J.A., *et al.*, *Proc. Natl. Acad. Sci. USA 85*:6547-6550 (1988)), 5,7-dichlorokynurenic acid

(McNamara, D., *et al.*, *Neuroscience Lett. 120*:17-20 (1990)) and indole-2-carboxylic acid (Gray, N.M., *et al.*, *J. Med. Chem. 34*:1283-1292 (1991)) cannot penetrate the blood/brain barrier and therefore have no utility as therapeutic agents;

B. The only available glycine antagonist that sufficiently penetrates the blood/brain barrier--the drug HA-966 (Fletcher and Lodge, *Eur. J. Pharmacol. 151*:161-162 (1988))--is a partial agonist with only micromolar affinity for the glycine binding site. A neuroprotective efficacy for HA-966 *in vivo* has, therefore, not been demonstrated, nor has it been demonstrated for the other available glycine antagonists because they lack bioavailability *in vivo*.

However, one recent success in identifying orally active glycine receptor antagonists was reported by Kulagowski *et al.*, *J. Med. Chem. 37*:1402-1405 (1994), who disclose that 3-substituted 4-hydroxyquinoline-2(1*H*)-ones are selective antagonists possessing potent *in vivo* activity.

International published application WO93/08188 discloses tricyclic quinoxalinediones which are selective glutamate receptor antagonists. The compounds have the generalized formula:



wherein X represents alkyl, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, alkylamino, alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonyl, amino, or acylamino;

R^1 represents hydrogen, alkyl, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, alkylamino, alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^2 represents hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, or substituted aryl; and

W represents hydrogen, CO_2R^3, CO_2Y, $CONR^3R^4$, $CONR^3Y$, $CON(OR^3)R^4$, COR^3, CN, tetrazolyl, or substituted alkyl. These compounds are disclosed as selective antagonists of glutamate receptors for the treatment and prevention of various diseases such as minimizing damage to the central nervous system induced by ischemic or hypoxic conditions, treatment and/or prevention of neurodegenerative disorders, as analgesics, antidepressants, anxiolytics and anti-schizophrenics.

Nagata, R. *et al.*, *American Chemical Society meeting abstract*, San Diego (March 1994) and Nagata *et al.*, *J. Med. Chem.* *37*:3956 (1994) disclose tricyclic quinoxalinediones. A series of substituted 6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dionesandsubstituted5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-2,3-diones were synthesized and tested for binding at the glycine receptor. The compounds are reported to have high binding to the glycine receptor.

The tricyclic quinoxalinediones, 6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione and 5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-2,3-dione are described in Richardson, Jr., A., *J. Org. Chem.* *25*:2589 (1965).

An amine-substituted tricyclic quinoxalinedione, 6,7-dihydro-6-(di-*n*-propylamino)-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione is disclosed in PCT published application WO 90/15058, and Moon, M.W. *et al.*, *J. Med. Chem.* *35*:1076 (1992) as an example of series of imidazoquinolinones and related compounds having dopaminergic and serotonergic activities, and especially, as a selective and potent D_2 agonist.

A phenyl-substituted tricyclic quinoxalinedione, 6-phenyl-1*H*-pyrolo[1,2,3-*de*]quinoxaline-2,5[3*H*,6*H*]-dione is disclosed in U.S. Patent No. 4,133,884 as an example of a series of substituted pyrroloquinoxolinones and diones which are taught to be anti-inflammatory agents.

There have been a number of reports in the literature of substituted 1,4-dihydroquinoxaline-2,3-diones that are useful for treating pathophysiologic conditions mediated by the non-NMDA, NMDA, and glycine receptors. For example, U.S. Patent No. 4,975,430 discloses 1,4-dihydroquinoxaline-2,3-dione compounds reportedly useful for the treatment of neuronal conditions associated with stimulation of the NMDA receptor.

U.S. Patent Nos. 4,812,458 and 4,948,794 discloses 1,4-dihydroquinoxaline-2,3-dione compounds reportedly useful for treatment of indications caused by hyperactivity of the excitatory neurotransmitters, particularly the quisqualate receptors, and as neuroleptics.

International Application Publication No. WO91/13878 discloses N-substituted 1,4-dihydroquinoxaline-2,3-diones, which bind to the glycine receptor, and pharmaceutically acceptable salts thereof.

Epperson *et al.*, *Bioorganic & Medicinal Chemistry Letters, 3(12)*:2801-2804 (1993) report the synthesis and amino acid pharmacology of twelve N-substituted quinoxalinediones. The compounds are reported to have significant antagonism at both the AMPA and glycine-site NMDA receptors.

Certain quinoxalinediones and benzo[1,2-*f*]qunoxalinediones have been shown to have antagonist activities against glutamate receptors including glycine modulatory site of NMDA receptors and AMPA receptors (For example, Pellegrini-Giampietro, D.E. *et al.*, *Br. J. Pharmacol. 98*:1281-1286 (1989), Sheardown, M.J. *et al.*, *Eur. J. Pharmacol. 174*:197-204 (1989), Yoneda and Ogita, *Biochem. Biophys. Res. Commun. 164*:841-849 (1989), and Sheardown M. J. *et al.*, *Science 247*:571 (1990)).

For recent reviews on glycine antagonists, reference is made to Leeson, P.D., "Glycine-Site N-Methyl-D-Aspartate Receptor Antagonists," Chapter 13 in *Drug Design for Neuroscience*, Kozikowski, A.P. (ed.), Raven

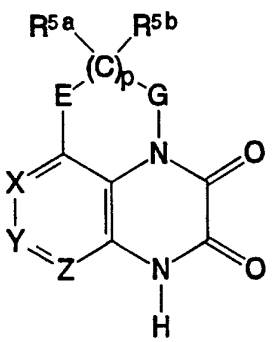
Press, New York, pp. 338-381 (1993); and Leeson & Iversen, *J. Med. Chem.* *37*: 4053-4067 (1994).

A need continues to exist for potent and selective glycine/NMDA antagonists that:

- lack the PCP-like behavioral side effects common to the PCP-like NMDA channel blockers, such as, MK801, or to the competitive NMDA receptor antagonists, such as, CGS19755;
- show potent anti-ischemic efficacy because of the non-competitive nature of their glutamate antagonism at the NMDA receptor;
- cross the blood-brain barrier at levels sufficient for efficacy;
- have utility as novel anticonvulsants with fewer side-effects than the PCP-like NMDA channel blockers or the competitive NMDA antagonists;
- help in defining the functional significance of the glycine binding site of the NMDA receptor *in vivo*.

Summary of the Invention

The present invention is broadly directed to methods of treating, preventing, or decreasing neuronal degeneration associated with ischemia, pathophysiologic conditions associated with neuronal degeneration, convulsions, anxiety, chronic pain, and inducing anesthesia by administering a tricyclic quinoxalinedione represented by Formula *I*:



I

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

X represents one of $C(R^1)$ or $N(O)_n$;

Y represents one of $C(R^2)$ or $N(O)_n$;

Z represents one of $C(R^3)$ or $N(O)_n$, with the proviso that when either or both of X and Z are $N(O)_n$, then Y is $C(R^2)$;

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

G represents one of $-C(R^{6a})(R^{6b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo (=O) or thiooxo (=S), or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^{6a} and R^{6b} (i) together represent oxo or thiooxo, or (ii) R^{6a} and R^{6b} independently represent hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl,

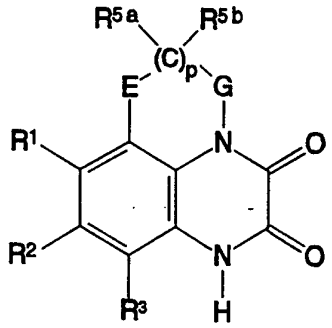
heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond;

n is zero or one; and

p is zero or one.

The present invention is also drawn to the the following novel subclasses of compounds falling within the definition of Formula *I*. These novel compounds are represented by Formulae *IA*, *IB*, *IC* and *ID*. One subclass of novel compounds according to the present invention is represented by compounds of Formula *IA*:



IA

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

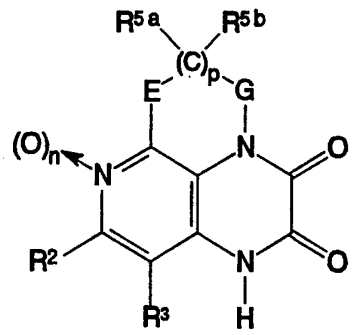
R^1, R^2, R^3, E, G, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^7, R^8, R^9 and p are defined as above for Formula *I*;

preferably

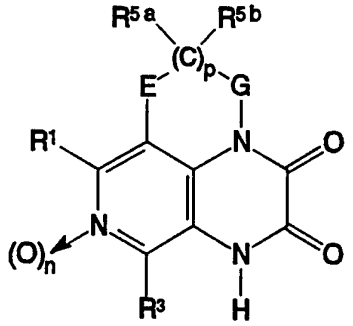
(a) when E is $-C(R^{4a})(R^{4b})-$, G is $-C(R^{6a})(R^{6b})-$ and p is one, then one of the combination of either (i) R^{5a} and R^{5b} or (ii) R^{6a} and R^{6b} is oxo or thiooxo; or

(b) when E is $-N(R^9)-$, G is $-C(R^{6a})(R^{6b})-$ and p is one, then R^{6a} and R^{6b} do not represent hydrogen, alkyl or substituted alkyl.

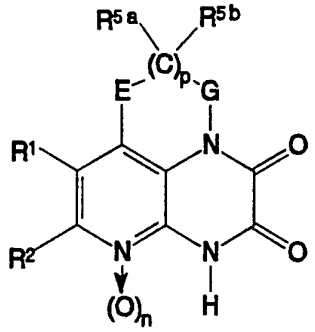
Another sub-class of novel compounds according to the present invention are aza and aza(N-oxy) compounds represented one of Formulae *IB*, *IC* or *ID*:



IB



IC



ID

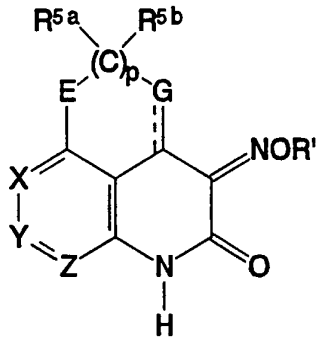
or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1, R^2, R^3, E, G, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^7, R^8, R^9 and p are defined as above for Formula *I*; and

n is zero or one.

An additional aspect of the present invention relates to tricyclic systems based upon 1,2,3,4-tetrahydroquinoline-2,3-dione-3-oximes. These compounds have the following generalized formula:



II

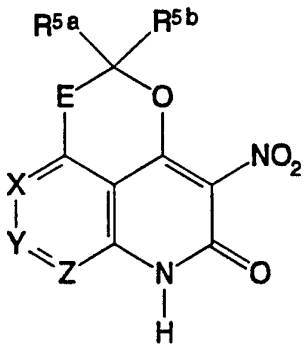
or a pharmaceutically acceptable salt or tautomer thereof;

wherein

X, Y, Z, R^1, R^2, R^3, E, G, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^7, R^8, R^9, n and p are defined as above for Formula *I*; and

R′ is one of hydrogen, alkyl, aryl, heteroaryl, acyl, halogen-substituted acyl or aryloyl.

An additional aspect of the present invention relates to tricyclic systems based upon 4-hydroxy-3-nitro-2-quinolones. In these compounds the 4 and 5 carbons of a 4-hydroxy-3-nitro-2-quinolone are bridged to form compounds having the following generalized structure:



III

or a pharmaceutically acceptable salt or tautomer thereof

wherein

X represents one of $C(R^1)$ or $N(O)_n$;

Y represents one of $C(R^2)$ or $N(O)_n$;

Z represents one of $C(R^3)$ or $N(O)_n$ with the proviso that when either or both of X and Z are $N(O)_n$, then Y is $C(R^2)$;

R_1 and R_2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents one of hydrogen or flourine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

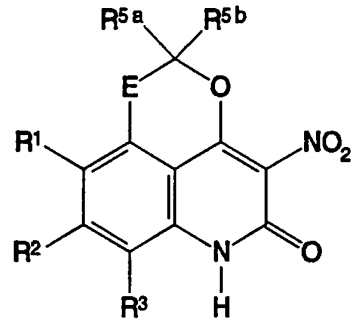
R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo (=O) or thiooxo (=S), or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

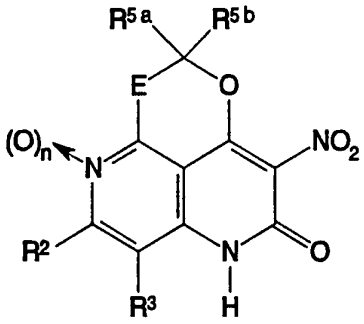
R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond;

n is zero or one.

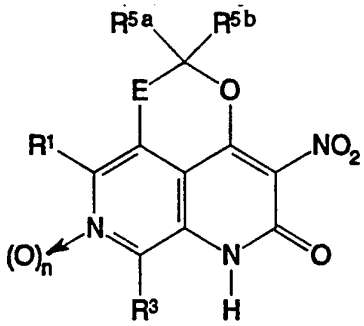
Compounds having the following subgeneric formulae are contemplated in this aspect of the invention:



IIIA



IIIB



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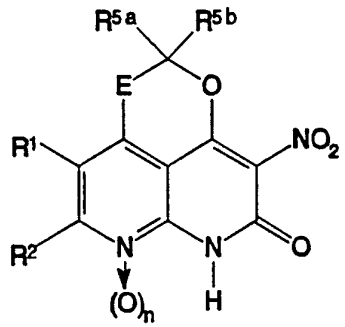


IIID

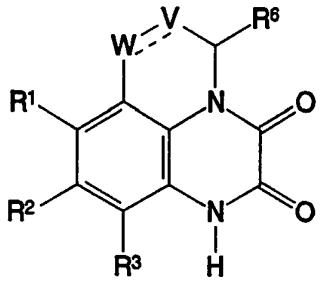
or a pharmaceutically acceptable salt or tautomer thereof;

wherein

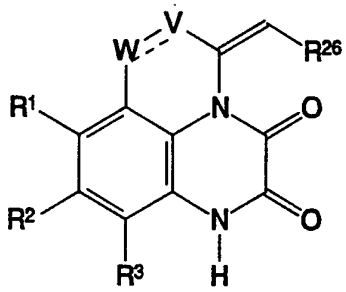
R^1, R^2, R^3, E, R^{4a}, R^{4b}, R^{5a}, R^{5b} and R^9 are defined as above for Formula *III*; and

n is zero or one.

A further embodiment of the invention relates to tricyclic quinoxalinediones which incorporate a nitrone group in the bridge between C-5 and N-4 of a quinoxalinedione. These compounds have the one of the following formulae:



IVA



IVB

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

W represents one of $C(R^4)$ or $N(O)_n$;

V represents one of $C(R^5)$ or $N(O)_n$ with the proviso that one of W and V is $N(O)_n$, and the other of W and V is $C(R^4)$ or $C(R^5)$, respectively;

R^4 and R^5 independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl;

R^6 represents hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^{26} represents alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl; and

n is zero or one.

The dashed line between W and Z indicates that the bond between W and Z can be either a single or double bond.

In one embodiment, the present invention relates to novel tricylic compounds having Formulae *I*, *II*, *III*, *IVA* and *IVB*, tautomers or pharmaceutically acceptable salts thereof.

In a second embodiment, the present invention relates to a method of treating or preventing (A) neuronal loss associated with stroke, ischemia, CNS trauma, or hypoglycemia or (B) the adverse neurological consequences of surgery, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a third embodiment, the present invention relates to a method of treating a neurodegenerative disease selected from Alzheimer's disease,

amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, comprising administering to an animal in need of such treatment an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a fourth embodiment, the present invention relates to a method of antagonizing excitatory amino acids at the NMDA receptor complex, comprising administering to an animal in need thereof an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a fifth embodiment, the present invention relates to a method of treating or preventing the adverse consequences of the hyperactivity of the NMDA receptor, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a sixth embodiment, the present invention relates to a method of treating chronic pain, comprising administering to an animal in need of such treatment an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a seventh embodiment, the present invention relates to a method of treating or preventing anxiety, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In an eighth embodiment, the present invention relates to a method of treating or preventing convulsions, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a ninth embodiment, the present invention relates to a method of inducing anesthesia, comprising administering to an animal in need of such anesthesia an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a tenth embodiment, the present invention relates to a method of treating or preventing NMDA receptor-ion channel related psychosis, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In an eleventh embodiment, the present invention relates to a method of inducing a hypnotic effect, comprising administering to an animal in need of such treatment an effective amount of a compound defined by one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

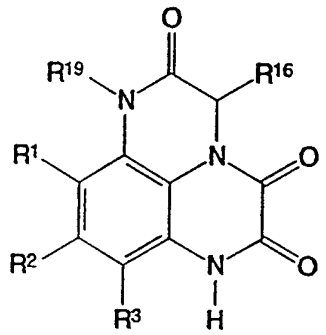
In a twelfth embodiment, the present invention relates to a radiolabelled compound having one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a thirteenth embodiment, the present invention relates to a method of preventing opiate tolerance, comprising administering to an animal in need of such prevention an effective amount of a compound having one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof.

In a fourteenth embodiment, the present invention relates to a pharmaceutical compositions comprising a compound having one of Formulae *I*, *II*, *III*, *IVA* and *IVB*, or a tautomer or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Description of the Preferred Embodiments

The present invention provides novel quinoxalinediones depicted by Formula *I* above and tautomers and pharmaceutically acceptable salts thereof. The tricyclic compounds provided for by the following formulae are included in this aspect of the present invention:



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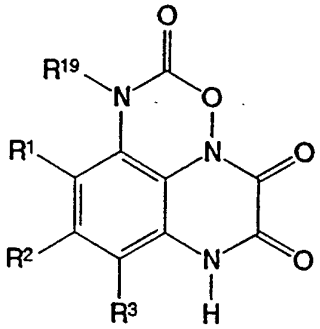

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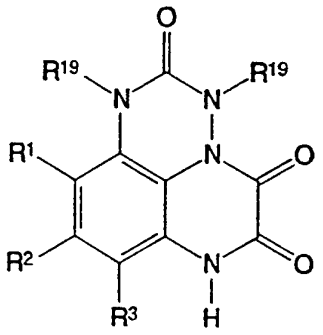

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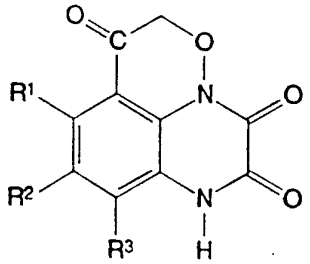
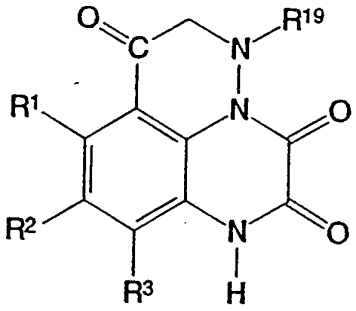


VIII



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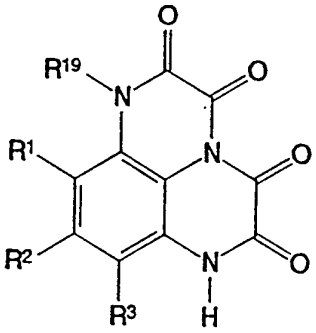
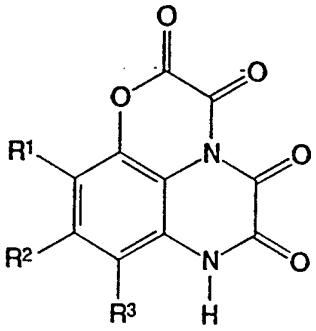


X



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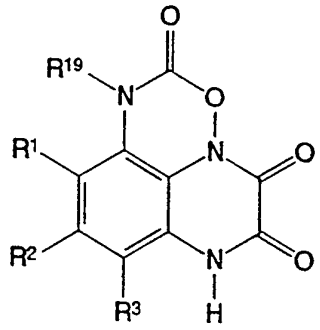

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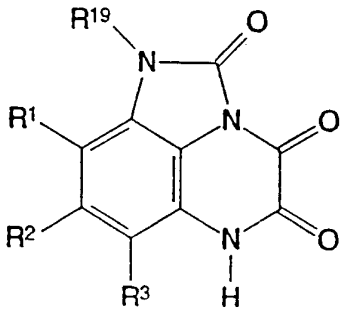

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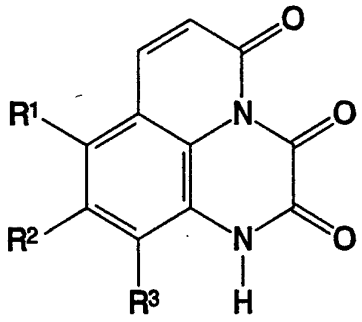
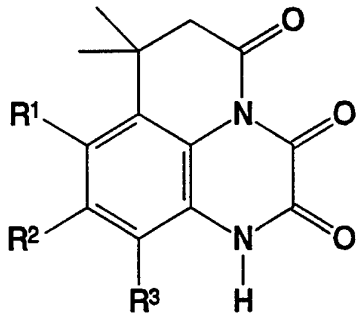


XIV



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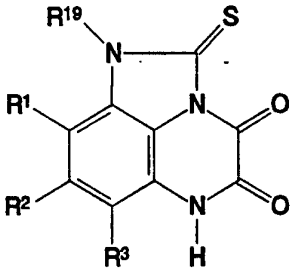

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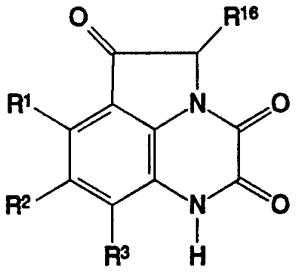
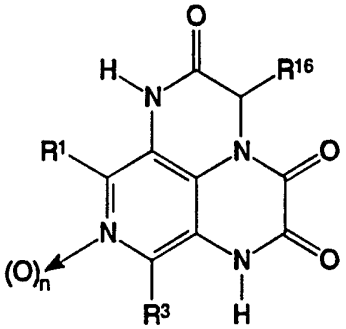
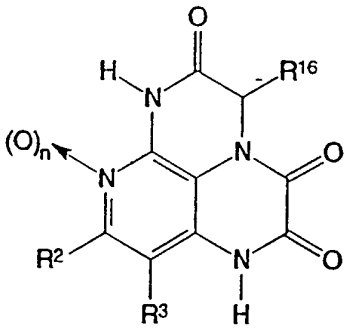


XVII



XVIII



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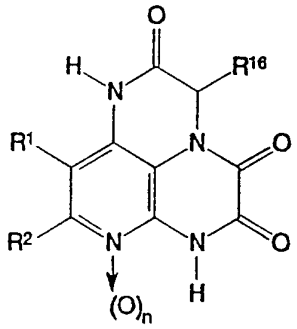
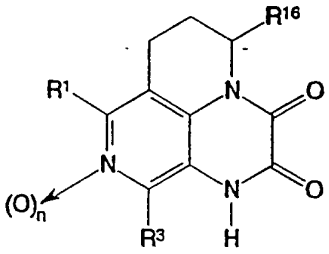
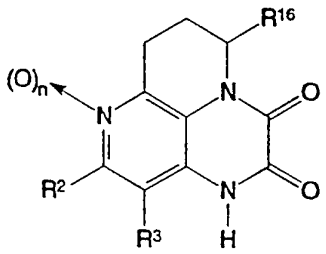


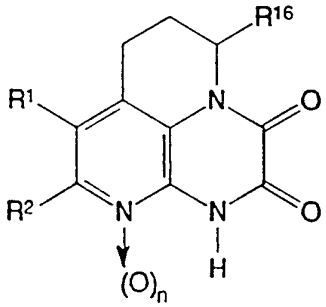
XX



XXI



XXII



XXIII

wherein R^1, R^2 and R^3 are each as defined for Formula *I* above;

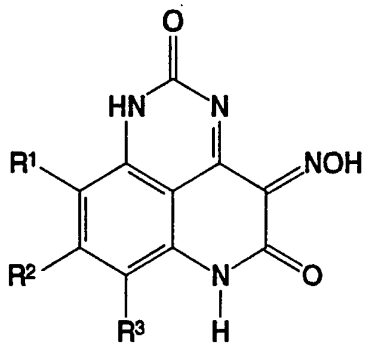
R^{16} represents hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

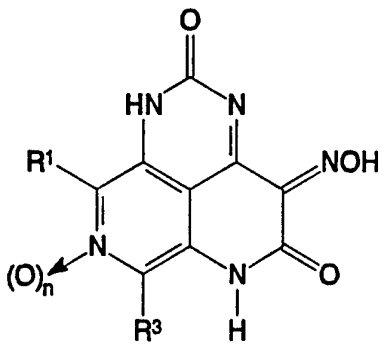
R^{19} represents hydrogen or alkyl; and

n is zero or one.

