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(54) **Pyrrolo-pyridazinone derivatives and pharmaceutical uses thereof**

(57) A class of 4-hydroxy-pyrrolo[1,2-b]pyridazin-2(1H)-one derivatives, substituted at the 3-position by an optionally substituted aryl substituent, are selective non-competitive antagonists of NMDA receptors and/or are antagonists of AMPA receptors, and are therefore of utility in the treatment of conditions, such as neurodegenerative disorders, convulsions or schizophrenia, which require the administration of an NMDA and/or AMPA receptor antagonist.

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PYRROLO-PYRIDAZINONE DERIVATIVES

5 This invention relates to a class of 4-hydroxy-  
pyrrolo[1,2-b]pyridazin-2(1H)-ones which are substituted  
in the 3-position by an optionally substituted aryl  
substituent. These compounds are selective non-  
competitive antagonists of N-methyl-D-aspartate (NMDA)  
receptors. More particularly, the class of compounds  
10 provided by the present invention are ligands for the  
strychnine-insensitive glycine modulatory site of the  
NMDA receptor and are therefore useful in the treatment  
and/or prevention of neurodegenerative disorders arising  
as a consequence of such pathological conditions as  
15 stroke, hypoglycaemia, cerebral palsy, transient cerebral  
ischaemic attack, cerebral ischaemia during cardiac  
pulmonary surgery or cardiac arrest, perinatal asphyxia,  
epilepsy, Huntington's chorea, Alzheimer's disease,  
Amyotrophic Lateral Sclerosis, Parkinson's disease,  
20 Olivo-ponto-cerebellar atrophy, anoxia such as from  
drowning, spinal cord and head injury, and poisoning by  
exogenous and endogenous NMDA receptor agonists and  
neurotoxins, including environmental neurotoxins.

By virtue of their NMDA receptor antagonist  
25 properties, the compounds according to the present  
invention are also useful as anticonvulsant and  
antiemetic agents, as well as being of value in the  
prevention or reduction of dependence on dependence-  
inducing agents such as narcotics.

30 NMDA receptor antagonists have recently been  
shown to possess analgesic (see, for example, Dickenson  
and Aydar, Neuroscience Lett., 1991, 121, 263; Murray *et*  
*al.*, Pain, 1991, 44, 179; and Woolf and Thompson, Pain,  
1991, 44, 293) and anxiolytic (see, for example,

US-5145866; and Kehne et al., Eur. J. Pharmacol., 1991, 193, 283) effects, and the compounds of the present invention may accordingly be useful in the management of pain and anxiety.

5                   Compounds possessing functional antagonist properties for the NMDA receptor complex are stated in WO-A-91/19493 to be effective in the treatment of mood disorders, including major depression, bipolar disorder, dysthymia and seasonal affective disorder (cf. also  
10 Trullas and Skolnick, Eur. J. Pharmacol., 1990, 185, 1). The compounds of the present invention may consequently be of benefit in the treatment and/or prevention of such disorders.

                  The association of NMDA receptor antagonists  
15 with regulation of the dopaminergic system has recently been reported (see, for example, Werling et al., J. Pharmacol. Exp. Ther., 1990, 255, 40; Graham et al., Life Sciences, 1990, 47, PL-41; Hutson et al., Br. J. Pharmacol., 1991, 103, 2037; and Turski et al., Nature (London), 1991, 349, 414). This suggests that the  
20 compounds of the present invention may thus be of assistance in the prevention and/or treatment of disorders of the dopaminergic system such as schizophrenia and Parkinson's disease.

25                   It has also been reported recently (see Lauritzen et al., Journal of Cerebral Blood Flow and Metabolism, 1991, vol. 11, suppl. 2, Abstract XV-4) that NMDA receptor antagonists block cortical spreading depression (CSD), which may thus be of clinical  
30 importance since CSD is a possible mechanism of migraine. The class of substituted 2-amino-4-phosphonomethylalk-3-ene carboxylic acids and esters described in EP-A-0420806, which are stated to be selective NMDA

antagonists, are alleged thereby to be of potential utility in the treatment of inter alia migraine.

Excitatory amino acid receptor antagonists, including inter alia antagonists of NMDA receptors, are alleged in EP-A-0432994 to be of use in suppressing emesis.