A second aspect of the present invention relates to tricyclic compounds based upon 1,2,3,4-tetrahydroquinoline-2,3-dione-3-oximes having Formula *II* above. Preferred compounds for this aspect of the invention include compounds having the formulae:



XXIV

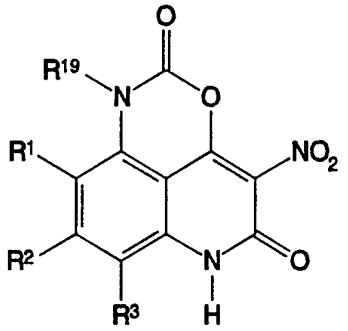


XXV

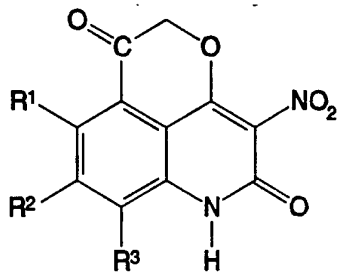
wherein R^1, R^2 and R^3 are each as defined for Formula *I* above; and n is zero or one.

An additional aspect of the present invention relates to tricyclic compounds based upon 4-hydroxy-3-nitro-2-quinolones. In these compounds the 4 and 5 carbons of a 4-hydroxy-3-nitro-2-quinolone are bridged to form compounds of the general structure of Formula *III* above.

Preferred compounds for this aspect of the invention have the following structures:



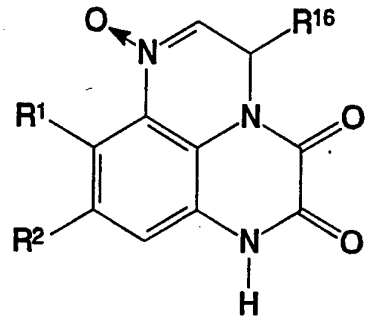
XXVI



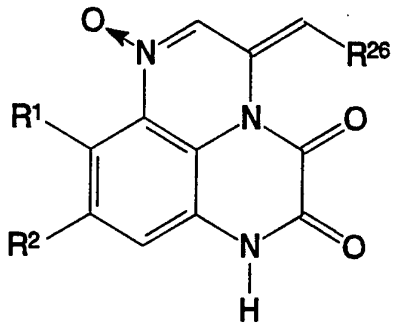
XXVII

wherein R^1, R^2 and R^3 are each as defined for Formula *III* above, and R^{19} represents hydrogen or alkyl.

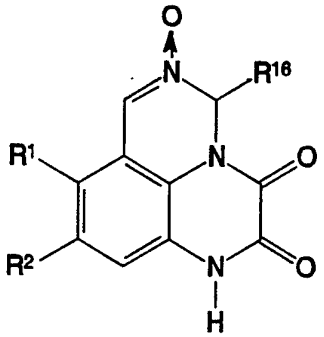
A further embodiment of the invention relates to tricyclic quinoxalinediones which incorporate a nitrone group in the bridge between C-5 and N-4 of a quinoxalinedione. These compounds have the general Formulae *IVA* and *IVB* shown above. Preferred compounds within this embodiment have the following structure:



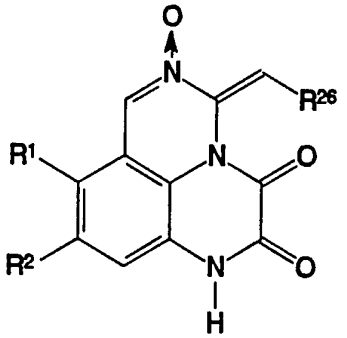
XXVIII



XXIX



XXX



XXXI

wherein R^1 and R^2 are defined as above for Formula *I*;

R^{16} represents hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl,

substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl; and

R^{26} represents alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl.

The term "aryl" as used herein includes aryl groups having 6 to 14 carbon atoms. Typical examples are phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups.

The term "aryloxy" as used herein includes any of the C_{6-14} aryl groups linked by oxygen, e.g., phenoxy and 1-naphthyloxy groups.

The term "substituted aryl" as used herein includes any of the C_{6-14} aryl groups substituted by one or more halo, nitro, cyano, alkyl, haloalkyl, alkenyl, and alkynyl groups, e.g., 2-chlorophenyl, 2,4-dibromophenyl, and the like.

The term "substituted aryloxy" as used herein includes any of the C_{6-14} aryl groups substituted by one or more halo, nitro, cyano, alkyl, haloalkyl, alkenyl, and alkynyl groups, and linked by oxygen, e.g., 2-chlorophenoxy, 2,4-dibromophenoxy, and the like.

The term "aryloyl" as used herein includes any of the above-mentioned aryl groups substituted by a carbonyl group.

The term "amino" as used herein includes NH_2, NHR^{11}, and $NR^{11}R^{12}$, wherein R^{11} and R^{12} are C_{1-4} alkyl groups.

The term "alkyl" as used herein includes straight-chained or branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples are methyl, ethyl, *n*-propyl, isopropyl, *sec*-butyl, *tert*-butyl, neopentyl, *n*-pentyl, and *n*-hexyl.

The term "alkylamino" as used herein includes mono- and dialkylamino groups, wherein an alkyl group contains from 1 to 6 carbon atoms which may be straight-chained or branched. Typical examples are methylamino, methylethylamino, diethylamino, propylamino, diisopropylamino, and hexylamino.

The terms "halogen" or "halo" as used herein include fluorine, chlorine, bromine, and iodine. Typical examples are chlorine and bromine.

The term "alkoxy" as used herein includes straight-chained or branched alkoxy groups containing from 1 to 6 carbon atoms. Typical examples are methoxy, ethoxy, propoxy, isopropoxy, *sec*-butoxy, *tert*-butoxy, neopentoxy, pentoxy, and hexoxy.

The term "alkanoyl" as used herein includes straight-chained or branched alkanoyl groups containing from 1 to 6 carbon atoms. Typical examples are formyl, acetyl, propanoyl, *n*-butanoyl, and pivaloyl.

The term "alkoxycarbonyl" as used herein includes straight-chained or branched alkoxycarbonyl groups containing from 1 to 6 carbon atoms. Typical examples are methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, *sec*-butoxycarbonyl, and *tert*-butoxycarbonyl.

The term "alkylthio" as used herein includes straight-chained or branched alkylthio groups containing from 1 to 6 carbon atoms. Typical examples are methylthio, ethylthio, *n*-propylthio, isopropylthio, *sec*-butylthio, *tert*-butylthio, neopentylthio, *n*-pentylthio, and *n*-hexylthio.

The term "alkylsulfinyl" as used herein includes straight-chained or branched alkylsulfinyl groups containing from 1 to 6 carbon atoms. Typical examples are methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl, *tert*-butylsulfinyl, neopentylsulfinyl, *n*-pentylsulfinyl, and *n*-hexylsulfinyl.

The term "alkylsulfonyl" as used herein includes straight-chained or branched alkylsulfonyl groups containing from 1 to 6 carbon atoms. Typical examples are methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl, *tert*-butylsulfonyl, neopentylsulfonyl, *n*-pentylsulfonyl, and *n*-hexylsulfonyl.

The term "alkylcarbamoyl" as used herein includes mono- and dialkylcarbamoyl, wherein an alkyl moiety contains from 1 to 6 carbon atoms which may be straight-chained or branched. Typical examples are methyl-

carbamoyl, methylethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, diisopropylcarbamoyl, and hexylcarbamoyl.

The term "alkylsulfamoyl" as used herein includes sulfamoyl groups substituted with 1 or 2 alkyl groups containing from 1 to 6 carbon atoms which may be straight-chained or branched. Typical examples are methylsulfamoyl, methylethylsulfamoyl, diethylsulfamoyl, propylsulfamoyl, diisopropylsulfamoyl, and hexylsulfamoyl.

The term "alkylsulfonylamino" as used herein includes straight-chained or branched alkylsulfonylamino groups containing from 1 to 6 carbon atoms. Typical examples are methylsulfonylamino, ethylsulfonylamino, *n*-propylsulfonylamino, isopropylsulfonylamino, *sec*-butylsulfonylamino, *tert*-butylsulfonylamino, neopentylsulfonylamino, *n*-pentylsulfonylamino, and *n*-hexylsulfonylamino.

The term "acylamino" as used herein includes straight-chained or branched alkanoylamino groups containing from 1 to 6 carbon atoms. The term "acylamino" as used herein also includes aroylamino groups containing from 7 to 11 carbon atoms. Typical examples are formylamino, acetylamino, propanoylamino, butanoylamino, *sec*-butanoylamino, *n*-pentanoylamino, *n*-hexanoylamino, benzoylamino, and 1- or 2-naphthoylamino.

The term "cycloalkyl" as used herein includes cycloalkyl groups containing from 3 to 8 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "alkenyl" as used herein includes straight-chained or branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples are vinyl, allyl, 1-propenyl, and 1-, 2- or 3-butenyl.

The term "alkynyl" as used herein includes straight-chained or branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples are ethynyl, propargyl, 1- or 2-propynyl, 1- or 2-butynyl, and pentynyl.

The term "cycloalkylalkyl" as used herein includes straight-chained or branched alkyl groups attached with cycloalkyl groups, which contains up to

13 carbon atoms. Typical examples are cyclopropylmethyl, cyclopentylethyl, cyclohexylmethyl, and cyclohexylpropyl.

The term "arylalkyl" as used herein includes straight-chained or branched alkyl groups attached with aryl groups, which contains up to 15 carbon atoms. Typical examples are benzyl, phenylethyl, 1- or 2-naphthylmethyl, and 1- or 2-naphthylpropyl.

The term "haloalkyl" as used herein includes C_{1-4} alkyl groups substituted by one or more fluorine, chlorine, bromine, or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, and trichloromethyl groups.

The term "haloalkoxy" as used herein includes one of the alkoxy groups mentioned above substituted by one or more fluoro, chloro, bromo, or iodo groups, e.g., trifluoromethoxy, trichloromethoxy, 2-chloroethoxy, 2-bromoethoxy, pentafluoroethyl, 3,3,3-trichloropropoxy, 4,4,4-trichlorobutoxy, and the like.

The term "trialkylsilyl-substituted alkoxy" as used herein includes any one of the C_{1-4} alkoxy groups substituted by a C_{3-6} trialkylsilyl group, e.g. 2-trimethylsilylethoxy, 2-triethylsilylethoxy and 2-(*t*-butyldimethylsilyl)ethoxy, and the like.

Preferred heterocyclic groups are those having 3 to 10 carbon atoms and having one or more 4, 5, 6, or 7 member saturated or unsaturated rings containing 1, 2, or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heterocyclic radicals are: tetrahydrofuran, 1,4-dioxane, 1,3,5-trioxane, pyrrolidine, piperidine, piperazine, imadazoline, isoindoline, chromane, isochromane, pyrazolidine, quinuclidine, pyridine, pyrrole, oxazole, indole, purine, pyrimidine, 1,3-dithiane, azetidine, tetrahydropyran, imidazole, thiazole, isoxazole, pyrazole, quinoline, cytosine, thymine, uracil, adenine, guanine, pyrazine, 1-methyl-1,4-dihydronicotine, picolinic acid, picoline, furoic acid, furfural, furfuryl alcohol, carbazole, isoquinoline, 3-pyrroline, thiophene, furan, hexamethyleneimine, ϵ-caprolactone, ϵ-caprolactam, omega-thiocaprolactam, and morpholine).

The term "heteroaryl" as used herein includes groups which have 3 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and contain carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

The term "heteroarylalkyl" as used herein includes straight-chained or branched alkyl groups containing up to 6 carbon atoms, which is attached with a heteroaryl group. The heteroaryl group is as defined above. Typical examples are pyridylmethyl, quinolylethyl, isoquinolylpropyl, pyridazinylmethyl, pyrimidinylethyl, pyrazinylpropyl, pyrrolylmethyl, indolylethyl, pyranylpropyl, furylmethyl, benzofurylethyl, thienylpropyl, benzothienylmethyl, imidazolylethyl, oxazolylpropyl, thiazolylmethyl, isoxazolylmethyl, isothiazolylethyl, oxadiazolylethyl, thiadiazolylproyl, tetrazolylmethyl, benzoxazolylethyl, benzothiazolylpropyl, benzisoxazotylmethyl, benzisothiazolylethyl, benzimidazolylpropyl, and benzotriazolylmethyl.

The term "heterocycloalkyl" as used herein includes heterocycloalkyl groups containing up to 6 carbon atoms together with 1 or 2 heteroatoms which are selected from nitrogen, oxygen and sulfur atoms. Typical examples are piperidyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, and dithianyl. The term "heterocycloalkyl" as used herein also includes heterocycloalkyl groups fused with benzene-ring containing up to 10 carbon atoms together with 1 or 2 heteroatoms which are selected from nitrogen, oxygen and sulfur atoms. Typical examples are indolinyl,

isoindolinyl, tetrahydro-1-quinolinyl, and tetrahydro-2-quinolinyl, tetrahydroquinoxalinyl.

The alkyl groups of the term "substituted alkyl" as used in R^4, R^5, R^6, R^{6a} and R^{6b} include straight-chained or branched alkyl groups containing from 1 to 4 carbon atoms. Typical examples are methyl, ethyl, propyl, and butyl.

The substituent of the term "substituted alkyl" as used in R^4, R^5, R^6, R^{6a}, R^{6b}, and R^{16} includes CO_2R^3, $CONR^{13}R^{14}$, $CON(OR^{13})R^{14}$, COR^{15}, CN, $NR^{13}CO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, phthalimido, heteroaryl, substituted heteroaryl, heterocycloalkyl, $NR^{13}R^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COCO_2R^{14}$, $NR^{13}COCONR^{14}R^{15}$, $NR^{13}COCOR^{14}$, OR^{13}, $OCOR^{13}$, OCOY, OCO_2R^{13}, $OCONR^{13}R^{14}$, $OCOCO_2R^{13}$, $OCOCOR^{13}$, $OCOCONR^{13}R^{14}$, OSO_2R^{13}, $PO(OR^{13})_2$, SR^{13}, SOR^{13}, SO_2R^{13}, SO_3R^{13}, $SO_2NR^{13}R^{14}$, F, Cl, Br, and I;

wherein R^{13}, R^{14}, and R^{15} independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl or heterocycloalkyl; and

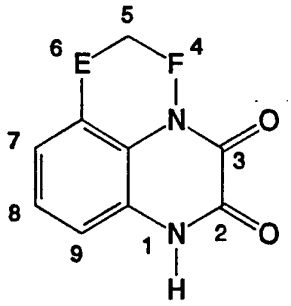
The number of the substituents on substituted aryl, substituted arylalkyl, substituted heteroaryl, or substituted heteroarylalkyl, respectively, as used herein may be one, two, or three, up to the maximum number permitted, and the substituents include alkyl, halogen, cyano, trifluoromethyl, nitro, hydroxy, mercapto, amino, alkylamino, alkoxy, alkanoyl, alkoxycarbonyl, carboxy, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, acylamino, substituted alkyl, substituted alkenyl, and substituted alkynyl.

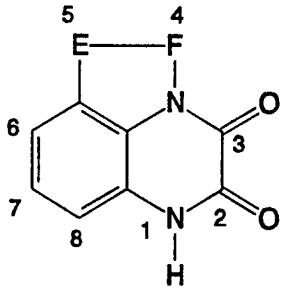
It is also to be understood that the compounds of the present invention exist as tautomeric isomers. The present invention is also directed to such tautomeric isomers and mixtures of such isomers. It is to be understood that all tautomeric forms of the compounds of Formulae *I*, *II*, *III*, *IVA* and *IVB*, as well as all possible mixtures thereof, are included within the scope of the present invention.

Where the compounds according to the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The pyridine(N-oxide) analogs of the present invention are expected to have increased water solubility compared to glycine receptor antagonists in the prior art. As such, the compounds overcome problems encountered with many known glycine receptor antagonists: difficulty in formulating injectable solutions and a low bioavailability.

The numbering system used for the novel quinoxaline systems is illustrated in the following figures:





The invention also relates to a method of treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids; treating anxiety, convulsions, chronic pain, or psychosis; preventing opiate tolerance; or inducing a hypnotic effect or anesthesia treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia, and surgery; treating neurodegenerative diseases, including, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, and Down's syndrome; comprising administering to an animal in need of such treatment or prevention a tricyclic quinoxalinedione, a tricyclic 3-nitro-2-quinolone, or pyridine(N-oxide) or nitrone analogs thereof, as defined herein, having high

affinity for the glycine binding site and the capability of crossing the blood brain barrier at high levels, while lacking PCP side effects.

The compounds disclosed herein are active in treating or preventing neuronal loss, neurodegenerative diseases, and chronic pain and are active as anticonvulsants and in inducing anesthesia without untoward side effects caused by non-selective binding with other receptors, particularly, kainate, AMPA, and quisqualate receptors and the PCP and glutamate receptors associated with the NMDA receptor. In addition, these compounds are effective in treating or preventing the adverse consequences of the hyperactivity of the excitatory amino acids, e.g., those that are involved in the NMDA receptor system, by blocking the glycine receptors and preventing the ligand-gated cation channels from opening and allowing excessive influx of Ca^{++} into neurons, as occurs during ischemia.

Neurodegenerative diseases that may be treated with the disclosed compounds include those selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome.

These compounds also find particular utility in the treatment or prevention of neuronal loss associated with multiple strokes that give rise to dementia. After a patient has been diagnosed as suffering from a stroke, the compounds can be administered to ameliorate the immediate ischemia and prevent further neuronal damage that may occur from recurrent strokes.

Moreover, these compounds are able to cross the blood/brain barrier, in contrast to 6-cyano-7-nitro-1,4-dihydroquinoxaline-2,3-dione, 6,7-dinitro-1,4-dihydroquinoxaline-2,3-dione, and other 6,7-disubstituted 1,4-dihydroquinoxaline-2,3-diones that are incapable of crossing the blood/brain barrier after i.p. administration (*see* Turski, L. *et al., J. Pharm. Exp. Ther. 260*: 742-747 (1992)). *See also*, Sheardown *et al., Eur. J. Pharmacol. 174*:197-204 (1989), who disclose that 5,7-dinitro-1,4-dihydroquinoxaline-2,3-dione, 6,7-dinitro-1,4-dihydroquinoxaline-2,3-dione, and 6-cyano-7-nitro-1,4-dihydroquinoxaline-2,3-dione have poor access to the central nervous system.

For a compound to begin to show *in vivo* efficacy and, thus, the ability to cross the blood-brain barrier, the compound should exhibit an ED_{50} of less than about 100 mg/kg body weight of the animal. Preferably, the compounds of the present invention exhibit an ED_{50} of less than about 20 mg/kg and, more preferably, less than about 10 mg/kg.

These compounds find particular utility in treating or preventing the adverse neurological consequences of surgery. For example, coronary bypass surgery requires the use of heart-lung machines, which tend to introduce air bubbles into the circulatory system that may lodge in the brain. The presence of such air bubbles robs neuronal tissue of oxygen, resulting in anoxia and ischemia. Pre- or post- surgical administration of the 1,4-dihydroquinoxalines of the present invention will treat or prevent the resulting ischemia. In a preferred embodiment, the compounds are administered to patients undergoing cardiopulmonary bypass surgery or carotid endarterectomy surgery.

These compounds also find utility in treating or preventing pain, e.g., chronic pain. Such chronic pain can be the result of surgery, trauma, headache, arthritis, or other degenerative disease. The compounds of the present invention find particular utility in the treatment of phantom pain that results from amputation of an extremity. In addition to treatment of pain, the compounds of the invention are also useful in inducing anesthesia, either general or local anesthesia, as, for example, during surgery.

Compounds having Formulae ***V***, ***IX***, ***XVIII***, ***XX***, ***XXIV***, ***XXV***, ***XXVI*** and ***XXVII*** are preferred.

Especially preferred compounds within the scope of Formulae ***IA-IC*** include 8-aza-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-aza-4-(ethoxycarbonyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-4-(ethoxycarbonyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-aza-4-(phenylcarbamoyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-4-(phenylcarbamoyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-aza-4-

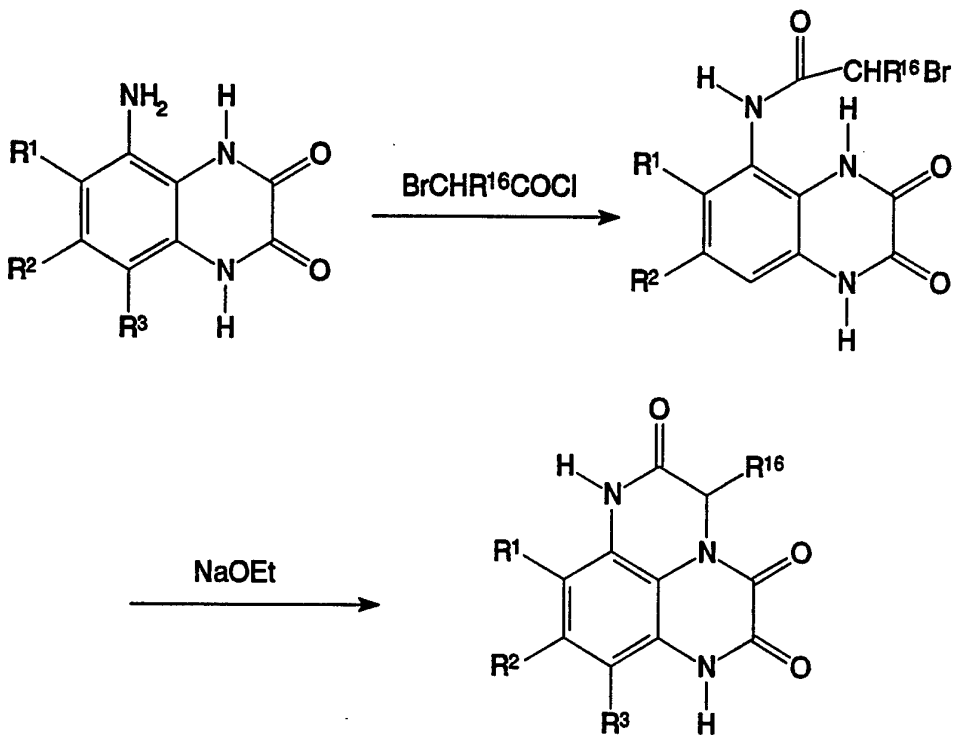
(phenylcarbamoylmethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-4-(phenylcarbamoylmethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-aza-4-(phenylethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-4-(phenylethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-aza-4-(phenylpropyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 8-(N-oxy)aza-4-(phenylpropyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-4-(ethyl carboxyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-4-(ethyl carboxyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-4-(phenylcarbamoyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-4-(phenylcarbamoyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-4-(phenylcarbamoylmethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-4-(phenylcarbamoylmethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-4-(phenylethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-4-(phenylethyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-aza-4-(phenylpropyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione, 7-(N-oxy)aza-4-(phenylpropyl)-1,4,6-trihydropyrazino[1,2,3-*de*]quinoxaline-2,3,5-trione.

With respect to Formulae ***IIIA-IIID***, preferred compounds include 8-chloro-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-bromo-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-methyl-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-fluoro-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-nitro-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 7,8-dichloro-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-aza-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione, 8-(N-oxy)aza-3-nitro-1,6-dihydro-4-oxopyrido[2,3,4-*de*]quinoline-2,5-dione.

The aza(N-oxy) group of the (N-oxy) pyridine analogs is considered to function as an electron withdrawing substituent similar to NO_2, and can replace a -CH- group on the aromatic ring. It is therefore expected that the (N-oxy)pyridine analogs of tricyclic dihydroquinolin-2-ones and tetrahydroquinaline-2,3-diones described herein should behave similarly to the corresponding tricyclic dihydroquinolin-2-ones and tetrahydroquinaline-2,3-diones that have high binding to the glycine receptor. It is also expected that the (N-oxy)pyridine analogs of tricyclic dihydroquinolin-2-ones and tetrahydroquinaline-2,3-diones will be easier to formulate in pharmaceutical compositions that are soluble in aqueous solutions, compared to the tricyclic dihydroquinolin-2-ones and tetrahydroquinaline-2,3-diones themselves. Since $\log P_{benzene} = 2.15$ and $\log P_{pyridine\ N\text{-}oxide} = -1.69$ (*see*, Leo *et al.*, *Chem. Rev.* *71*:525 (1971)), there is a difference in log P of -3.84 from benzene to pyridine N-oxide. It is therefore expected that the N-oxide pyridine analogs of the tricyclic dihydroquinolin-2-ones and tetrahydroquinoline-2,3-diones will have a lower log P and will be more water soluble compared to the corresponding tricyclic (4,5 bridged) dihydroquinolin-2-ones and tetrahydroquinoline-2,3-diones.

The compounds of Formula *V* can be prepared by the following synthetic route:

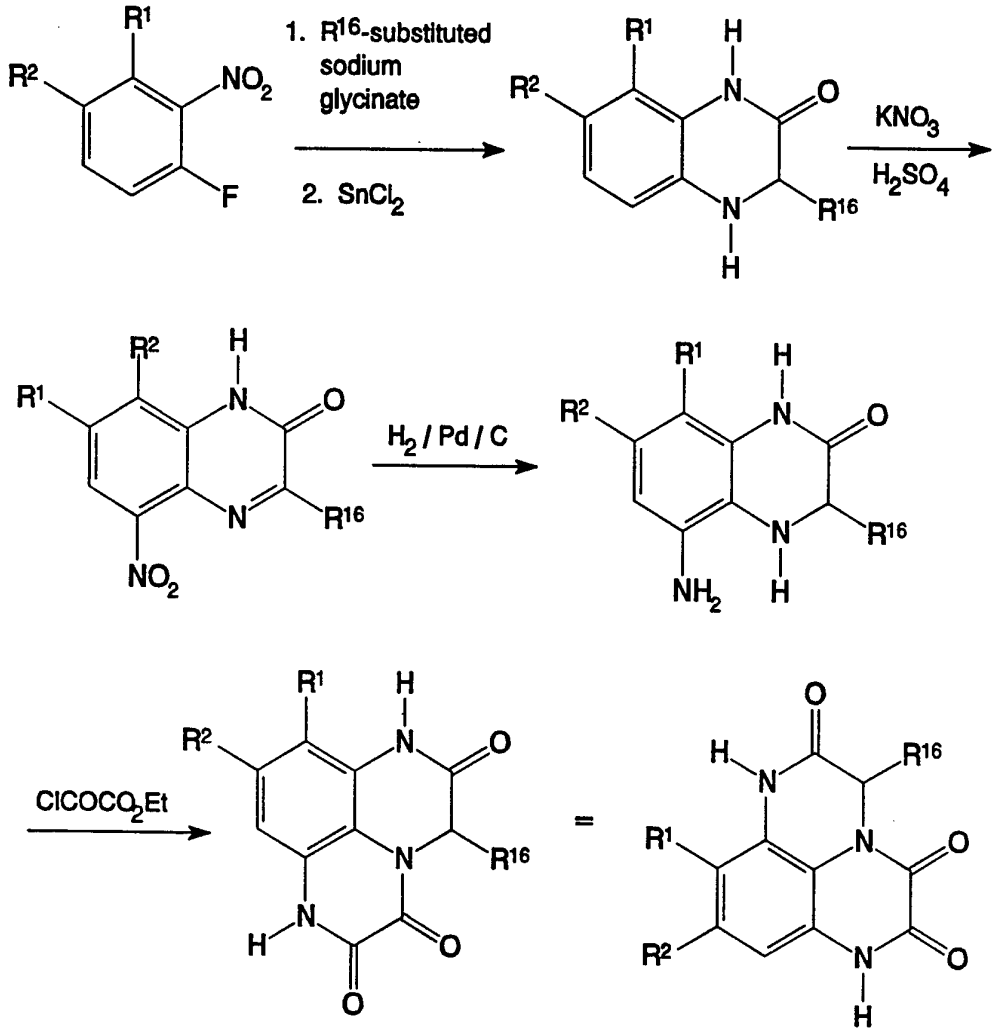
Scheme I



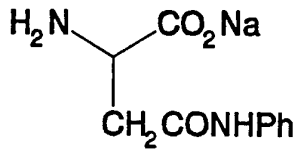
wherein R^1, R^2, R^3 and R^{16} are defined as above.

Alternatively, compounds within the scope of Formula *V* can be prepared by the route outlined below:

Scheme II

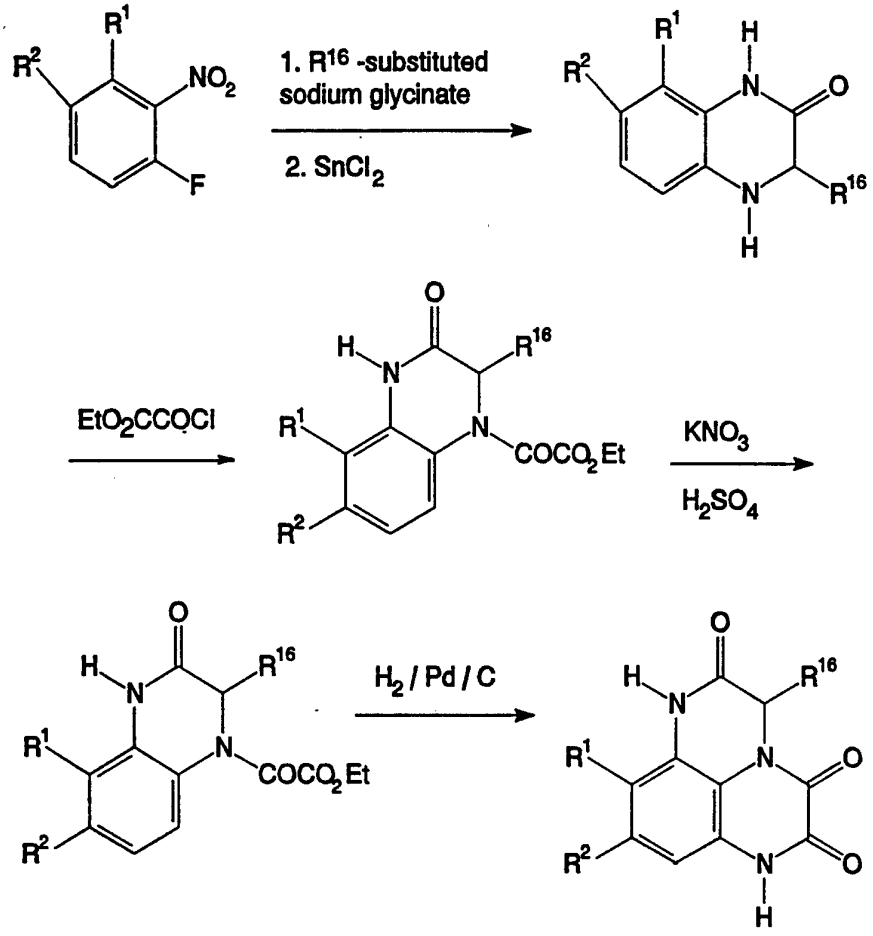


wherein R^1, R^2 and R^{16} are as defined above. An example of the substituted sodium glucinate is the following aspartic acid derivative:



Alternatively, the amine could be protected before nitration as shown in Scheme III.

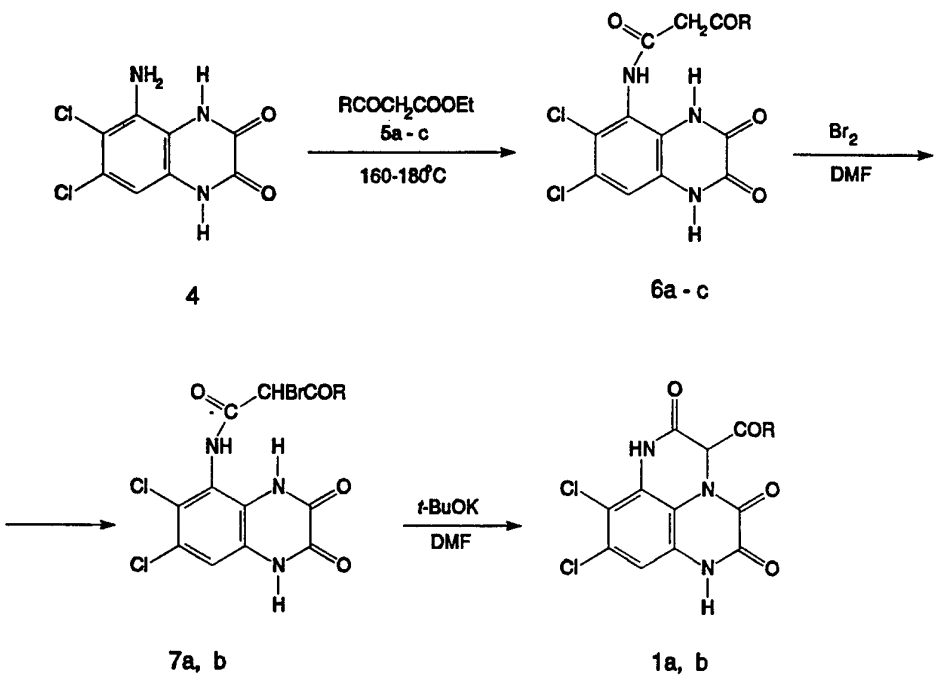
Scheme III



wherein R^1, R^2 and R^{16} are defined as above.

Compounds of Formula *V*, where R^{19} is one of CO_2R^7 or COR^7, can be prepared by the following route:

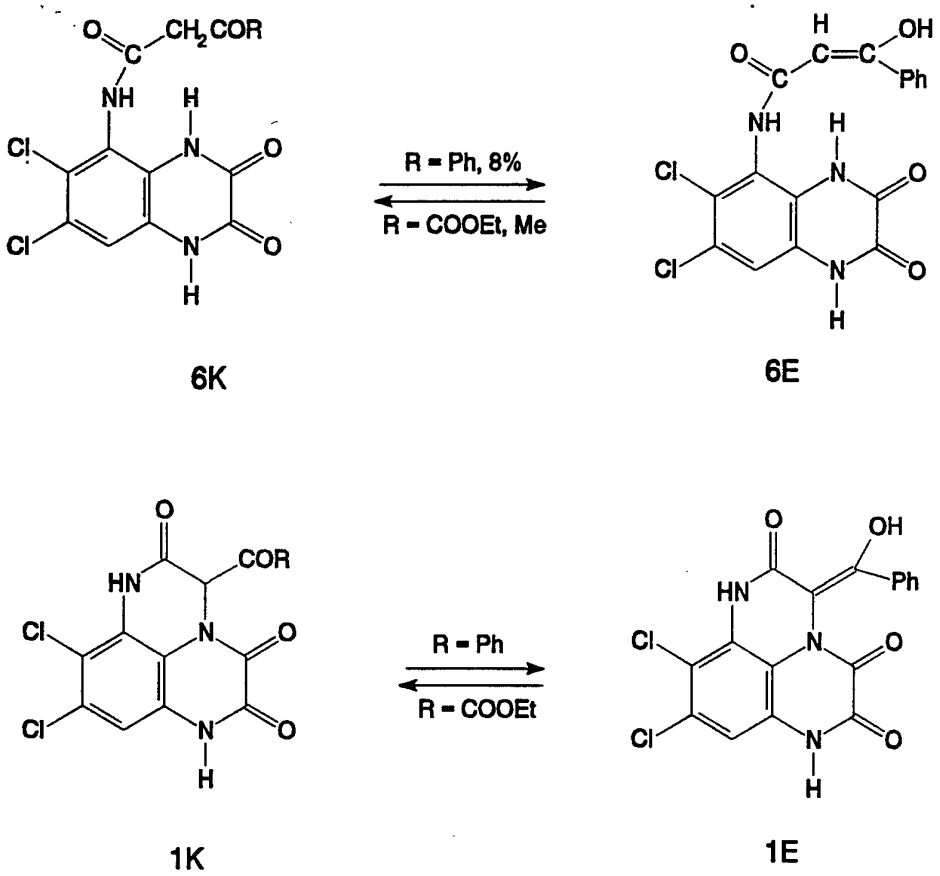
Scheme IV



1, 5, 6, 7. a. R = OEt; b. R = Ph; c. R = Me

The starting amine **4** is prepared from the corresponding 5-nitro derivative by $SnCl_2$ reduction. *See*, PCT Published Application WO94/00124. The amine **4** is acylated by heating in excess of an appropriate β-dicarbonyl compound **5a-c** to give an acyl derivative **6a-c**. The acyl derivative **6a,b** is then reacted with bromine in DMF to give the corresponding bromo derivative **7a,b**. Cyclization of the bromide **7a,b** into the final tricyclic compound 1 **a,b** is performed with potassium tert-butoxide in DMF.

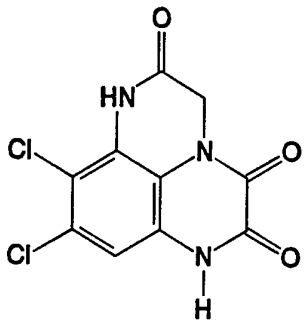
According to ^1H NMR data β-carbonyl amides **6** exist in dicarbonyl (keto) form **6K** (only compound **6b** had about 8% of the enolic form **6E** in DMSO-D_6 solution). Tricyclic compound **1a** exists in keto form **1K**, while phenyl derivative **1b** exists exclusively in enolic form **1E**.



6K 6E

1K 1E

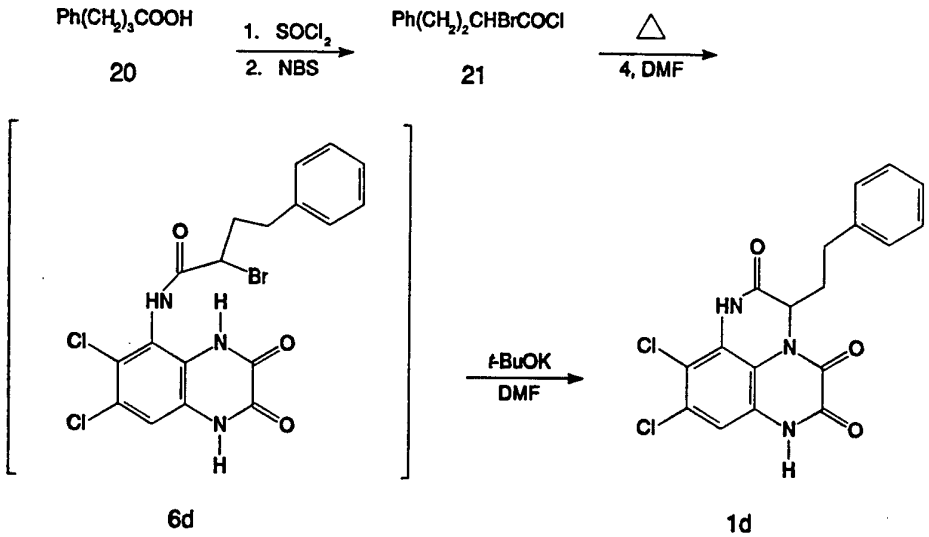
It was found that in the in the first step of Scheme *IV*, the acylation reaction is limited to β-dicarbonyl compounds that are unsubstituted at the central carbon atom. The second step the Scheme *IV* works well for β-dicarbonyl derivatives only. Attempts to introduce functional or alkyl groups in tricyclic compounds **1** were restricted by very limited solubility in conventional solvents making separation of the reaction products difficult. Reactions studied for compound **1a** included alkylation, nitrosation and oximation. In each instance, the starting material gave inseparable (due to a low solubility) mixtures of products. Basic hydrolysis of the compound **1a** gave tricycle **11** in a quantative yield. This reaction proceeds in 1N NaOH within 15 min and does not require acidification to achieve decarboxylation.



11

Compounds of Formula *V* where R^{19} is alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl, any of which is optionally substituted, can be prepared according to Scheme *V*.

Scheme V



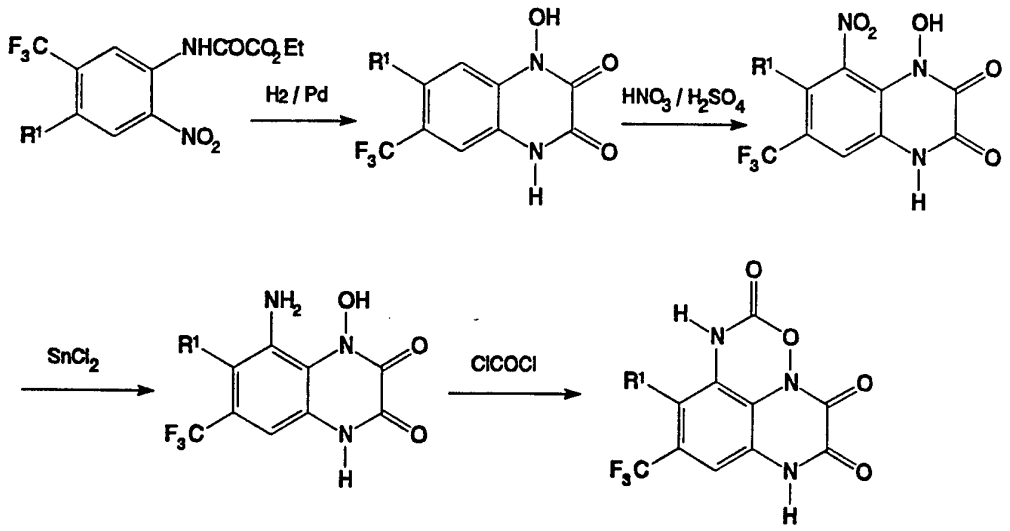
6d 1d

This synthesis utilized the $SOCl_2$/NBS alternative to Hell-Volgardt-Zelinsky reaction (Harpp *et al.*, *Org. Synth. Coll. Vol. IV*:190) for preparing

the α-bromo acyl chloride **21**. Intermediate bromo derivative **6d** was not isolated and was treated *in situ* with an excess of base. This sequence allows the use of any aliphatic carboxylic acid for preparation of tricyclic compounds **1**.

The compounds of Formula *VI* can be prepared by the route outlined below:

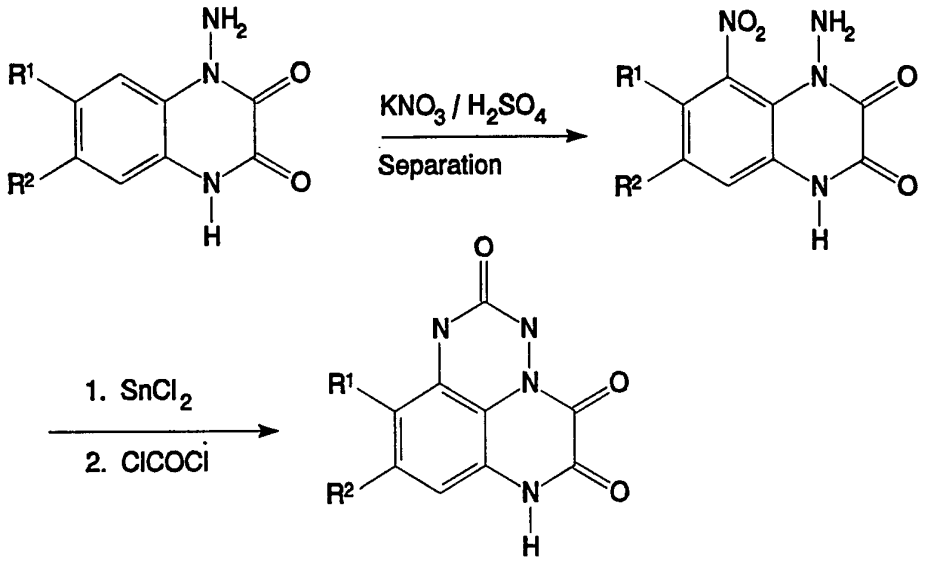
Scheme VI



wherein R^1 is defined above.

Compounds of Formula *VII* can be prepared by the following route:

Scheme VII

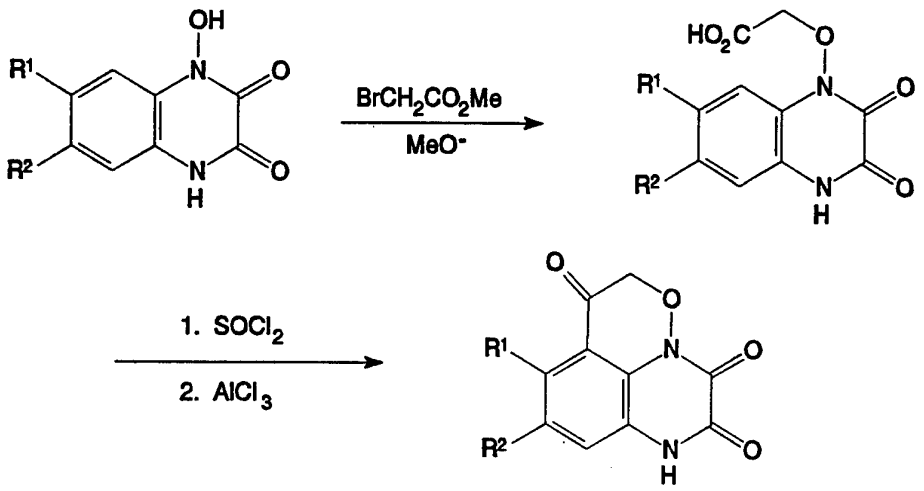


where R^1 and R^2 are defined above.

The N-amino-1,4-dihydroquinoxaline-2,3-dione starting material is prepared by N-nitrosylating one of the amide nitrogen atoms of 1,4-dihydroquinoxaline-2,3-dione, followed by reduction. See International Published application WO94/00124, which is fully incorporated by reference herein.

Compounds having the structure represented by Formula *VIII* can be prepared as illustrated in the following synthetic scheme:

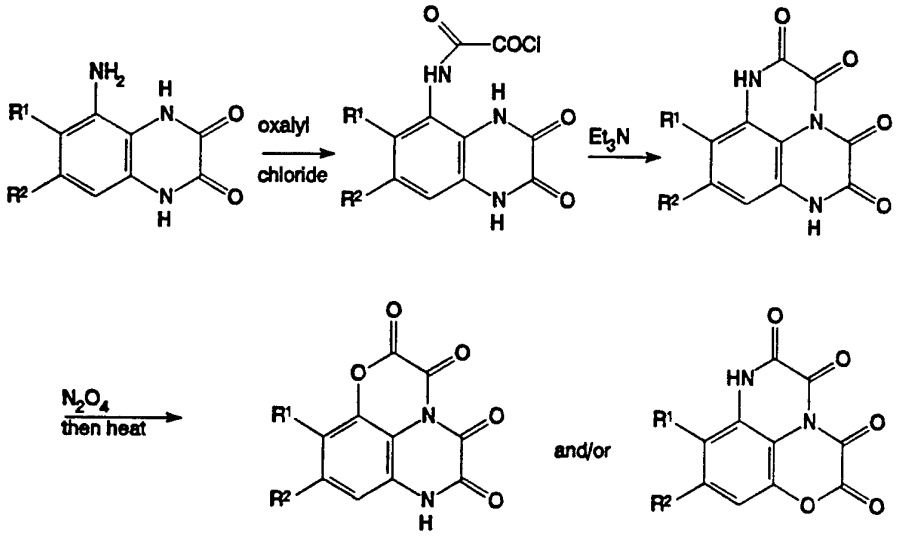
Scheme VIII



wherein R^1 and R^2 are defined above. In this reaction, R^1 and R^2 may preferably be Cl.

Compounds having the structure represented by Formula *X* or Formula *XI* can be prepared by the following scheme:

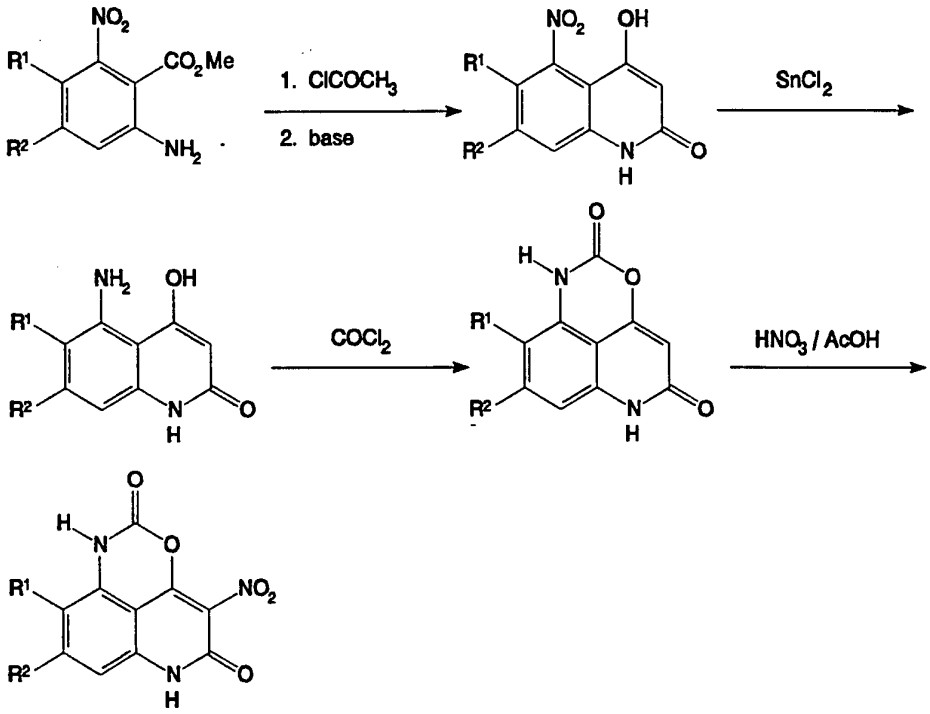
Scheme IX



wherein R^1 and R^2 are defined above. In this reaction, R^1 and R^2 may preferably be Cl.

Compounds having a structure included within Formula *XXIV* can be prepared according to the scheme:

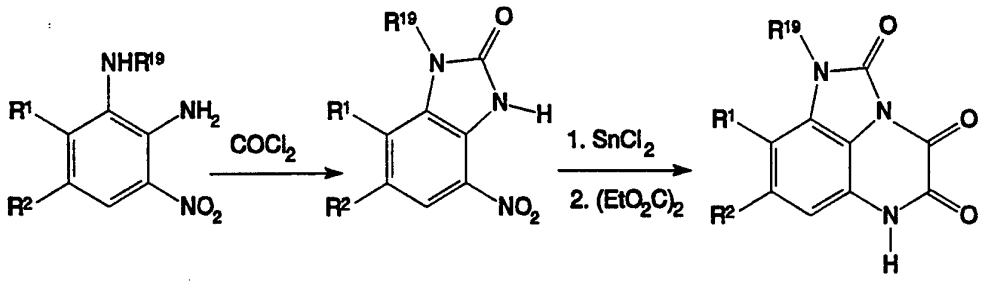
Scheme X



wherein R^1 and R^2 are defined above. In this reaction, R^1 may preferably be hydrogen and R^2 may preferably be Cl.

Compounds having a structure represented by Formula *XIII* can be prepared as illustrated in the following scheme:

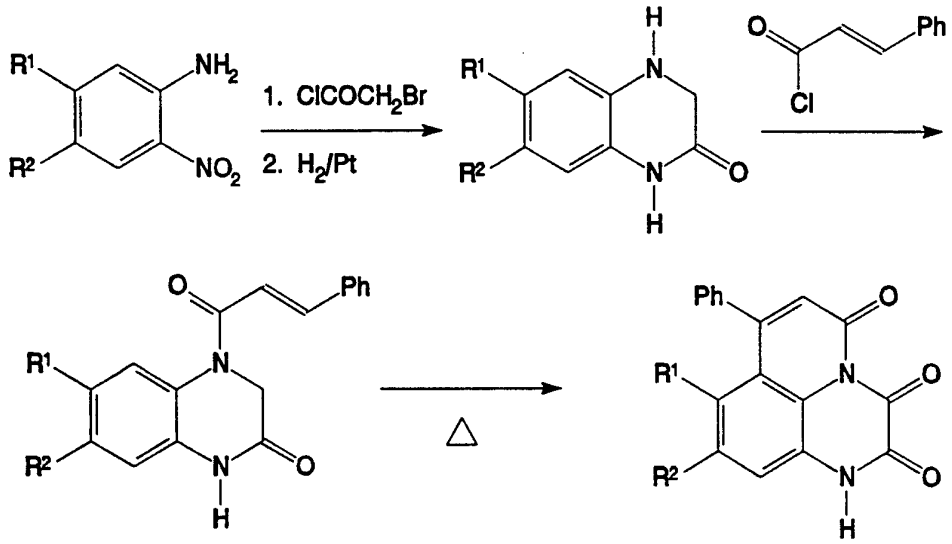
Scheme XI



wherein R^1, R^2 and R^{19} are defined above.

Compounds having a structure represented by Formula *XIV* can be prepared as illustrated in the following scheme:

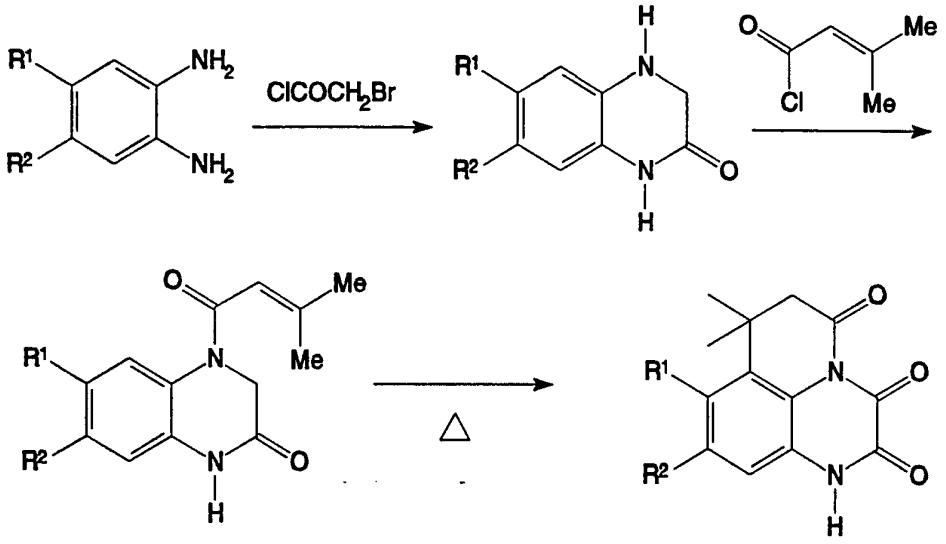
Scheme XII



wherein R^1 and R^2 are defined above.

Compounds having a structure represented by Formula *XV* can be prepared as illustrated in the following scheme:

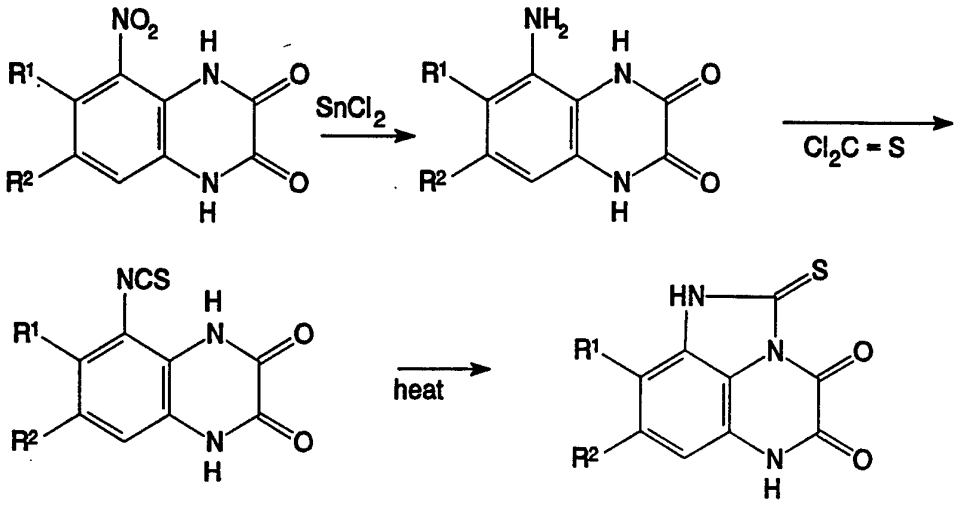
Scheme XIII



wherein R^1 and R^2 are defined above.

Compounds having a structure represented by Formula *XVI* can be prepared as illustrated in the following scheme:

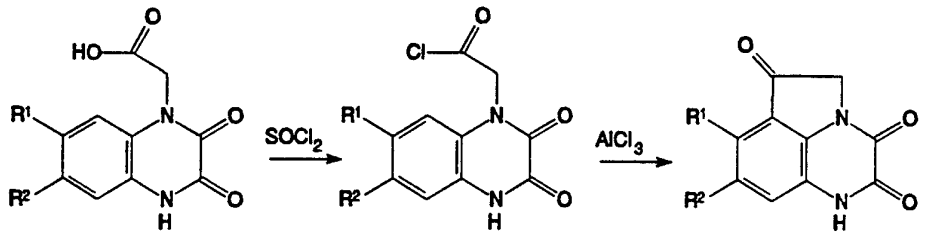
Scheme XIV



wherein R^1 and R^2 are defined above. In this reaction, R^1 and R^2 may preferably be Cl. The 5-nitro-QX starting material for Scheme *XIV* can be prepared according to the method disclosed in International Published application WO94/00124, *supra*.

Compounds having a structure represented by Formula *XVII* can be prepared as illustrated in the following scheme:

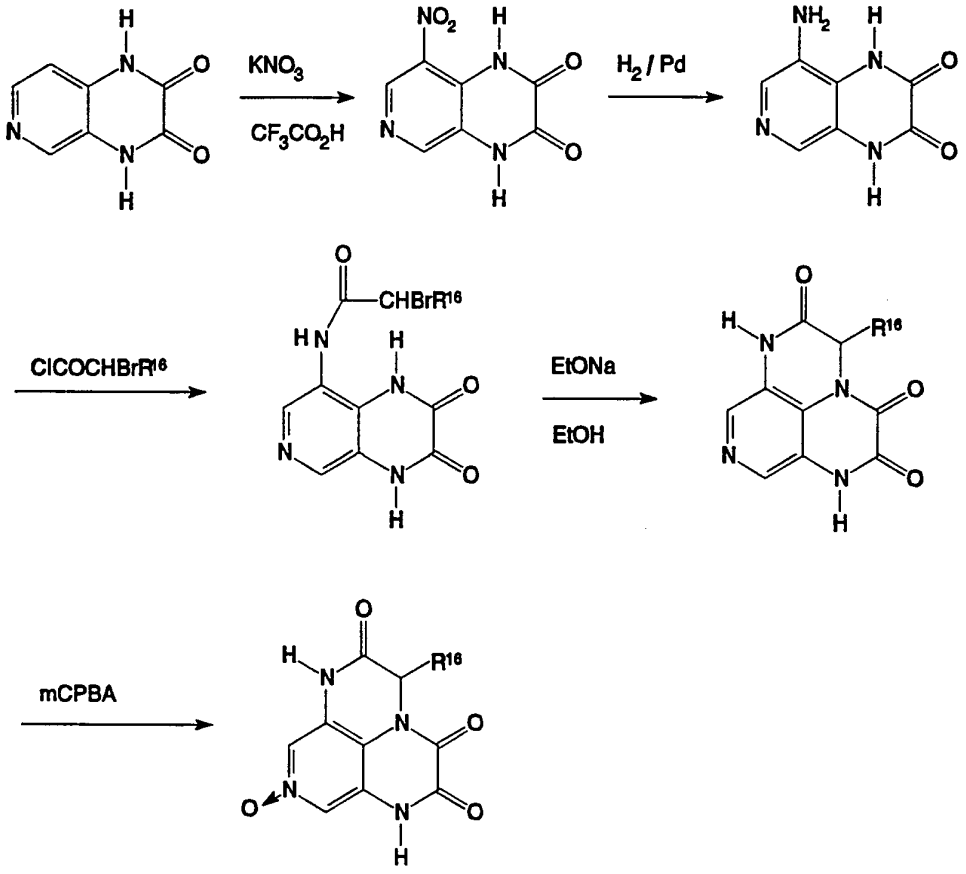
Scheme XV



wherein R^1 and R^2 are defined above. In this reaction, R^1 and R^2 may preferably be Cl.

Aza and aza(N-oxy) compounds having a structure represented by Formula *XVIII* can be prepared as illustrated in the following scheme:

Scheme XVI

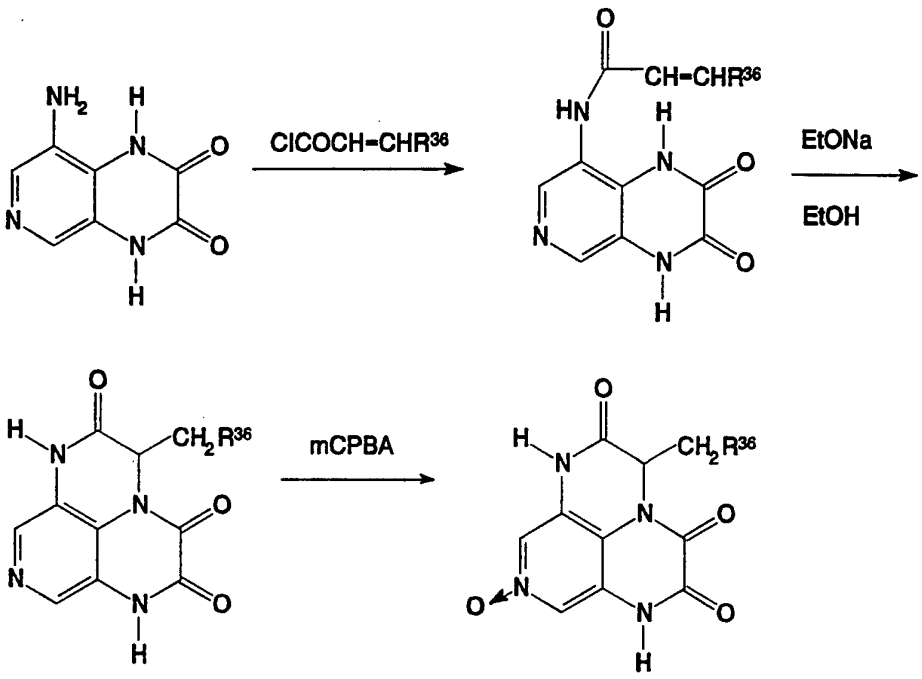


wherein R^{16} is defined as above.

Alternatively, compounds within the scope of the Formula *XVIII* can be prepared as illustrated in Scheme *XVII*.

5

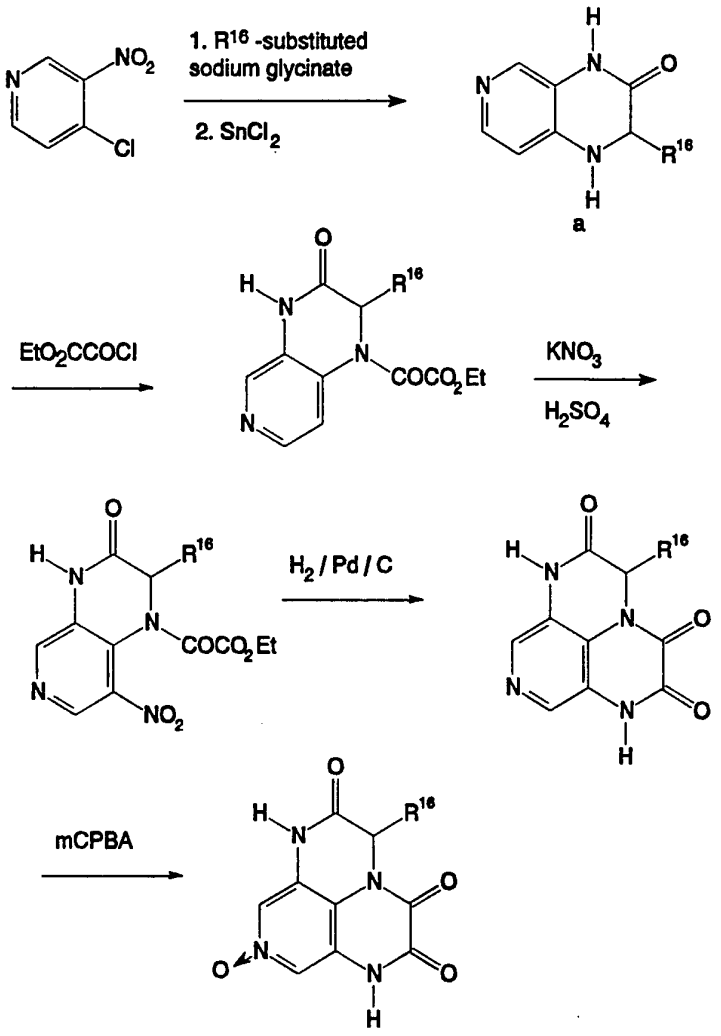
Scheme XVII



wherein R^{36} represents hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, heteroarylalkyl, substituted heteroaryl, substituted heteroarylalkyl or heterocycloalkyl.

A third approach to preparing aza and aza(N-oxy) compounds is shown in Scheme *XVIII*:

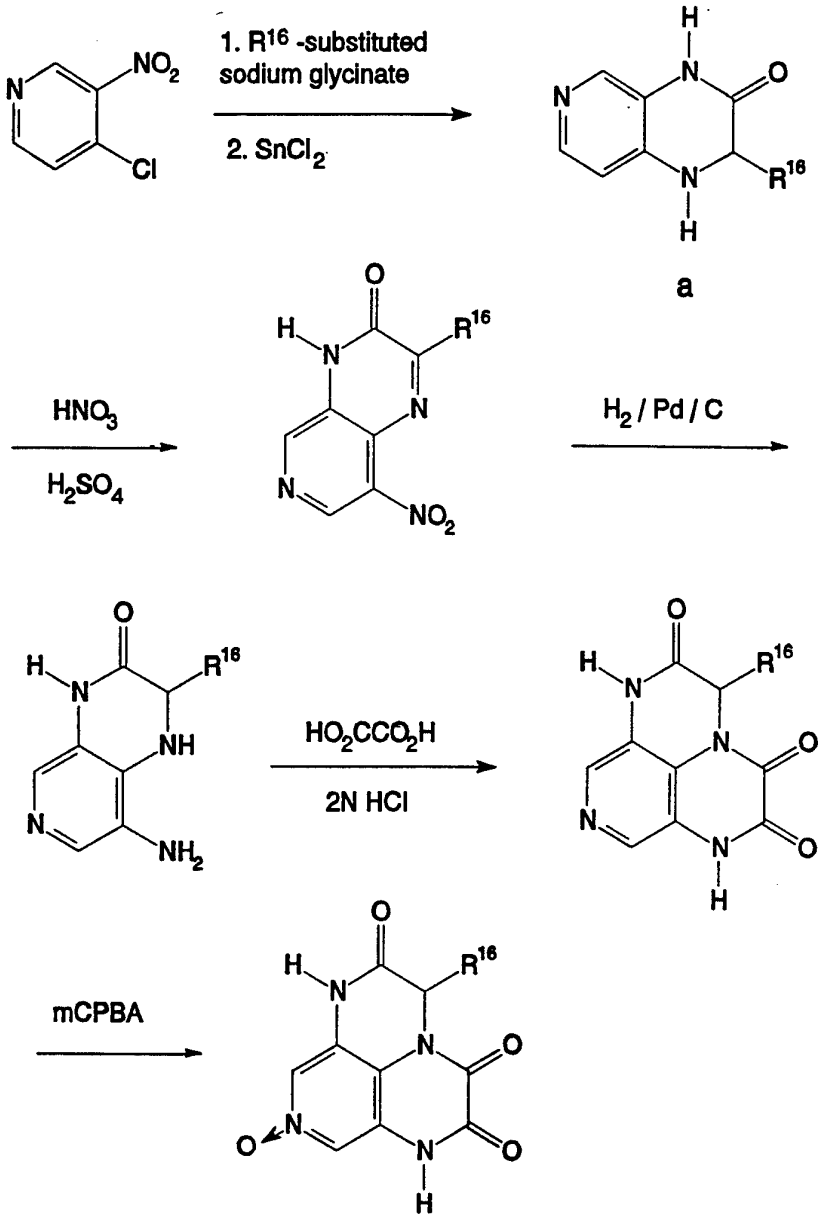
Scheme XVIII



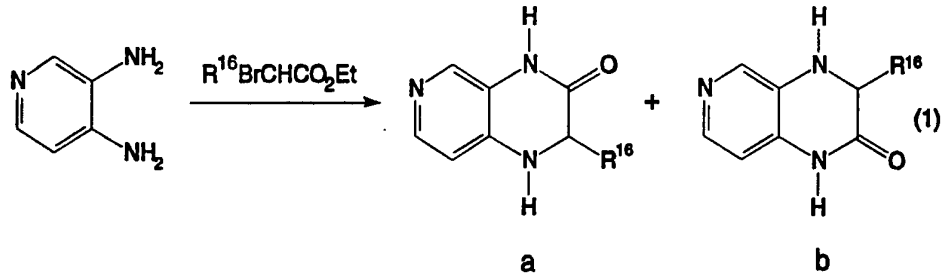
wherein R^{16} is defined as above.

Alternatively, the nitration step may occur earlier as shown in Scheme *XIX*:

Scheme XIX

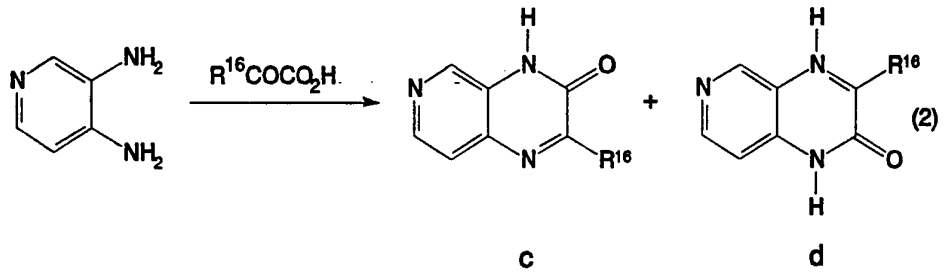

1. R16 -substituted sodium glycinate
2. SnCl2
a
HNO3
H2SO4
H2 / Pd / C
HO2CCO2H
2N HCl
mCPBA

The starting material, compound a, in Schemes *XVIII* and *XIX* can also be prepared as shown in equation 1.



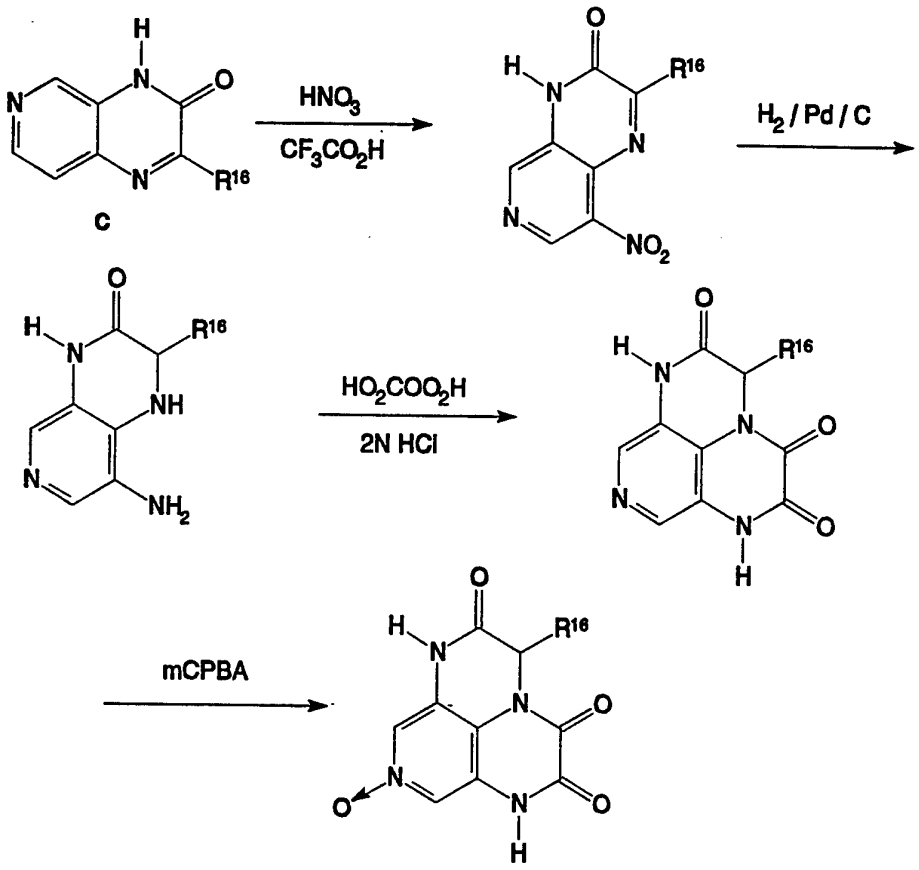
where R^{16} is defined as above.

An additional approach to forming aza and aza(N-oxy) compounds is shown in equation 2 and Scheme *XX*. Equation 2 shows the preparation of the starting materials for Scheme *XX*.



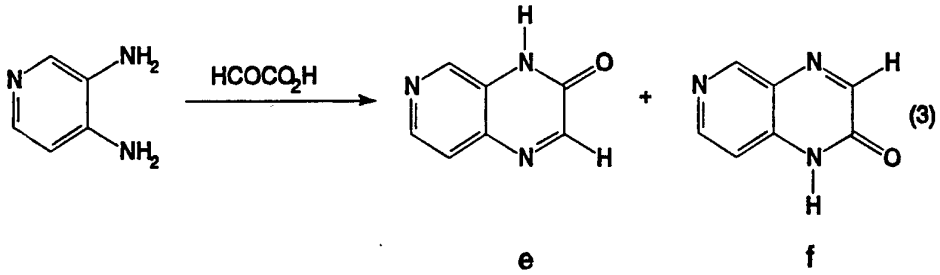
wherein R^{16} is defined as above.

Scheme XX



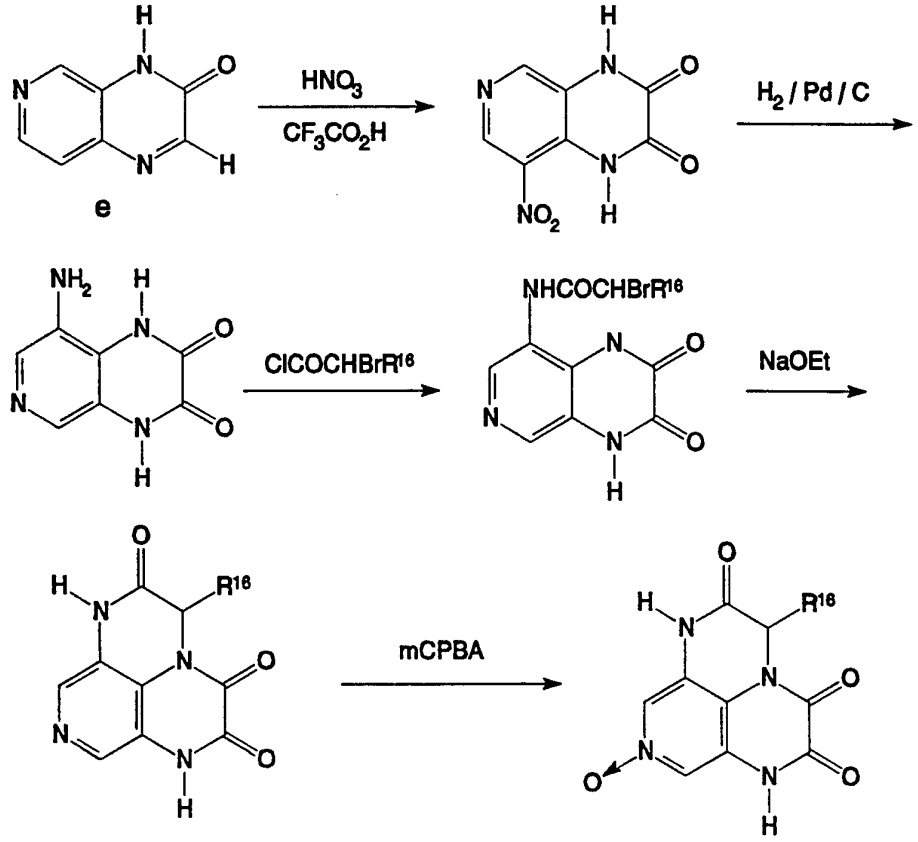
where R^{16} is defined as above.

Alternatively, an oxidative nitration approach as shown in equation 3 and Scheme *XXI* may be employed. Equation 3 shows the preparation of compound **e**, the starting material for Scheme *XXI* and compound **f**, the starting material for Scheme *XXII*.



e f

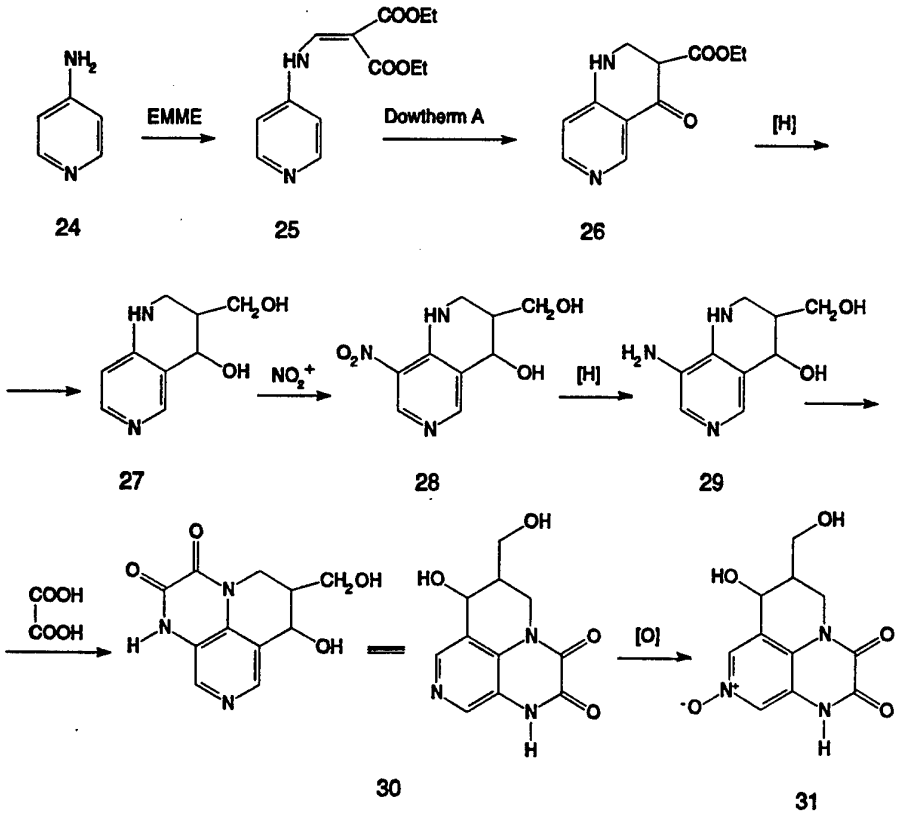
Scheme XXI



where R^{16} is defined as above.

Bridged pyrazinopyridines of Formula *IC* can be formed by the following scheme:

Scheme XXII

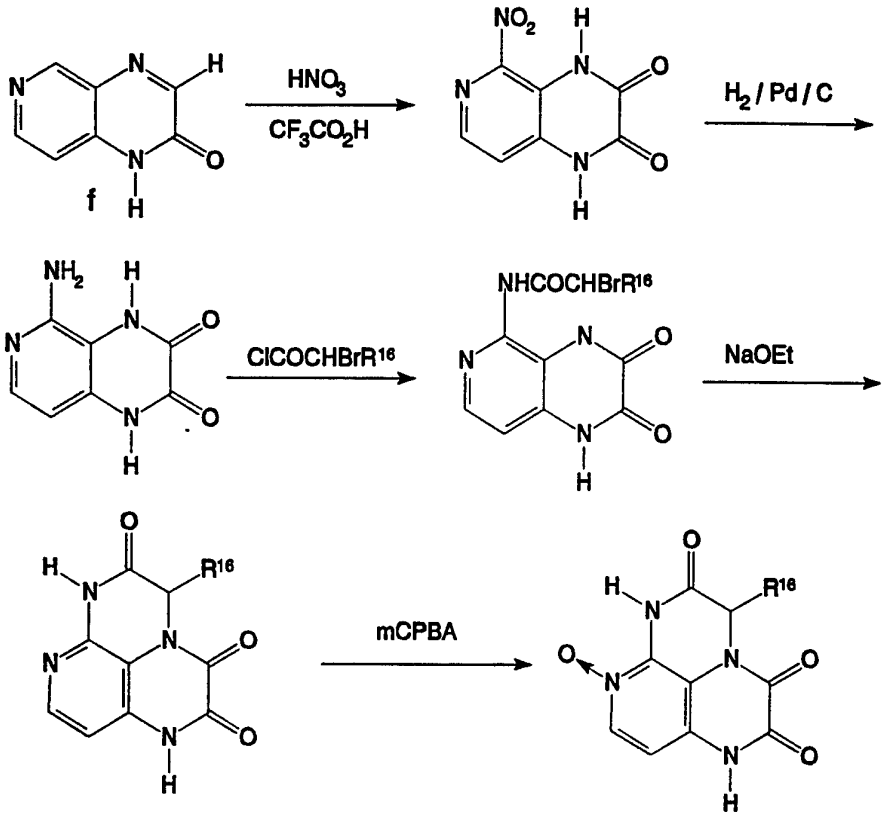


4-Aminopyridine **24** is reacted with diethylethoxymethylene maleate (Ethoxy Methylene Malonic Ester, EMME) to give a dicarboxyl derivative **25**. Compound **25** is heated in Dowtherm A resulting in thermal cyclization to form a 1,6-naphtyridine system in compound **26**. Compound **26** was previously prepared by this route and after hydrolysis and decarboxylation was used for synthesis of the unsubstituted parent heterocycle (Czuba, W., *Chem.*

Heterocycl. Comp 1 (1979) (Engl. transl.); Hauser and Reynolds, *J. Org. Chem 15*:1224 (1950); Albert, *J. Chem. Soc*:1790 (1960)). Reduction of compound **26** is expected to be selective with retention of the aromatic character in the 4-aminosubstituted pyridine ring (Czuba, W., *Chem. Heterocycl. Comp 1* (1979) (Engl. transl.); Yoshinobu, *Chem. Pharm. Bull. 8*:427 (1960)). However, reduction with $LiAlH_4$ gives a complex mixture of products. The ester grouping in the compound **26** can be easily removed, if necessary by hydrolysis-decarboxylation (Czuba, W., *Chem. Heterocycl. Comp 1* (1979) (Engl. transl.)). Compound **27** has only one center for nitration, giving the nitro derivative **28**. Reduction of this compound will not effect the aromatic ring and will give amine **29**. Condensation with oxalic acid (or oxalyl chloride) will result in pyrazine ring closure to form compound **30**. This compound can be tested for binding and can be oxidized to N-oxide derivative **31**.

The 7-aza and 7-(N-oxy)aza analogs with Formula ***XIX*** could be prepared similarly using compounds **f** from equation 3 as shown in Scheme ***XXIII***.

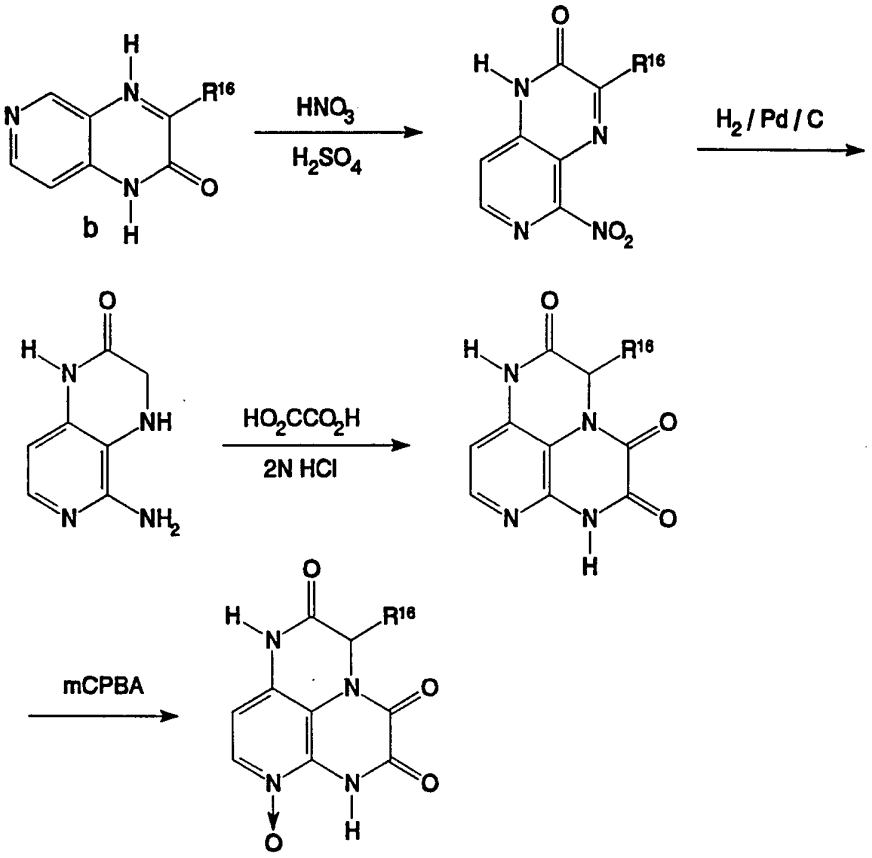
Scheme XXIII



wherein R^{16} is defined as above.

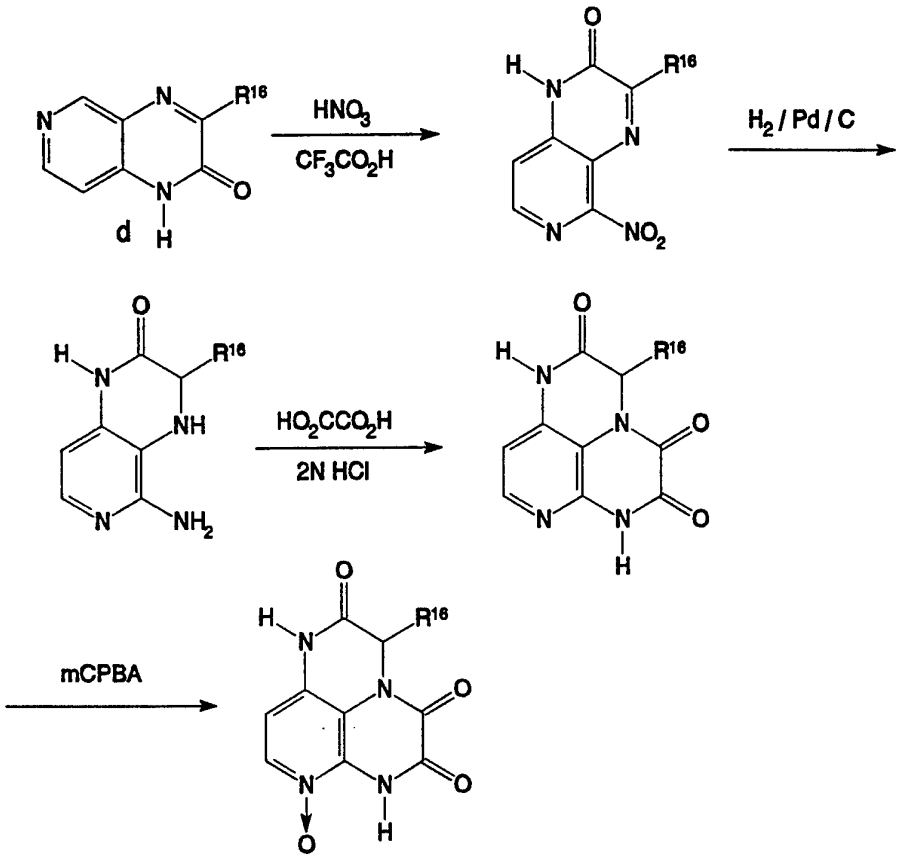
Compounds having a structure represented by Formula *ID* can be prepared as illustrated in the Schemes *XXIV* and *XXV* using compound **b** and compound **d**, which compounds are prepared according to equations (1) and (2) above.

Scheme XXIV



wherein R^{16} is defined as above.

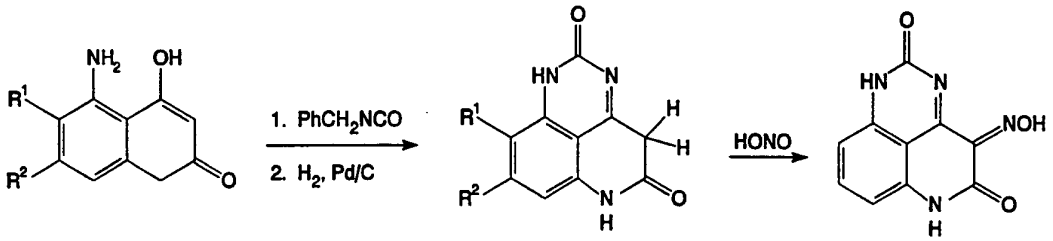
Scheme XXV



wherein R^{16} is defined as above.

Tricyclic compounds having a 3-oxime substituent (Formula **XXIV**) can be formed by the following general reaction scheme.

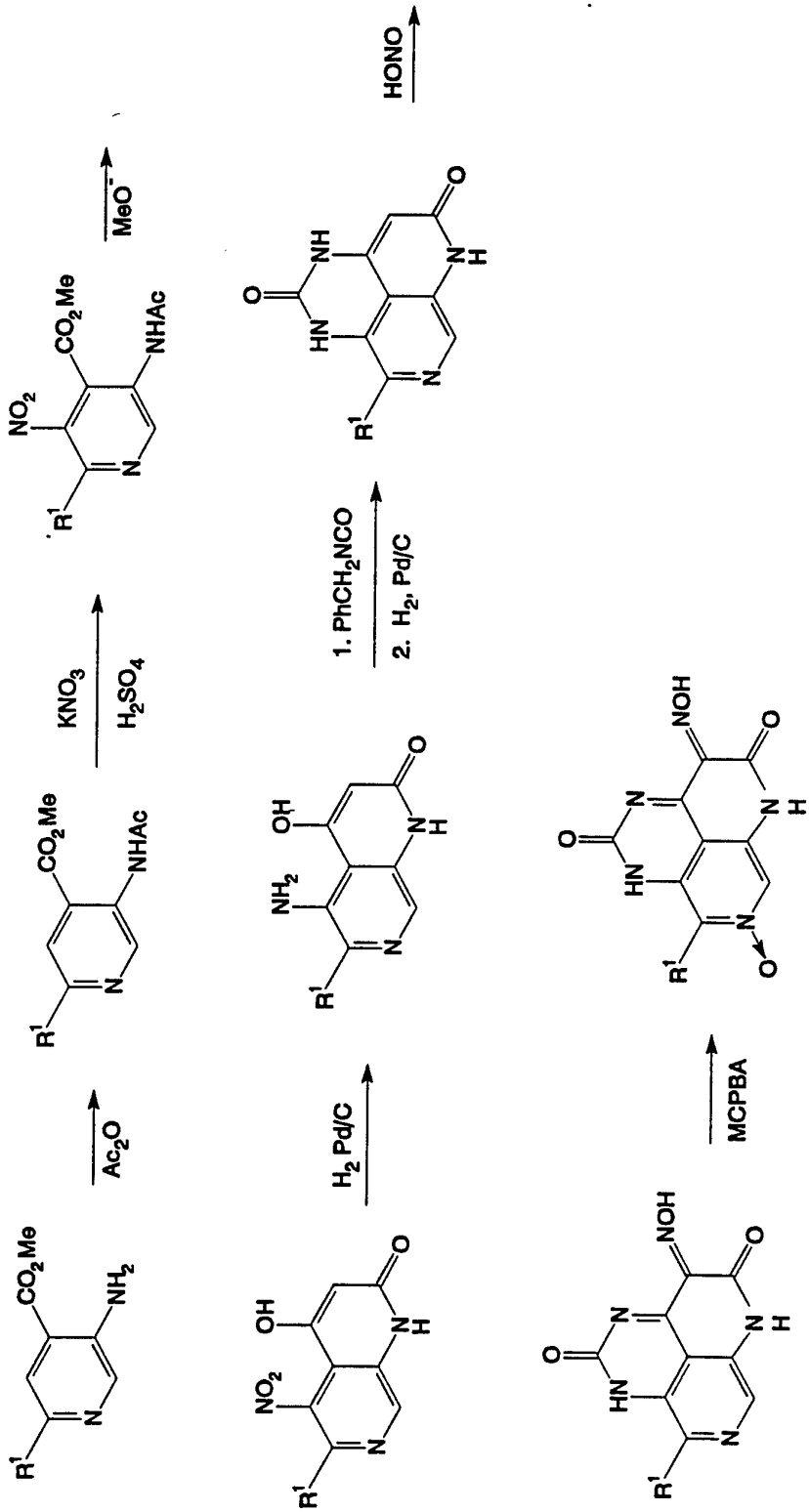
Scheme XXVI



wherein R^1 and R^2 are defined as above.

Similarly, aza- and (N-oxy)aza derivatives of 3-oxime substituted tricyclic compounds (Formula **XXV**) are formed by the following scheme:

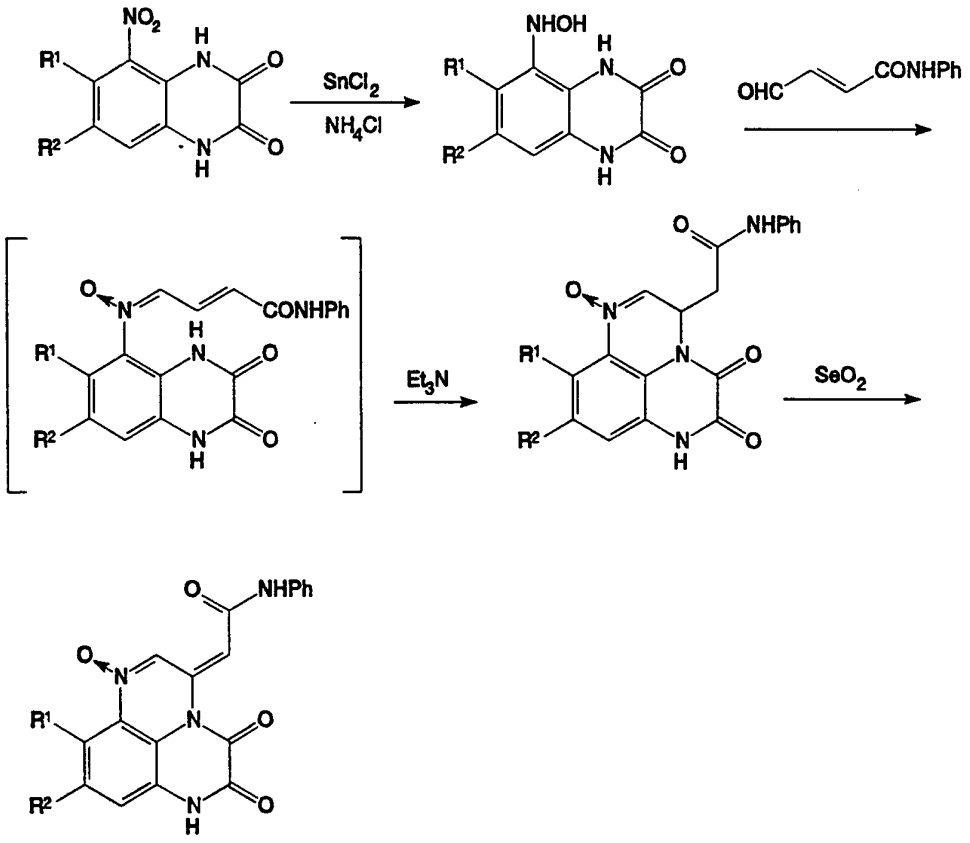
Scheme XXVII



wherein R^1 is defined as above.

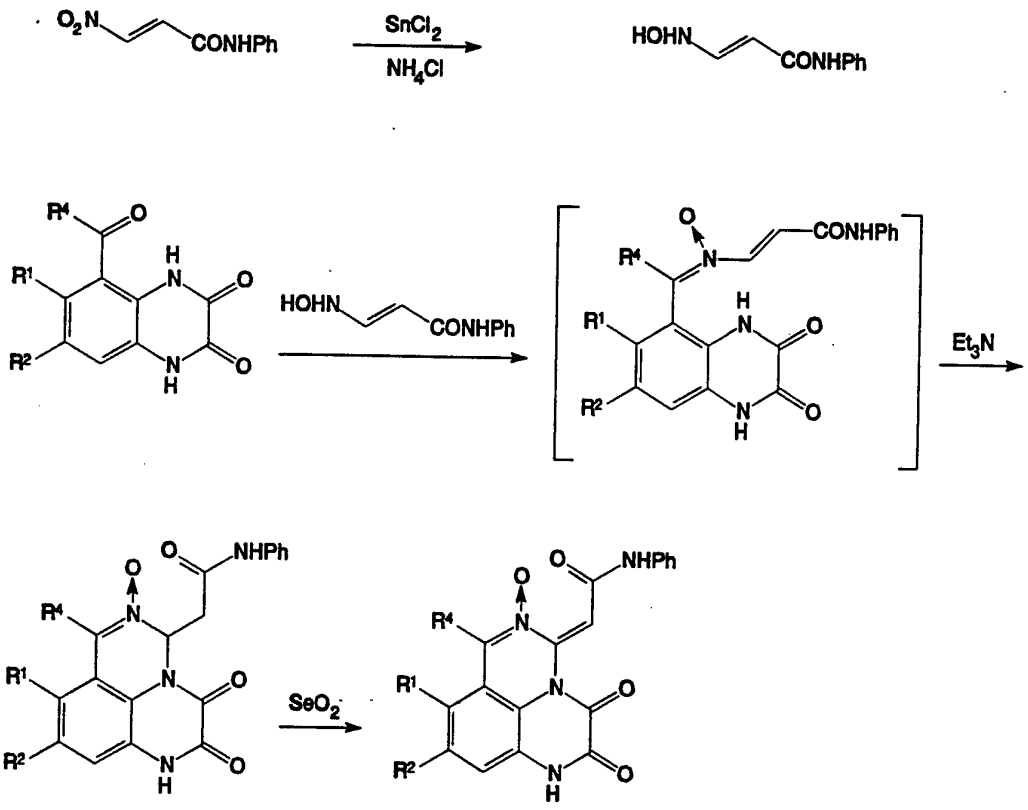
Compounds having a nitrone in the 4-nitrogen, 5-carbon bridging moiety (Formulae *XXVIII-XXXI*) can be synthesized according to one of the following schemes:

Scheme XXVIII



wherein R^1 and R^2 are defined above. In this reaction, R^1 and R^2 may preferably be Cl.

Scheme XXIX

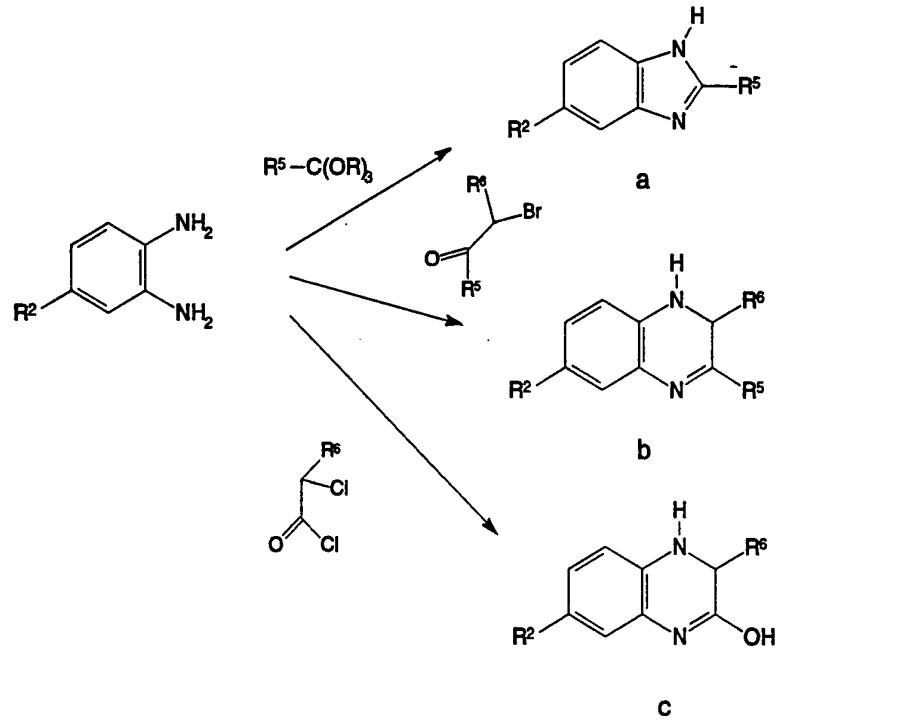


wherein R^1, R^2 and R^4 are defined above. In this reaction, R^1 and R^2 may preferably be Cl.

A general method for preparing 5-substituted 1,4-dihydroquinoxaline-2,3-dione starting materials is disclosed in International Published application WO94/00124, *supra*.

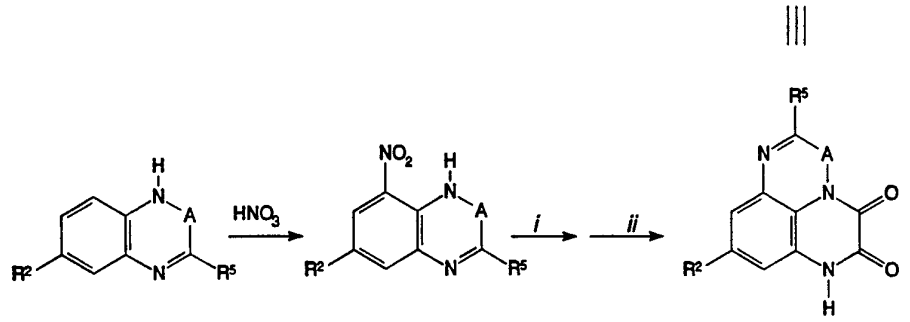
In addition to the synthetic routes disclosed above, the following generalized synthetic routes are considered to be useful for obtaining tricyclic-4-5 bridged quinoxaline compounds of the present invention.

Scheme A



General Structure of a, b, c

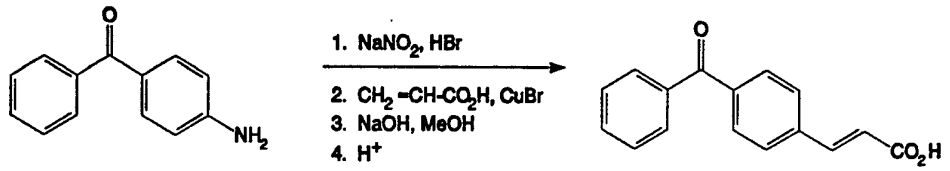
A = CHR^6 or a bond.



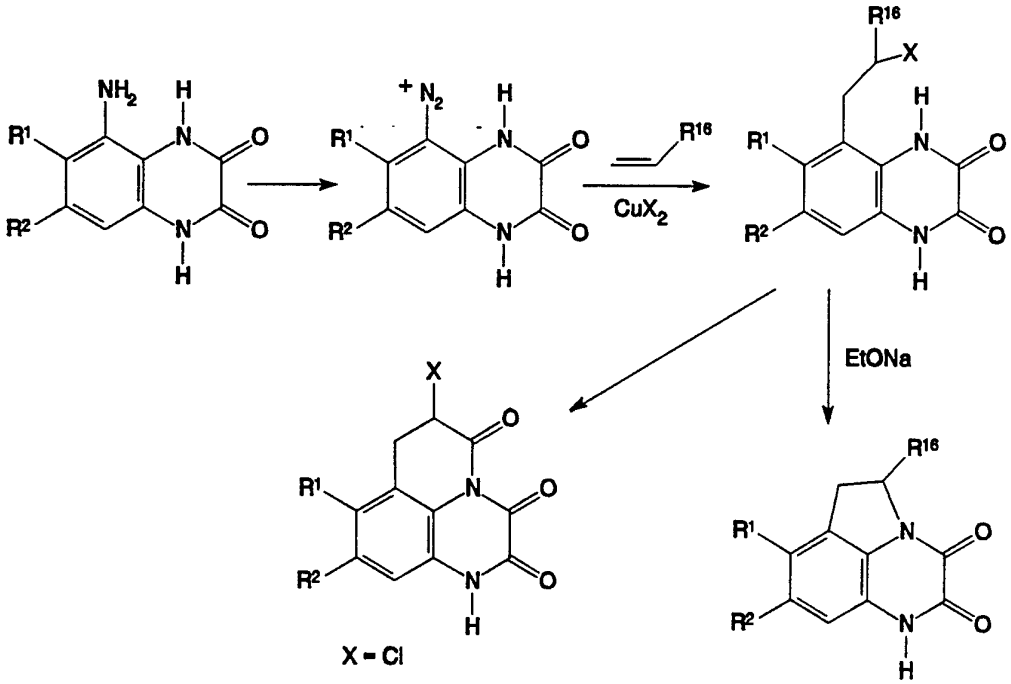
i, Reduction ($SnCl_2$ or $Na_2S_2O_4$); *ii*, ClCOCOCl

wherein R^2, R^5 and R^6 are defined above.

Scheme B shows a synthetic route that employs a diazonium salt of a quinoxalinedione to form compounds of Formula *I*. The reaction of a diazonium salt with acrylic acid is well known and is called a Meerwein arylation. For example:



Scheme B



wherein R^1, R^2 and R^{16} are defined above. 5-Amino-1,4-dihydroxyquinoxaline-2,3-dione can be prepared by the method disclosed in International Published application WO94/00124, *supra*.

The compounds of the present invention can be tested for potential glycine antagonist activity by observing the inhibition of binding of 1 μM glycine-stimulated [^{3}H]-MK-801 in rat or guinea pig brain membrane homogenates. The more potent the glycine antagonist, the less [^{3}H]-MK-801 can bind since the [^{3}H]-MK801 binding site (PCP receptor) is accessible only upon the opening of the ion channel by glutamate *and* glycine (Fletcher, E.L. *et al.*, in *Glycine Neurotransmission*, Otterson, P., *et al.*, eds., John Wiley and Sons, New York (1990); Johnson, J.W., *et al.*, *Nature 325*:529 (1987)).

The binding affinities of the compounds at NMDA receptor glycine sites may also be estimated by electrophysiological assays with either cloned rat NMDA receptors expressed in Xenopus oocytes, or non-NMDA receptors expressed in oocytes by whole rat brain poly(A)$^+$ RNA. K_i values were estimated by assuming competitive inhibition and assaying suppression of membrane current responses elicited by fixed concentrations of agonist: 1mM glycine and 100 mM glutamate for NMDA receptors; 20 mM kainic acid for non-NMDA receptors. For NMDA receptors K_is were approximated by averaging values at three subtype combinations (NR1A / NR2A, NR1A / NR2B, and NR1A / NR2C). See International Published application WO94/00124, *supra*.

Preferably, the compounds of the invention exhibit a binding affinity to the glycine binding site of K_i = about 10 μM or less, more preferably, 1 μM or less, and more preferably, 500 nM or less, and more preferably, 100 nM or less, and most preferably, about 10 nM or less. Also preferable are compounds that exhibit binding at the kainate and AMPA sites of not less than K_i = 1 μM and, more preferably, not less than 10 μM.

The novel glycine antagonists can be tested for *in vivo* activity after intraperitoneal injection using a number of anticonvulsant tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures

in mice, NMDA-induced death in mice, and MES in mice). Preferred compounds exhibit ataxia side effects in the rotorod ataxia test at dosage levels of greater than about 100 mg/kg, more preferably, greater than about 200 mg/kg.

The compounds can also be tested in drug discrimination tests in rats trained to discriminate PCP from saline. It is expected that most of the compounds will not generalize to PCP at any dose. In addition, it is also expected that none of the compounds will produce a behavioral excitation in locomotor activity tests in the mouse. It is expected that such results will suggest that the glycine, AMPA, kainate, and quisqualate antagonists of the present invention do not show the PCP-like behavioral side effects that are common to NMDA channel blockers such as MK-801 and PCP or to competitive NMDA antagonists such as CGS19755.

The glycine and excitatory amino acid antagonists are also expected to show potent activity *in vivo* after intraperitoneal injection suggesting that these compounds can penetrate the blood/brain barrier.

Thus, the present invention is directed to compounds having high binding to the glycine receptor and low binding to the kainate and AMPA sites. The glycine antagonist potency *in vitro* can be determined using a 1μM glycine-stimulated [^{3}H]-MK801 binding assay. This assay takes advantage of the dependence of the binding of [^{3}H]-MK801 to the PCP receptor inside the pore of the NMDA channel on the presence of both glutamate and glycine. In the absence of glycine, but in the presence of glutamate, [^{3}H]-MK801 cannot bind effectively to the PCP receptor because the NMDA channel remains closed and access of [^{3}H]-MK801 to the PCP receptor inside the closed channel pore is severely restricted.

The assay is conducted using rat brain membrane homogenates that are enriched in NMDA receptors. The membranes are prepared as follows. Frozen rat brains (obtained from Pel-Freez, Rogers, Arkansas) are homogenized in 15 volumes (w/v) of ice cold 0.32 M sucrose. The homogenate is spun at 1,000 x g for ten minutes. The supernatant is collected

and spun for 20 minutes at 44,000 x g. The pellet is suspended in 15 volumes of water (relative to original brain weight). The homogenate is again spun at 44,000 x g for twenty minutes. The pellet is resuspended in 5 volumes of water and the suspension is freeze-thawed 2 times. After the final thaw cycle, the suspension is brought to 15 volumes with water and spun at 44,000 x g for twenty minutes. The pellet is resuspended in 5 volumes of ice-cold 10 mM HEPES, and is titrated to pH 7.4 with KOH containing 0.04% Triton X-100. Membranes are incubated with the Triton/HEPES buffer at 37°C for 15 minutes. The volume is then brought to 15 with ice-cold 10 mM HEPES, pH 7.4, and spun/washed three times with spins of 44,000 x g between washes. The final pellet is suspended in three volumes of 50 mM HEPES, pH 7.4, and the protein concentration is determined with a standard dye-binding protein assay (Bio-Rad, Richmond, CA). The suspension is stored at -80°C until used. Only HPLC grade water is used for all buffers and suspensions/washings. The extensive washings are necessary to remove as much endogenous glycine from the membrane preparation as possible.

On the day of the assay, the previously prepared membranes are thawed and 5 mM Tris/HCl buffer, pH 7.4, is added to yield a final protein concentration of 0.156 mg/mL. For binding assays, 0.8 mL of membranes are pipetted into polypropylene tubes followed by 0.033 mL of 15.1 μM 5,7-dichlorokynurenic acid (DCK), 0.033 ml of 30.3 μM glycine in buffer (or buffer alone), 0.033 mL of 303 μM glutamate in buffer (or for controls, 0.1 mL 1mM PCP instead of DCK/gly/glu), 0.033 mL glycine antagonist in buffer (or buffer alone) and 0.1 mL buffer containing 200,000 cpm [^{3}H]-MK801. Nonspecific binding is defined as the difference in binding that occurs in the absence or presence of PCP (final concentration: 100 μM). To determine the effect of 1 μM glycine on the binding of [^{3}H]-MK801, bound radioactivity in the presence of 10 μM glutamate alone (final concentration) is subtracted from the bound radioactivity in the presence of both 10 μM glutamate and 1 μM glycine (final concentration). A 500 nM concentration (final) of 5,7-dichlorokynurenic (DCK) acid is added to all assay tubes. This

concentration of the glycine antagonist DCK "buffers" most of the residual endogenous glycine that is not removed by the extensive washing steps that are carried out during the membrane preparation procedure. The 500 nM DCK does not interfere with the stimulation of [^{3}H]-MK801 binding that is effected by the addition of 1 μM exogenous glycine.

The assays are incubated for 120 minutes at room temperature after which time the membrane-bound radioactivity is isolated from the free radioactivity by vacuum filtration through Whatman glass fiber filters that had been pretreated with 0.3% polyethyleneimine. Filtration is accomplished using a Brandel 48 well cell harvester. Filtered membranes are washed three times with 3 mL each of ice cold buffer. Filters are transferred to scintillation vials and 5 mL of scintillation cocktail is added. The vials are shaken overnight and the radioactivity is counted by liquid scintillation spectroscopy. The assays are done in triplicate and all experiments are conducted at least three times.

Inhibition dose response curves are constructed using increasing concentrations of glycine antagonists from 5 nM to 330 μM. IC_{50}values are determined for compounds active in inhibiting 1 μM glycine-stimulated [^{3}H]-MK801 binding by computer-assisted plotting of the inhibition curves and interpolation. When compounds are found to inhibit glycine-stimulated [^{3}H]-MK801 binding, experiments are conducted to determine whether the inhibition of the glycine-stimulated [^{3}H]-MK801 binding is indeed mediated at the glycine binding site of the NMDA receptor. In these experiments, a fixed concentration of antagonist sufficient to produce a >95% inhibition of the 1 μM glycine-stimulated [^{3}H]-MK801 binding is incubated with the membranes without any additional glycine (above 1 μM) and in the presence of increasing concentrations of additional glycine (2 μM to 1 μM). If the inhibition of [^{3}H]-MK801 binding by the drug in the presence of 1 μM glycine is fully reversed by adding increasing concentrations of glycine, then the inhibition of [^{3}H]-MK801 binding is mediated by the drug acting as an antagonist at the glycine binding site of the NMDA receptor.

After constructing inhibition dose response curves and determination of glycine reversibility, K_i values for the glycine antagonists are calculated using the Cheng and Prusoff equation employing the experimentally determined IC_{50} values, the known concentration of glycine in the assay (1μM) and the known affinity of glycine for the glycine binding site of the NMDA receptor (100 nM).

The same rat brain membrane homogenates used for the 1 μM glycine-stimulated [^{3}H]-MK801 binding assay are used for the [^{3}H]-AMPA radioligand binding assay. On the day of the assay the frozen membranes (prepared as described above) are thawed and diluted with 30mM Tris/HCl buffer containing 2.5 mM $CaCl_2$ and 100 mM KSCN, pH 7.4, to yield a final membrane concentration of 1.25 mg/mL membrane protein. For the binding assay, 0.8 mL of membrane homogenate is added to polypropylene tubes followed by 0.033 mL drug and 0.067 mL buffer (or, for controls, by 0.1 mL buffer alone) and 0.1 mL buffer containing 200,000 cpm of [^{3}H]-AMPA. The assay is incubated for 30 minutes on ice. Bound radioactivity is separated from free radioactivity by filtration over Whatman glass fiber filters (pretreated with 0.3% polyethyleneimine) using a Brandel 48 well cell harvester.

Filtered membranes are washed three times with 3 mL each of ice cold buffer. The filters are transferred to scintillation vials and 5 mL of scintillation cocktail is added. The vials are shaken overnight and radioactivity is counted by liquid scintillation spectroscopy. Nonspecific binding is determined by the radioactivity that remains bound to the membranes in the presence 10 mM glutamate. Inhibition dose response curves

are constructed by adding increasing concentrations of drug from 10 nM to 100 μM.

The same membrane preparation as that used for the [^{3}H]-AMPA binding assay can be used for the [^{3}H]-Kainate radioligand binding assay. On the day of the assay the frozen rat brain membranes are thawed and 5 mM Tris/HCl buffer, pH 7.4, is added to yield a final concentration of 0.5 mg/mL membrane protein. For the binding assay, 0.8 mL of membrane homogenate is added to polypropylene tubes followed by 0.033 mL drug and 0.067 mL buffer (or, for controls, by 0.1 mL buffer alone) and 0.1 mL buffer containing 200,000 cpm of [^{3}H]-kainate. The assay is incubated for 2 hours on ice. Bound radioactivity is separated from free radioactivity by filtration over Whatman glass fiber filters (pretreated with 0.3% polyethyleneimine) using a Brandel 48 well cell harvester. Filtered membranes are washed three times with 3 mL each of ice cold buffer. The filters are transferred to scintillation vials and 5 mL of scintillation cocktail is added. The vials are shaken overnight and radioactivity is counted by liquid scintillation spectroscopy. Nonspecific binding is determined by the radioactivity that remains bound to the membranes in the presence 10 mM glutamate. Inhibition dose response curves are constructed by adding increasing concentrations of drug from 250 nM to 330 μM.

The anxiolytic activity of any particular compound of the present invention can be determined by use of any of the recognized animal models for anxiety. A preferred model is described by Jones, B.J. *et al.*, *Br. J. Pharmacol. 93*:985-993 (1988). This model involves administering the compound in question to mice that have a high basal level of anxiety. The test is based on the finding that such mice find it aversive when taken from a dark home environment in a dark testing room and placed in an area that is painted white and brightly lit. The test box has two compartments, one white and brightly illuminated and one black and non-illuminated. The mice have access to both compartments via an opening at floor level in the divider between the two compartments. The mice are placed in the center of the

brightly illuminated area. After locating the opening to the dark area, the mice are free to pass back and forth between the two compartments. Control mice tend to spend a larger proportion of time in the dark compartment. When given an anxiolytic agent, the mice spend more time exploring the more novel brightly lit compartment and exhibit a delayed latency to move to the dark compartment. Moreover, the mice treated with the anxiolytic agent exhibit more behavior in the white compartment, as measured by exploratory rearings and line crossings. Since the mice can habituate to the test situation, naive mice should always be used in the test. Five parameters can be measured: the latency to entry into the dark compartment, the time spent in each area, the number of transitions between compartments, the number of lines crossed in each compartment, and the number of rears in each compartment. The administration of the compounds of the present invention is expected to result in the mice spending more time in the larger, brightly lit area of the test chamber.

In the light/dark exploration model, the anxiolytic activity of a putative agent can be identified by the increase of the numbers of line crossings and rears in the light compartment at the expense of the numbers of line crossings and rears in the dark compartment, in comparison with control mice.

A second preferred animal model is the rat social interaction test described by Jones, B.J. *et al.*, *supra*, wherein the time that two mice spend in social interaction is quantified. The anxiolytic activity of a putative agent can be identified by the increase in the time that pairs of male rats spend in active social interaction (90% of the behaviors are investigatory in nature). Both the familiarity and the light level of the test arena can be manipulated. Undrugged rats show the highest level of social interaction when the test arena is familiar and is lit by low light. Social interaction declines if the arena is unfamiliar to the rats or is lit by bright light. Anxiolytic agents prevent this decline. The overall level of motor activity can also be measured to allow detection of drug effects specific to social behaviors.

The efficacy of the glycine and excitatory amino acid antagonists to inhibit glutamate neurotoxicity in a rat brain cortex neuron cell culture system can be determined as follows. An excitotoxicity model modified after that developed by Choi (Choi, D.W., *J. Neuroscience 7*:357 (1987)) can be used to test anti-excitotoxic efficacy of the glycine and excitatory amino acid antagonists. Fetuses from rat embryonic day 19 are removed from time-mated pregnant rats. The brains are removed from the fetuses and the cerebral cortex is dissected. Cells from the dissected cortex are dissociated by a combination of mechanical agitation and enzymatic digestion according to the method of Landon and Robbins (*Methods in Enzymology 124*:412 (1986)). The dissociated cells are passed through an 80 micron nitex screen and the viability of the cells are assessed by Trypan Blue. The cells are plated on poly-D-lysine coated plates and incubated at 37°C in an atmosphere containing 91% O_2/9% CO_2. Six days later, fluoro-d-uracil is added for two days to suppress non-neural cell growth. At culture day 12, the primary neuron cultures are exposed to 100 μM glutamate for 5 minutes with or without increasing doses of glycine and excitatory amino acid antagonist or other drugs. After 5 minutes, the cultures are washed and incubated for 24 hours at 37°C. Neuronal cell damage is quantitated by measuring lactate dehydrogenase (LDH) activity that is released into the culture medium. The LDH activity is measured according to the method of Decker *et al.* (Decker *et al.*, *J. Immunol. Methods 15*:16 (1988)).

The anticonvulsant activity of the glycine and excitatory amino acid antagonists can be assessed in the audiogenic seizure model in DBA-2 mice as follows. DBA-2 mice can be obtained from Jackson Laboratories, Bar Harbor, Maine. These mice at an age of <27 days develop a tonic seizure within 5-10 seconds and die when they are exposed to a sound of 14 kHz (sinus wave) at 110 dB (Lonsdale, D., *Dev. Pharmacol. Ther. 4*:28 (1982)). Seizure protection is defined when animals injected with drug 30 minutes prior to sound exposure do not develop a seizure and do not die during a 1 minute exposure to the sound. 21 day old DBA-2 mice are used for all experiments.

Compounds are given intraperitoneally in either saline, DMSO, or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

The anticonvulsant efficacy of the glycine receptor antagonists can be assessed in the pentylenetetrazol (PTZ)-induced seizure test as follows. Swiss/Webster mice, when injected with 50 mg/kg PTZ (i.p.) develop a minimal clonic seizure of approximately 5 seconds in length within 5-15 minutes after drug injection. Anticonvulsant efficacy of a glycine/excitatory amino acid antagonist (or other) drug is defined as the absence of a seizure when a drug is given 30 minutes prior to PTZ application and a seizure does not develop for up to 45 minutes following PTZ administration. Glycine/excitatory amino acid antagonist or other drugs are given intraperitoneally in either saline, DMSO, or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

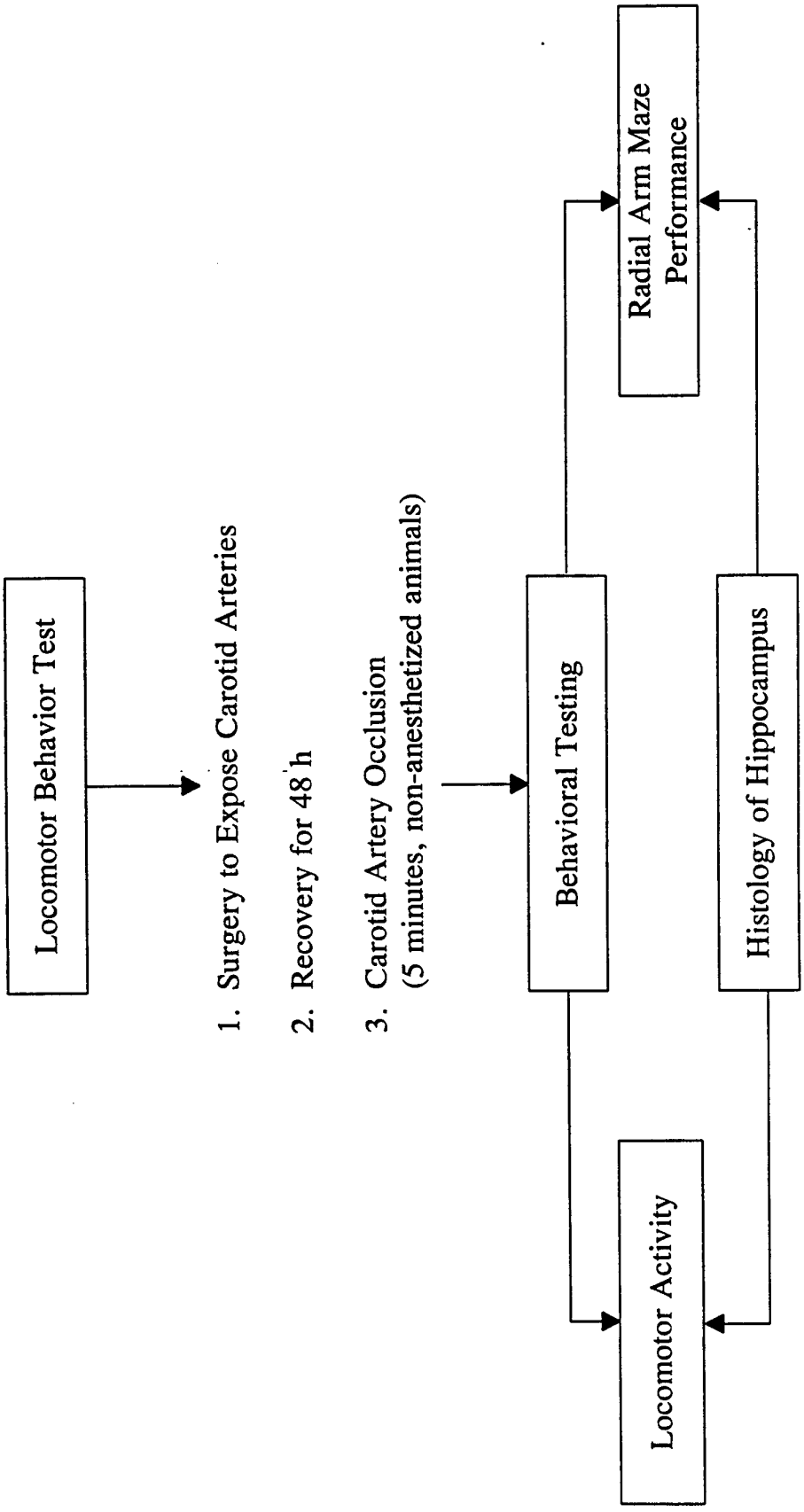
The efficacy of glycine/excitatory amino acid antagonists to protect mice from NMDA-induced death can be assessed as follows. When mice are injected with 200 mg/kg N-methyl-D-aspartate (NMDA) i.p., the animals will develop seizures followed by death within 5-10 minutes. Glycine/excitatory amino acid antagonists are tested for their ability to prevent NMDA-induced death by giving the drugs i.p. 30 minutes prior to the NMDA application. Glycine/excitatory amino acid antagonist or other drugs are given intraperitoneally in either saline, DMSO, or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

The anticonvulsant activity of the glycine antagonists can be assessed in the MES assays in mice. Electroshock was applied to male Swiss/Webster mice (20-30 g, Simonsen) through corneal electrodes (Swinyard, E.A., in *Anticonvulsant Drugs*, Mercier, J., ed., Pergamon Press, Oxford (1973), pp. 47-65). The seizure stimulus parameters were: 50 mA, 60 Hz, rectangular pulse, width 0.8 msec, duration 200 msec. Tonic hind limb extension observed after application of the electrical stimulus was recorded as occurrence of seizure. The drug was applied i.v. as an aqueous Tris (Tromethamine) solution.

A series of different evaluations can be conducted on doses of the glycine/excitatory amino acid antagonists of the invention to determine the biological activity of the compounds both in normal gerbils and in animals exposed to 5 minutes of bilateral carotid occlusion. *See* Scheme ***XXX***.

Scheme XXX

Gerbil Ischemia Model



These studies are conducted in animals who are conscious and have no other pharmacological agents administered to them. Gerbils are preinstrumented 48-hours prior to ischemia to allow for the complete elimination of the pentobarbital anesthetic that is employed. When tested with drugs, animals are given i.p. injections of the glycine/excitatory amino acid antagonist or vehicle. In the case of multiple injections, animals are given i.p. injections 2 hours apart and the final injection is given 30 minutes prior to the ischemic period or in the case of post treatment, the animals are given injections at 30 minutes, 2 hours, 4 hours, and 6 hours post-ischemic reperfusion.

In order to assess the direct pharmacological activity or potential activity of the glycine/excitatory amino acid antagonists, naive gerbils are injected with either saline or differing doses of the antagonist. The behavioral changes are assessed using a photobeam locomotor activity chamber, which is a two foot circular diameter arena with photobeam detection. Animals are individually placed in the 2 foot diameter chambers. The chambers are housed in a cabinet that is closed and noise is abated using both a background white noise generator and a fan. Animals are placed in these chambers in the case of the initial pharmacological evaluation for a period of 6 hours and the total activity during each successive hour is accumulated using the computer control systems.

Saline results in an initial high rate of activity, with the control animals showing a first hour activity level of about 1600 counts. This level of control activity is typical for the gerbil under these experimental conditions. As the session progresses, animals decrease their exploratory activity and at the terminal period the activity declines to about 250 counts per hour. It is expected that the glycine/excitatory amino acid antagonists of the present invention will have no significant effect on either the initial exploratory rate or the terminal rate of exploration.

In a next phase of the evaluation of the glycine/excitatory amino acid antagonists, gerbils are pretreated with varying doses of the antagonists and

then exposed to a five minute period of bilateral carotid occlusion. Following the initiation of reperfusion, animals are placed into the circular locomotor activity testing apparatus and the activity at the beginning of the first hour following reperfusion is monitored for the subsequent four hours.

Control animals not exposed to ischemia and given injections of saline prior to being placed in the locomotor activity chamber show a characteristic pattern of activity, which in the first hour of locomotor activity is substantially higher than during all other hours and progressively declines over the four hours to a very low value. In contrast to the progressive decline in activity over the four hour testing period, control animals that are exposed to five minutes of cortical ischemia demonstrate a completely different pattern of locomotor activity. During the first hour, there is a significant decline in activity that is followed by a progressive increase in which the activity during the fourth hour is ten-fold higher than that demonstrated by animals not exposed to carotid occlusion. These results are typical and are a reliable result of the alterations caused by five minutes of bilateral carotid occlusion in the gerbil.

Separate groups of gerbils are pretreated with the glycine/excitatory amino acid antagonists of the invention 30 minutes before the onset of carotid occlusion and then placed into the locomotor activity following one hour of reperfusion. It is expected that pretreatment of the gerbils with the glycine/-excitatory amino acid antagonists of the invention will prevent both the post-ischemic decrease and increase in activity. Post-ischemic decreases in activity are expected to be near zero during the first hour following reperfusion. Pretreatment with the glycine/excitatory amino acid antagonists of the invention is expected to reduce or prevent this early depression of behavior. In addition, the glycine/excitatory amino acid antagonists of the invention are expected to prevent the post-ischemic stimulation of behavior.

Subsequent to completion of the single dose pretreatment evaluations, gerbils are also evaluated with multiple injections of the glycine/excitatory

amino acid antagonists of the invention. Doses are administered i.p. at 6 hours, 4 hours, 2 hours, and 30 minutes prior to the onset of 5 minutes of ischemia.

At 24 hours, all animals are evaluated for differences in patrolling behavior using an 8-arm radial maze. In this procedure, animals are placed into the center start chamber of the maze, the barrier is removed, and the amount of time and the number of times the animal makes an error is recorded prior to completion of exploration in all 8 arms of the maze. An error is defined as the revisiting of an arm by an animal entering to the extent of its entire body without including its tail. If the animal perseveres or fails to leave the arm for longer than five minutes, the session is terminated. In the control population of the animals, the number of errors and exploration of the maze with no prior experience (naive) is approximately 6 errors. This is an average value for an N of 28 gerbils. Following 5 minutes of bilateral carotid occlusion and testing at 24 hours, gerbils make an average number of errors of 21. When animals are pretreated with the glycine/excitatory amino acid antagonists of the invention, there is expected to be a significant reduction in the number of errors made. There is also expected to be a significant sparing of the behavioral changes that are induced in the radial arm maze performance.

It is also expected that post treatment with the glycine/excitatory amino acid antagonists of the invention will reduce the short term memory impairment 24 hours post ischemic/reperfusion.

The effects of 5 minutes of bilateral carotid occlusion on neuronal cell death in the dorsal hippocampus can be evaluated in animals 7 days after ischemia reperfusion injury. Previous studies have demonstrated that neuronal degeneration begins to occur around 3 days following cerebral ischemia. By 7 days those neurons that have been affected will undergo cytolysis and have either completed degeneration or are readily apparent as dark nuclei and displaced nuclei or as cells with eosinophilic cytoplasm and pycnotic nuclei. The lesion with 5 minutes of ischemia is essentially restricted within the

hippocampus to the CA1 region of the dorsal hippocampus. The intermedial lateral zone of the horn is unaffected and the dentate gyrus and/or cells in CA3 do not show pathology. Gerbils are anesthetized on day 7 following ischemia with 60 mg/kg of pentobarbital. Brains are perfused transcardiac with ice-cold saline followed by buffered paraformaldehyde (10%). Brains are removed, imbedded, and sections made. Sections are stained with hematoxylin-eosin and neuronal cell counts are determined in terms of the number of neuronal nuclei/100 micrometers. Normal control animals (not exposed to ischemia reperfusion injury) will not demonstrate any significant change in normal density nuclei within this region. Exposure to five minutes of bilateral carotid occlusion results in a significant reduction in the number of nuclei present in the CA1 region. In general, this lesion results in a patchy necrosis instead of a confluent necrosis, which is seen if 10 minutes of ischemia is employed. Pretreatment with the glycine receptor antagonists of the invention is expected to produce a significant protection of hippocampal neuronal degeneration.

It is known that NMDA receptors are critically involved in the development of persistent pain following nerve and tissue injury. Tissue injury, such as that caused by injecting a small amount of formalin subcutaneously into the hindpaw of a test animal, has been shown to produce an immediate increase of glutamate and aspartate in the spinal cord (Skilling, S.R., *et al.*, *J. Neurosci. 10*:1309-1318 (1990)). Administration of NMDA receptor blockers reduces the response of spinal cord dorsal horn neurons following formalin injection (Dickenson and Aydar, *Neuroscience Lett. 121*:263-266 (1991); Haley, J.E., *et al.*, *Brain Res. 518*:218-226 (1990)). These dorsal horn neurons are critical in carrying the pain signal from the spinal cord to the brain and a reduced response of these neurons is indicative of a reduction in pain perceived by the test animal to which pain has been inflicted by subcutaneous formalin injection.

Because of the observation that NMDA receptor antagonists can block dorsal horn neuron response induced by subcutaneous formalin injection,

NMDA receptor antagonists have potential for the treatment of chronic pain, such as, pain caused by surgery, by amputation (phantom pain), or by infliction of other wounds (wound pain). However, the use of conventional NMDA antagonists, such as, MK801 or CGS 19755, in preventing or treating chronic pain is severely limited by the adverse PCP-like behavioral side effects that are caused by these drugs. It is expected that the glycine receptor antagonists that are the subject of this invention will be highly effective in preventing chronic pain in mice induced by injecting formalin subcutaneously into the hindpaw of the animals. Because the glycine/excitatory amino acid antagonists of this invention are expected to be free of PCP-like side effects, these drugs are highly useful in preventing or treating chronic pain without causing PCP-like adverse behavioral side effects.

The effects of the glycine receptor antagonists of the present invention on chronic pain can be evaluated as follows. Male Swiss/Webster mice weighing 25-35 grams are housed five to a cage with free access to food and water and are maintained on a 12 hour light cycle (light onset at 0800h). The glycine receptor antagonist is dissolved in DMSO at a concentration of 1-40 and 5-40 mg/mL, respectively. DMSO is used as vehicle control. All drugs are injected intraperitoneally (1 μl/g). The formalin test is performed as described (Dubuisson and Dennis, *Pain 4*:H161-174 (1977)). Mice are observed in a plexiglass cylinder, 25 cm in diameter and 30 cm in height. The plantar surface of one hindpaw is injected subcutaneously with 20 μl of 5% formalin. The degree of pain is determined by measuring the amount of time the animal spends licking the formalin-injected paw during the following time intervals: 0-5′ (early phase); 5′-10′, 10′-15′ and 15′-50′ (late phase). To test whether the glycine/excitatory amino acid antagonists prevent chronic pain in the test animals, vehicle (DMSO) or drugs dissolved in vehicle at doses of 1 mg/kg to 40 mg/kg are injected intraperitoneally 30 minutes prior to the formalin injection. For each dose of drug or vehicle control at least six animals are used.

Compared to vehicle control, it is expected that the intraperitoneal injection of the glycine receptor antagonists 30 minutes prior to formalin injection into the hindpaw will significantly inhibit formalin-induced chronic pain in a dose-dependent manner as determined by the reduction of the time the mouse spends licking the formalin injected hindpaw, caused by increasing doses of glycine/excitatory amino acid antagonist.

It is well known to use opiates, e.g., morphine, in the medical field to alleviate pain. (As used herein, the term "opiates" is intended to mean any preparation or derivative of opium, especially the alkaloids naturally contained therein, of which there are about twenty, e.g., morphine, noscapine, codeine, papaverine, and thebaine, and their derivatives.) Unfortunately, with continued use, the body builds up a tolerance for the opiate, and, thus, for continued relief, the patient must be subjected to progressively larger doses. This, in itself, can be detrimental to the patient's health. Furthermore, a time can come when the tolerance is substantially complete and the pain killing properties of the drug are no longer effective. Additionally, administration of higher doses of morphine may lead to respiratory depression, causing the patient to stop breathing. Recent studies have suggested a modulatory role for the NMDA receptor in morphine tolerance. It has now been found that administration of quinoxaline diones can inhibit opiate tolerance by blocking the glycine co-agonist site associated with the NMDA receptor.

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g., humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for anxiety disorders, e.g., generalized anxiety disorder, phobic disorders, obsessional compulsive disorder, panic disorder, and post traumatic stress disorders. Preferably,

about 0.01 to about 10 mg/kg is orally administered to treat or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, for treatment or prevention of anxiety, a suitable intramuscular dose would be about 0.0025 to about 15 mg/kg, and most preferably, from about 0.01 to about 10 mg/kg.

In the method of treatment or prevention of neuronal loss in ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, and surgery, as well as for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's Syndrome, or in a method of treating a disease in which the pathophysiology of the disorder involves hyperactivity of the excitatory amino acids or NMDA receptor-ion channel related neurotoxicity or psychosis, the pharmaceutical compositions of the invention can comprise the compounds of the present invention at a unit dose level of about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. When used to treat chronic pain or to induce anesthesia, the compounds of the invention may be administered at a unit dosage level of from about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of a pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. Of course, it is understood that the exact treatment level will depend upon the case history of the animal, e.g., human being, that is treated. The precise treatment level can be determined by one of ordinary skill in the art without undue experimentation.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg, of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention can be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising

excipients and auxiliaries that facilitate processing of the compounds into preparations that can be used pharmaceutically. Preferably, the preparations, particularly those preparations that can be administered orally and that can be used for the preferred type of administration, such as tablets, dragees, and capsules, and preparations that can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Basic salts are formed by mixing a solution of a particular tricyclic compound of the present invention with a solution of a pharmaceutically acceptable non-toxic base, such as, sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium carbonate, or an amino compound, such as, choline hydroxide, Tris, bis-Tris, N-methylglucamine, arginine, and the like. *See*, U.S. Application Serial No. 08/148,268, *supra*.

The pharmaceutical compositions of the invention can be administered to any animal that may experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

When the compositions of the invention are administered ocularly, one may achieve either local or systemic administration. For example, the compositions of the present invention may be administered in the form of eye

drops that are substantially isotonic with tear fluid to achieve systemic administration. Preferably, such compositions will also comprise a permeation-enhancing agent, which aids the systemic absorption of the compounds of the present invention. *See*, U.S. Patent No. 5,182,258. Alternatively, the compositions of the invention may be administered ocularly to treat or prevent optic nerve degeneration. In this embodiment, the compounds of the present invention are administered in the form of eye drops, as disclosed above, or may be injected into the vicinity of the optic nerve. In the alternative, thin ocular implants may be employed that slowly release the compounds of the present invention.

In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

The pharmaceutical preparations of the present invention are manufactured in a manner that is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers, such as, saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all,

flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers, such as, lactose, binders, such as, starches, and/or lubricants, such as, talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations that can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules, which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active

compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The characterization of glycine binding sites *in vitro* has been difficult because of the lack of selective drug ligands. Thus, the glycine ligands of the present invention can be used to characterize the glycine binding site. The particularly preferred compounds that can be used for this purpose are isotopically radiolabelled derivatives, e.g., where one or more of the atoms are replaced with ^{3}H, ^{11}C, ^{14}C, ^{15}N, or ^{18}F. Examples of preferred photoaffinity ligands are ^{3}H or ^{18}F-substituted 6-azido-5,7-difluoro-1,4-dihydroquinoxaline-2,3-dione and ^{3}H-substituted 6-azido-5,7-dichloro-1,4-dihydroquinoxaline-2,3-dione.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and obvious to those skilled in the art are within the spirit and scope of the invention.

Examples

Example 1: 5-(2-Bromoacetamido)-6,7-dichloroquinoxaline-2,3-dione (1)

To a stirred solution of 201 mg (0.817 mmol) of 5-amino-6,7-dichloroquinoxaline-2,3-dione (WO94/00124) and 229 mg (2.26 mmol) of triethylamine in 9 ml of anhydrous DMF was added 520 mg (3.30 mmol) of 2-bromoacetyl chloride and the resulting solution was stirred overnight. The solution was added into 40 ml of water and the mixture was stirred for 1 h,

filtered, washed with water, then dried to leave brown solid (202 mg, 67%). ^{1}H NMR (DMSO-d_6), 4.100 (s, 1), 4.329 (s, 1), 7.268 (s, 1), 10.060 (s, 0.5), 10.122 (s, 0.5), 11.699 (s, 1), 12.119 (s, 1). MS, 285 (M^+ - BrH, 70), 228 (100).

Example 2: 7,8-Dichloro-1,4,6-trihydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (2)

A mixture of 42 mg (0.11 mmol) of **1**, 25 mg (0.36 mmol) of sodium ethoxide (96%) and 2 ml of absolute alcohol was refluxed for 6 h. The mixture was cooled to room temperature and diluted by 3 ml of water. The resulting solution was acidified by 2 N HCl to pH 3 to give brown precipitate which was allowed to stand overnight. The mixture was filtered, washed with water and dried to leave brown solid (20 mg, 63%). ^{1}H NMR (DMSO-d_6), 4,486 (s, 2), 6.993 (s, 1), 10.680 (s, 1), 12.258 (s, 1). MS, 285 (M^+,75), 228 (100). HRMS calcd for $C_{10}H_5Cl_2N_3O_3$ 284.9703, found 284.9693.

Example 3: 5-(Ethyl oxalamido)-6,7-dichloroquinoxaline-2,3-dione (3)

To a stirred solution of 116 mg (0.471 mmol) of 5-amino-6,7-dichloroquinoxaline-2,3-dione and 89 mg (0.88 mmol) of triethylamine in 7 ml of anhydrous DMF was added 216 mg (3.30 mmol) of ethyl oxalyl chloride and the resulting solution was stirred overnight. The solution was diluted by 35 ml of water and it was allowed to stand for 1 day. Crystalline precipitate was observed and the mixture was filtered, washed with water, and dried to leave a white solid (118 mg, 72%). ^{1}H NMR (DMSO-d_6), 1,339 (t, 3, J = 7-1), 4.312 (q, 2, J = 7.1), 7.295 (s, 1), 10.582 (s, 1), 11.750 (s, 1), 12.152 (s, 1). HRMS calcd for $C_{12}H_9Cl_2N_3O_5$ 344.9913, found 344.9925.

Example 4: 5-(N-Oxalamido acid)-6,7-dichloroquinoxaline-2,3-dione (4)

A mixture of 68 mg (0.19 mmol) of **3**, 45 mg (0.63 mmol) of sodium ethoxide (96%) and 4 ml of absolute alcohol was refluxed for 2 days. The mixture was diluted by 2 ml of water and acidified by 2 N HCl to pH 4. It was filtered and the filtrate was allowed to stand overnight to give crystalline solid. The mixture was filtered, washed with water, and dried to leave a brown solid (22 mg, 36%). ^{1}H NMR (DMSO-d_6), 7.312 (s, 1), 10.464 (s, 1), 11.578 (s, 1), 11.692 (sb, 1). MS, 317 (M+,15), 272 (40), 245 (100), 216 (60). HRMS calcd for $C_{10}H_5Cl_2N_3O_5$ 316.9601, found 316.9605.

Example 5: 5-[2-(Ethyl carboxyl)acetamido]-6,7-dichloroquinoxaline-2,3-dione (5)

To a stirred solution of 173 mg (0.703 mmol) of 5-amino-6,7-dichloroquinoxaline-2,3-dione and 160 mg (1.58 mmol) of triethylamine in 6 ml of anhydrous DMF was added 266 mg (1.76 mmol) of ethyl malonyl chloride and the resulting mixture was stirred overnight. The mixture was added into 30 ml of water and the precipitate was stirred for 1 h. It was filtered and washed with water, and dried to leave a white solid (214 mg, 84%). ^{1}H NMR (DMSO-d_6), 1.205 (t, 3, J = 7.1), 3.538 (s, 2), 4.124 (q, 2, J = 7.1), 7.258 (s, 1), 9.928 (s, 1), 11.516 (s, 1), 12.113 (s, 1). HRMS calcd for $C_{13}H_{11}Cl_2N_3O_5$ 359.0069, found 359.0072.

Example 6: 5-[2-(Carboxylic acid)acetamido]-6,7-dichloroquinoxaline-2,3-dione (6)

A mixture of 136 mg (0.377 mmol) of **5**, 2 ml of methanol and 1.5 ml of 1 N NaOH was stirred at room temperature for 6 h. The mixture was acidified by 2 N HCl to pH 2. It was filtered, washed with water, and dried to leave a white solid (114 mg, 91%). ^{1}H NMR (DMSO-d_6), 3.463 (s, 2),

7.261 (s, 1), 9.948 (s, 1), 11.345 (s, 1), 12.120 (sb, 1). MS, 287 ($M^+ - CO_2$), 245 (100), 217 (70).

Example 7: 5-[2-(Phenylcarbamoyl)acetamido]-6,7-dichloroquinoxaline-2,3-dione (7)

To a mixture of 67 mg (0.20 mmol) of **6**, 20 mg (0.21 mmol) of aniline, 40 mg (0.21 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 31 mg (0.20 mmol) of 1-hydroxybenzotriazole and 22 mg (0.22 mmol) of triethyl amine was added 1.5 ml of anhydrous DMF and the mixture was stirred at RT overnight. The mixture was diluted by 10 ml of 0.2 N HCl and the mixture was filtered, washed with water, and dried to leave a white solid (60 mg, 73%). ^{1}H NMR (DMSO-d_6), 3.584 (s, 2), 7.074 (t, 1, J = 7.8), 7.270 (s, 1), 7.331 (t, 2, J = 7.8), 7.609 (d, 1, J = 7.8), 10.040 (s, 1), 10.245 (s, 1), 11.394 (s, 1), 12.130 (s, 1).

Example 8: 5-[2-Bromo-2-(ethyl carboxyl)acetamido]-6,7-dichloroquinoxaline-2,3-dione (8)

To 664 mg (4.41 mmol) of ethyl malonyl chloride heated at 70°C was added dropwise about 0.4 ml of bromine (1.24 g, 7.7 mmol). The bromine yellow color disappeared immediately after addition and addition of bromine was stopped after the bromine yellow color did not disappear. The resulting bromide was added dropwise into a solution of 491 mg (1.99 mmol) of 5-amino-6,7-dichloroquinoxaline-2,3-dione and 415 mg (4.10 mmol) of triethylamine in 14 ml of ice bath cold anhydrous DMF and the resulting mixture was stirred in an ice bath for 1 h and at room temperature overnight. The mixture was added into 60 ml of water and the precipitate was stirred for 10 min, filtered, washed with water, and dried to leave a white solid (558 mg, 64%). ^{1}H NMR (DMSO-d_6), 1.237 (m, 3, J = 7.1), 4.226 (m, 2), 5.355 (s, 0.5), 5.419 (s, 0.5), 7.280 (s, 1), 10.249 (s, 0.5), 10.286 (s, 0.5), 11.562 (s, 0.5), 11.615 (s, 0.5), 12.132 (s, 1).

Example 9: 7,8-Dichloro-4-(ethylcarboxyl)-1,4,6-trihydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (9)

A mixture of 68 mg (0.15 mmol) of **8**, 31 mg (0.45 mmol) of sodium ethoxide (96%) and 2 ml of anhydrous ethanol was heated at 60°C for 4 h. It was evaporated to dryness and the residue was treated by 1 N HCl (2 ml). The solid was filtered, washed with water, and dried to leave a brown solid (42 mg, 78%). ^{1}H NMR (DMSO-d_6), 1.182 (t, 3), 4.191 (q, 2), 5.501 (s, 1), 7.081 (s, 1), 11.134 (s, 1), 12.492 (s, 1). It also contain about 15% of **2**.

Example 10: 5-(Acyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-diones (12a-c) (general procedure)

A mixture of 5-amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**10**) (0.244 g, 1 mmol) in 3 mL of β-dicarbonyl compound (diethyl malonate **11a**, ethyl benzoylacetate **11b**, or ethyl acetoacetate **11c**) was stirred in open flask at 160-180°C for 16 h, then cooled to rt and diluted with ether (50 mL). Precipitated crude product **12a-12c** was filtered, washed with ether (5 x 10 mL), and dried on air.

5-(2'-Carboethoxyacetyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (12a)

Prepared from diethyl malonate **11a** according to above general procedure. Yield 84%; K_i = 4 μM, 6% DCK.

5-(2'-Benzoylacetyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (12b)

Prepared from ethyl benzoylacetate **11b** according to above general procedure. Yield 78%; grey solid: mp 281-282°C (from 50% DMF); IR (KBr) 3191, 3057, 2, 1717, 1697, 1665, 1599, 1532, 1437, 1391, 1339, 1279

and 1221 cm^{-1}; ^1H NMR (DMSO-D_6) δ 4.24 (s, 2H), 7.29 (s, 1H), 7.55 (m, 3H), 8.00 (m, 2H), 10.03 (s, 1H, NH), 11.36 (s, 1H, NH), 12.10 (s, 1H, NH). Signals of enol form (about 8% by integration) at 5.99 (s, 1H, CH), 9.99 (s, 1H, NH), 11,84 (s, 1H, NH) and 13.97 (s, 1H, OH); HPLC: 19.7 (99.6%). K_i = 0.6 μM, 39% DCK.

6,7-Dichloro-5-(3'-oxopropyloyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione (12c)

Prepared from ethyl acetoacetate **11c** according to above general procedure. Yield 79%; grey solid: mp 240-242°C (from 50% DMF); IR (KBr) 3452, 3203, 3059, 2827, 2855, 1710 (br), 1609, 1509, 1385, 1259 and 1171 cm^{-1}; ^1H NMR (DMSO-D_6) δ 2.21 (s, 3H), 3.60 (s, 2H), 7.23 (s, 1H), 9.90 (s, 1H, NH), 11.42 (s, 1H, NH), 12.10 (s, 1H, NH). HPLC: 17.5 (92%), 19.1 (7%, starting amine **10**). K_i = 4.4 μM, 5% DCK.

Example 11: (α-Bromoacyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-diones (13a,b) (general procedure)

To a stirred solution of compound **12a,b** (2 mmol) in DMF (10 mL) a solution of Br_2 in CCl_4 (1M, 5 mL, 5 mmol) was introduced dropwise. The mixture was stirred for 4 h, then evaporated. Water (50 mL) was added to a residue and precipitated crude product was filtered, washed with water (10 x 20 mL), dried on a filter and washed with ether (5 x 10 mL) to give compounds **13a,b**.

5-(2'-Bromo-2'-carboethoxyacetyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (13a)

Prepared from compound **12a** according to above general procedure. Yield 96%.

5-(2'-Benzoyl-2'-bromoacetyl)amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (13b)

Prepared from compound **12b** according to above general procedure and purified by recrystallization from EtOH. Yield 61%; brown solid: mp 198-200°C (from EtOH); ^{1}H NMR (DMSO-D_6) δ 6.40 (s, 1H), 7.25 (s, 1H), 7.60 (m, 3H), 8.04 (d, 2H), 10.27 (s, 1H, NH), 11.31 (s, 1H, NH), 12.12 (s, 1H, NH).

Example 12: 4-Acyl-7,8-dichloro-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-triones (14a,b) (general procedure)

To a stirred suspension of potassium *tert*-butoxide (0.112 g, 1 mmol) in DMF (3 mL) a solid bromide **13a,b** (0.2 mmol) was introduced. The mixture was stirred for 2 h, then AcOH (2 mL) was added and the mixture was evaporated. Water (20 mL) was added to the residue and precipitated crude product was filtered, washed with water to give compound **14a,b**.

7,8-Dichloro-5-ethoxycarbonyl-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (14a)

Prepared from bromide **13a** according to above general procedure. Yield 69%; K_i = 5.2 μM, 4% DCK.

4-Benzoyl-7,8-dichloro-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (14b)

Prepared from bromide **13b** according to above general procedure. Yield 87%; brown solid: mp 183-185°C (from EtOH-EtOAc 1:1); IR (KBr) 3445, 3068, 2940, 1713s, 1686, 1614, 1509, 1386 and 947 cm^{-1}; ^1H NMR (DMSO-D_6) δ 6.81 (s, 1H), 7.09 (s, 1H, OH), 7.60 (dd, 2H), 7.74 (dd, 1H), 8.18 (d, 2H), 11.09 (s, 1H, NH), 12.50 (s, 1H, NH); HPLC: 20.1 (96.8%); HRMS calcd for $C_{17}H_9N_3O_4Cl_2$ 388.9970. Found 388.9980; K_i = 0.72 μM, 32% DCK.

Example 13: 7,8-Dichloro-2-(2'-phenylethyl)-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (15)

To a stirred solution of 5-amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**10**) (0.610 g, 2.5 mmol) in DMF (20mL) and Et_3N (2 mL, apr. 15 mmol), a 2-bromobutyryl chloride (1.76 g, 6.7 mmol) prepared from 4-phenylbutyric acid according to procedure (Harpp *et al.*, *Org. Synth. Coll. Vol. IV*:190) was intoduced in one portion. The mixture was stirred at rt for 16 h and evaporated to dryness. Hexane (20 mL) was added to the residue and brown solid was filtered, washed with hexane (3 x 10 mL), water (3 x 10 mL) and dried on air. This crude product was dissolved in DMF (20 mL) and stirred for 2 h with t-BuOK (1.12 g, 10 mmol), then AcOH (10 mL) was added to a reaction mixture. The mixture was evaporated, solid residue was treated with water (20 mL), filtered, and washed with water (3 x 20 mL). Crude product was purified by chromatography on a silica gel column (2.5 x 30 cm), eluent 2% MeOH in $CHCl_3$ to give compound **15**, 0.244 g (25%) as a brown powder: mp 206-208 (dec.); IR (KBr) 3390, 3188, 2946, 2859, 1725s, 1703, 1684, 1610, 1500, 1455, 1374 and 1188 cm^{-1}; ^1H NMR (DMSO-D_6) δ 2.12 (m, 2H), 2.55 (m, 2H), 5.03 (t, 1H), 6.91 (s, 1H), 7.12 (m, 5H), 10.73 (s, 1H, NH), 12.07 (s,

1H, NH); HPLC: 21.7 (98.1%); HRMS calcd for $C_{18}H_{13}N_3O_3Cl_2$ 389.0334. Found 389.0331; K_i = inactive.

Example 14: 6,7-Dichloro-5-(3'-bromo-4'-methoxyphenylacetyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione (17)

6,7-Dichloro-5-(4'-methoxyphenylacetyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione (16)

A mixture of 4-methoxyphenylacetic acid (1.66 g, 10 mmol) and $SOCl_2$ (5 mL) was heated at 60°C for 2h, then evaporated. The residue was dissolved in DMF (3 mL) and added to a stirred suspension of amine **10** (1.230 g, 5 mmol) in DMF (10 mL) and Et_3N (1.3 mL, 10 mmol). The mixture became a solution after 15 min and after 4 h it was evaporated to dryness. The residue was treated with water (50 mL) and solid was filtered, washed with water (5 x 10 mL) and dried on a filter. Crude product was recrystallized from EtOAc-EtOH (2:1) mixture to give compound **16**, 0.890 g (45%) as yellowish solid: mp 261-263°C (from EtOAc); ^{1}H NMR (DMSO-D_6) δ 3.63 (s, 2H), 3.69 (s, 3H), 6.84 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.25 (s, 1H), 9.72 (s, 1H, NH), 11.68 (s, 1H, NH), 12.07 (s, 1H, NH).

6,7-Dichloro-5-(3'-bromo-4'-methoxyphenylacetyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione (17)

To a stirred solution of compound **16** (0.378 g, 1 mmol) in DMF (20 mL) a solution of Br_2 in CCl_4 (1M, 1.5 mL, 1.5 mmol) was introduced dropwise. The mixture was stirred for 4 h, then evaporated. Water (20 mL) was added to a residue and precipitated crude product was filtered, washed with water (5 x 10 mL) and dried on a filter to give compound **17**, 0.415 g (91%) as dark orange solid: mp 185-187°C (dec.; from DMF-H_2O (1:1), then from EtOH-EtOAc (1:1)); ^{1}H NMR (DMSO-D_6) δ 3.64 (s, 2H), 3.79 (s,

3H), 7.08 (d, J = 10 Hz, 2H), 7.21 (s, 2H), 7.29 (d, J = 10 Hz, 2H), 7.57 (s, 1H), 9.79 (s, 1H, NH), 11.70 (s, 1H, NH), 12.08 (s, 1H, NH).

Under similar conditions 6,7-dichloro-5-(phenylacetyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione was recovered (92%) unchanged.

Example 15: 7,8-Dichloro-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (18)

To a suspension of compound **14a** (0.907 g, 2.41 mmol) in EtOH (10 mL) a 1N NaOH (10 mL, 10 mmol) was added. The mixture became a solution in 5 min, then precipitation of the product began. The mixture was stirred for 3 h then diluted with water (50 mL) and acidified (2N HCl) to pH 1. Precipitate was filtered, washed with water (5 x 10 mL) and dried on air to give compound **18**, 0.719 g (98%) as a pale-yellowish solid. ^{1}H NMR, TLC and NMR of the initial reaction precipitate identified it as compound **18**.

Example 16: 9-Bromo-7,8-dichloro-1,2,3,3a,4,5,6-hexahydropyrazino[1,2,3-de]quinoxaline-2,3,5-trione (19)

A mixture of compound **18** (0.157 g, 0.5 mmol), NBS (0.178 g, 1 mmol), benzoyl peroxide (0.005 g, catalyst) in DMF (5 mL) was stirred at 70°C over 16 h. The mixture was cooled to rt and evaporated. Water (20 mL) was added to the residue and precipitated solid was filtered, washed with water (5 x 5 mL) and dried on a filter to give compound **19**, 0.178 g (98%) as a pale yellow solid: dec. above 350°C (from DMSO - H_2O (1:1)); IR (KBr) 3603, 3169, 2929, 1693, 1603, 1498, 1384 and 1265 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 4.74 (s, 2H), 10.72 (s, 1H, NH), 11.37 (s, 1H, NH); HPLC: 19.4 (99.4%); HRMS calcd for $C_{10}H_4N_3O_3BrCl_2$ 362.8814. Found 362.8820; K_i = inactive.

Example 17: ***6,7-Dichloro-4-(2',2'-diethoxycarbonylvinyl)amino-1,2,3,4-tetrahydroquinoxaline-2,3-dione (21)***

A mixture of 5-amino-6,7-dichloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (1.22 g, 5 mmol) and EMME (15 mL, 74 mmol) was stirred in open flask at 150°C for 16 h, then cooled to rt and diluted with ether (70 mL). Precipitated solid was filtered, washed with ether (5 x 20 mL), dried on air to yield compound **21**, 1.160 g (56%) as white solid: mp 256-258°C (from EtOH); IR (KBr) 3481, 3196, 3050, 2982, 1730, 1689, 1652, 1599, 1269 and 1239 cm^{-1}; ^1H NMR (DMSO-D_6) δ 1.14 (t, 3H), 1.23 (t, 3H), 4.03 (q, 2H), 4.16 (q, 2H), 7.22 (s, 1H), 7.67 (d, J = 14 Hz, 1H), 9.87 (d, J = 14 Hz, 1H, NH), 11.97 (s, 1H, NH), 12.11 (s, 1H, NH); HPLC: 18.0 (100%). HRMS calcd for $C_{16}H_{15}N_3O_6Cl_2$ 415.033; IC_{50} = 533 nm (in ^3H DCK binding).

Example 18 ***6,7-Dichloro-4-(2'-ethoxycarbonyl)ethyledene-1,2,3,3a,4,5-hexahydroimidazo[1,2,3-de]quinoxaline-2,3-dione (22)***

Compound **21** (0.100 g) was refluxed in Dowtherm A (2 mL) for 5 min. The mixture was cooled to rt and diluted with hexane (50 mL). Precipitated solid was washed with hexane (5 x 5 mL), and purified on preparative TLC (eluent - 10% MeOH in $CHCl_3$) to give compound **22**, 0.046 g (56%) as orange solid: mp 178-180°C, ^1H NMR (DMSO-D_6) δ 1.23 (t, 3H), 4.15 (q, 2H), 7.71 (s, 1H), 8.28 (s, 1H), 9.61 (s, 1H, NH), 12.66 (s, 1H, NH); HPLC: 11.0 (100%). HRMS calcd for $C_{13}H_9N_3O_4Cl_2$ 340.9970, IC_{50} = 20,930 (in ^3H DCK binding).

Example 19 ***4-(2',2'-Diethoxycarbonylvinyl)aminopyridine (25)***

A procedure by Hauser *et al.* (*J. Org. Chem. 15*:1224 (1950) was used with minor modifications. A mixture of 4-aminopyridine (**24**) (5.0 g, 53 mmol) and EMME (11.5 g, 53 mmol) was heated at 120°C for 2 h, cooled

to rt and left at 5°C for 16 h. Solidified crude product was recrystallized twice from ligroine to give compound **25**, 8.01 g (58%) as grey needles: mp 72-74°C (lit mp 74-75°C; Hauser *et al.*). ^{1}H NMR (DMSO-D_6) δ 1.22 (t, 3H), 1.27 (t, 3H), 4.12 (q, 2H), 4.18 (q, 2H), 7.35 (d, J = 5 Hz, 1H), 8.39 (d, J = 14 Hz, 1H), 8.41 (s, 1H), 10.49 (d, J = 14 Hz, 1H, NH).

Example 20 3-Ethoxycarbonyl-1,6-naphtyrid-4-one (26)

A procedure by Paudler *et al.* (*J. Heterocycl. Chem.* 2:393 (1965) was used with minor modifications. Compound **25** (5.00 g) was introduced in boiling Dowtherm A (150 mL) and refluxed for 15 min, then cooled to rt and allowed to stand for 50 h. Precipitated crude product was filtered, washed with hexane (10 x 20 mL) and recrystallized from EtOH to give compound **26**, 2.03 g (49%) as white powder: mp 289-290°C (lit mp 292-293°C, Hauser *et al.*). ^{1}H NMR (DMSO-D_6) δ 1.24 (t, 3H), 4.19 (q, 2H), 7.48 (d, J = 5.5 Hz, 1H), 8.59 (s, 1H), 8.63 (d, J = 5.5 Hz, 1H), 9.20 (s, 1H), 12.44 (s, 1H); ^{13}C (DMSO-D_6) d 14.74, 60.34, 113.03, 113.79, 122.32, 144.54, 146.78, 149.79, 149.84, 151.29, 164.63.

Example 21 4,5-Dichloro-2-nitro-N-(2',2'-diethyxocarbonylvinyl)aniline (27)

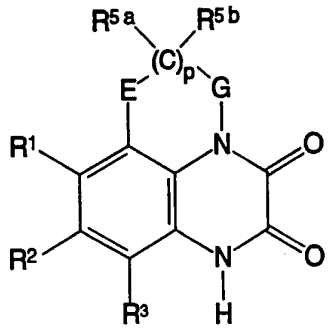
A mixture of 4,5-dichloro-2-nitroaniline (2.07 g, 10 mmol) and EMME (20 mL, apr. 100 mmol) was heated in open flask at 150°C for 5 h, then cooled to rt and diluted with ether (70 mL). Precipitated crude product was filtered, washed with ether (5 x 10 mL) and dried on air to give compound **27**, 3.37 g (98%) as bright yellow crystals (from EtOH); ^{1}H NMR (DMSO-D_6) δ 1.23 (t, 6H), 4.16 (q, 2H), 4.23 (q, 2H), 8.29 (s, 1H), 8.42 (s, 1H), 8.46 (d, J = 12 Hz, 1H), 12.20 (d, J = 12 Hz, 1H, NH); ^{13}C NMR (DMSO-D_6) d 14.53, 14.61, 60.61, 60.82, 100.13, 120.25, 125.52, 127.93, 135.73,

135.95, 139.54, 148.90, 164.98, 166.66. HRMS calcd for $C_{14}H_{14}N_2O_6Cl_2$ 376.0229.

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A compound having the formula:



IA

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

G represents one of $-C(R^{6a})(R^{6b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^{6a} and R^{6b} (i) together represent oxo or thiooxo, or (ii) R^{6a} and R^{6b} independently represent hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^9 (i) represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond;

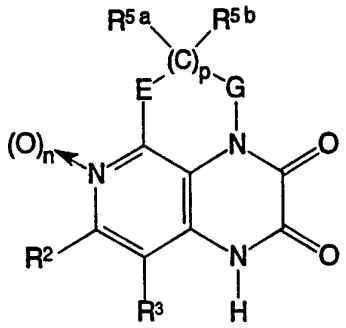
p is zero or one;

provided that:

(a) when E is $-C(R^{4a})(R^{4b})-$, G is $-C(R^{6a})(R^{6b})-$ and p is one, then one of the combination of either (i) R^{5a} and R^{5b} or (ii) R^{6a} and R^{6b} is oxo or thiooxo; or

(b) when E is $-N(R^9)-$, G is $-C(R^{6a})(R^{6b})-$ and p is one, then R^{6a} and R^{6b} do not represent hydrogen, alkyl or substituted alkyl.

2. A compound having the formula:



IB

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^2 represents hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

G represents one of $-C(R^{6a})(R^{6b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^{6a} and R^{6b} (i) together represent oxo or thiooxo, or (ii) R^{6a} and R^{6b} independently represent hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

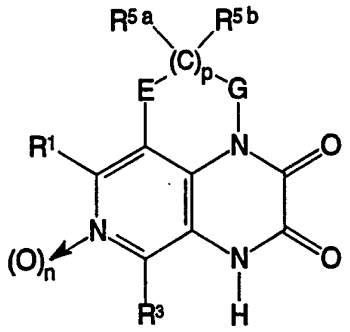
R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond;

p is zero or one; and

n is zero or one.

3: A compound having the formula:



IC

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1 represents hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

G represents one of $-C(R^{6a})(R^{6b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^{6a} and R^{6b} (i) together represent oxo or thiooxo, or (ii) R^{6a} and R^{6b} independently represent hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl,

substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

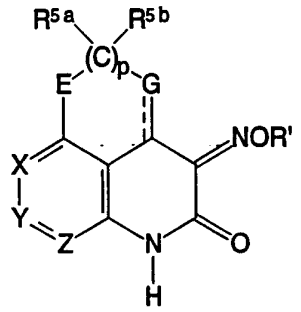
R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} forms a double bond;

n is zero or one; and

p is zero or one.

4. A compound having the formula:



II

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

X represents one of $C(R^1)$ or $N(O)_n$;

Y represents one of $C(R^2)$ or $N(O)_n$;

Z represents one of $C(R^3)$ or $N(O)_n$, with the proviso that when either or both of X and Z are $N(O)_n$, then Y is $C(R^2)$;

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

G represents one of $-C(R^{6a})(R^{6b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo or thiooxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^{6a} and R^{6b} (i) together represent oxo or thiooxo, or (ii) R^{6a} and R^{6b} independently represent hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

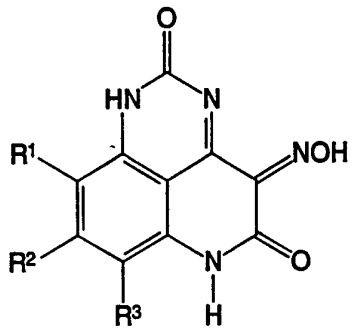
R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroarylalkenyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl, substituted heteroarylalkenyl, or heterocycloalkyl;

R^9 (i) represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond;

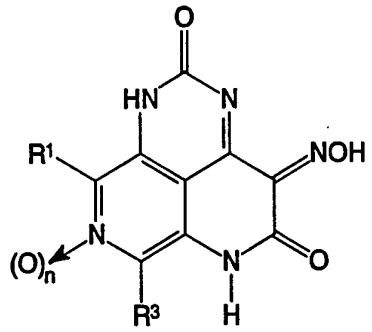
p is zero or one; and

R′ is one of halogen, alkyl, aryl, heteroaryl, acyl, halogen substituted acyl or aryloyl.

5. A compound of claim 4 having one of the following formulae:



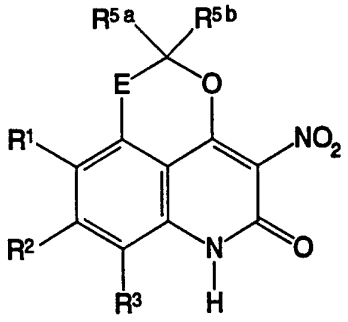
XXIV; or



XXV

wherein R^1, R^2 and R^3 are as defined above in claim 4; and n is zero or one.

6. A compound having the formula:



IIIA

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy,

haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

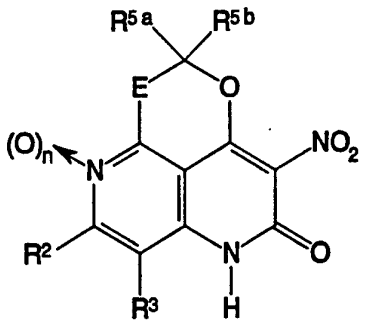
E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkyaryl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, or alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond.

7. A compound having the formula:



IIIB

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^2 represents hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl,

carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $-C(R^{4a})(R^{4b})-$, $-O-$ or $-N(R^9)-$;

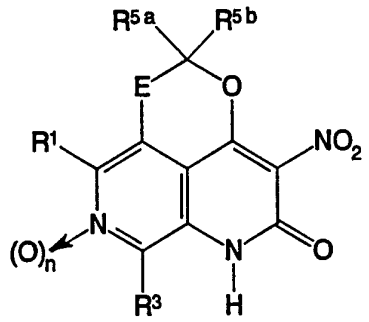
R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkyaryl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, or alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 form a double bond;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} form a double bond; and

n is zero or one.

8. A compound having the formula:



IIIC

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

R^1 represents hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl,

carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

E represents one of $—C(R^{4a})(R^{4b})—$, —O— or $—N(R^9)—$;

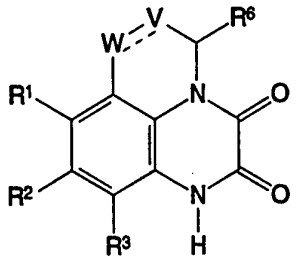
R^{4a} and R^{4b} (i) independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkyaryl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{4b} is hydrogen or alkyl, and R^{4a} together with R^{5a} forms a double bond;

R^{5a} and R^{5b} (i) independently represent hydrogen, or alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl, (ii) together represent oxo, or (iii) R^{5b} represents hydrogen or alkyl when R^{5a} together with R^{4a} or R^{5a} together with R^9 forms a double bond;

R^9 (i) independently represents hydrogen or lower alkyl, or (ii) R^9 together with R^{5a} forms a double bond; and

n is zero or one.

9. A compound having the formula:



IVA

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

W independently represents one of $C(R^4)$ or $N(O)_n$;

V independently represents one of $C(R^5)$ or $N(O)_n$ with the proviso that one of W and V is $N(O)_n$, and the other of W and V is $C(R^4)$ or $C(R^5)$, respectively;

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

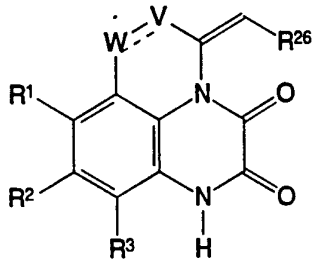
R^4 and R^5 independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl;

R^6 represents hydrogen, CO_2R^7, $CONR^7R^8$, $CON(OR^7)R^8$, COR^7, CN, tetrazolyl, alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl or heterocycloalkyl; and

n is zero or one.

10. A compound having the formula:



IVB

or a pharmaceutically acceptable salt or tautomer thereof;

wherein

W independently represents one of $C(R^4)$ or $N(O)_n$;

V independently represents one of $C(R^5)$ or $N(O)_n$ with the proviso that one of W and V is $N(O)_n$, and the other of W and V is $C(R^4)$ or $C(R^5)$, respectively;

R^1 and R^2 independently represent hydrogen, halogen, cyano, azido, nitro, hydroxy, amino, alkyl, haloalkyl, alkenyl, alkynyl, alkylamino, alkoxy, haloalkoxy, trialkylsilyl-substituted alkoxy, alkanoyl, alkoxycarbonyl, sulfamoyl, carbamoyl, alkylcarbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, alkylsulfonylamino, or acylamino;

R^3 represents hydrogen or fluorine;

R^4 and R^5 independently represent hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl or substituted aryl;

R^{26} represents alkyl, substituted alkyl, alkenyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl or heterocycloalkyl;

R^7 and R^8 independently represent hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroarylalkyl, heteroaryl, substituted heteroaryl, substituted heteroarylalkyl or heterocycloalkyl; and

n is zero or one.

11. A pharmaceutical composition comprising the compound of any one of claims 1-10 and a pharmaceutically acceptable carrier.

12. A method of treating or preventing (A) neuronal loss associated with stroke, ischemia, CNS trauma, or hypoglycemia or (B) the adverse neurological consequences of surgery, comprising administering to an animal

in need of such treatment or prevention an effective amount of a compound of any one of claims 1-10.

13. The method of claim 12 wherein said adverse neurological consequences occur as a result of air bubbles that lodge in the brain during or immediately after surgery.

14. The method of claim 12 wherein said adverse neurological consequences occur as a result of cardiopulmonary bypass surgery.

15. The method of claim 12 wherein said adverse neurological consequences occur as a result of carotid endarterectomy surgery.

16. The method of claim 12 wherein said neuronal loss occurs as a result of multiple strokes resulting in dementia.

17. A method of treating a neurodegenerative disease selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, comprising administering to an animal in need of such treatment an effective amount of a compound of any one of claims 1-10.

18. A method of antagonizing excitatory amino acids at the NMDA receptor complex, comprising administering to an animal in need thereof an effective amount of a compound of any one of claims 1-10.

19. A method of treating or preventing chronic pain, comprising administering to an animal in need of such treatment an effective amount of a compound of any one of claims 1-10.

20. A method of treating or preventing anxiety, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of any one of claims 1-10.

21. A method of treating or preventing convulsions, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of any one of claims 1-10.

22. A method of inducing anesthesia, comprising administering to an animal in need of such anesthesia an effective amount of a compound of any one of claims 1-10.

23. A method of treating or preventing NMDA receptor-ion channel related psychosis, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of any one of claims 1-10.

24. A method of treating or preventing opiate tolerance, comprising administering to an animal in need of such prevention an effective amount of a compound of any one of claims 1-10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10118

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
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)

U.S. : 514/214, 220, 222.8, 224.5, 227.5, 230.2, 250, 267; 540/548, 559, 579; 544/32, 101, 250, 344, 346

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P --- A, P	US, A, 5,436,240 (MOON ET AL.) 25 July 1995, see entire document.	1, 9-24 ------- 2-8

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

* Special categories of cited documents:

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

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
26 AUGUST 1996	11 SEP1996
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