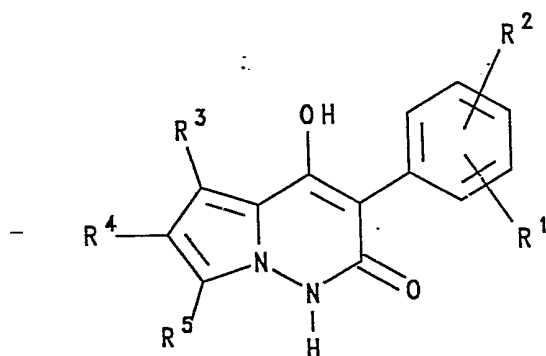
Recent reports in the literature have also suggested a link between the neurotoxicity of certain viruses and the deleterious effects of these viruses on an organism caused by the potentiation of neurotransmission via excitatory amino acid receptors. By virtue of their activity as antagonists of NMDA receptors, therefore, the compounds of the present invention may be effective in controlling the manifestations of neuroviral diseases such as measles, rabies, tetanus (cf. Bagetta et al., Br. J. Pharmacol., 1990, 101, 776) and AIDS (cf. Lipton et al., Society for Neuroscience Abstracts, 1990, 16, 128.11).

NMDA antagonists have, moreover, been shown to have an effect on the neuroendocrine system (see, for example, van den Pol et al., Science, 1990, 250, 1276; and Urbanski, Endocrinology, 1990, 127, 2223), and the compounds of this invention may therefore also be effective in the control of seasonal breeding in mammals.

In addition, certain compounds of the invention are antagonists of 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, also known as quisqualate receptors. An excitatory amino acid projection from the prefrontal cortex to the nucleus accumbens (a particular region of the forebrain possessing dopamine-sensitive neurones) is well known to exist (see, for example, J. Neurochem., 1985, 45, 477). It is also well known that dopaminergic transmission in the striatum is modulated by glutamate (see, for example,

Neurochem. Int., 1983, 5, 479), as also is the hyperactivity associated with presynaptic stimulation of the dopamine system by AMPA in the nucleus accumbens (cf. Life Sci., 1981, 28, 1597). Compounds which are  
5 antagonists of AMPA receptors are therefore of value as neuroleptic agents.

The present invention accordingly provides a compound of formula I, or a salt or prodrug thereof:



(1)

wherein

20 R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or -CONR<sup>a</sup>R<sup>b</sup>; or R<sup>1</sup> and R<sup>2</sup> together represent the residue of a  
25 carbocyclic or heterocyclic ring;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or  
30 -CONR<sup>a</sup>R<sup>b</sup>; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group.

The present invention also provides the use of a compound of formula I as defined above or a

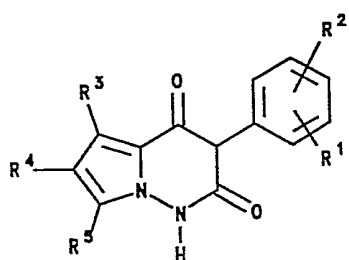
pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of conditions, in particular neurodegenerative disorders, which require the administration of a selective non-competitive antagonist of NMDA receptors.

The present invention further provides the use of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of conditions, such as schizophrenia, which require the administration of an antagonist of AMPA receptors.

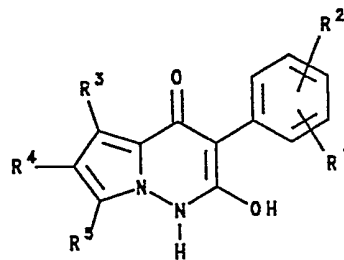
In a further aspect, the invention provides a pharmaceutical composition comprising a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with one or more pharmaceutically acceptable carriers and/or excipients.

In a still further aspect, the invention provides a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof for use in therapy.

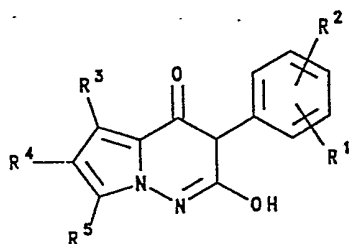
The compound of formula I will in general exist in equilibrium with its other tautomeric forms, including those structures of formulae A to D:



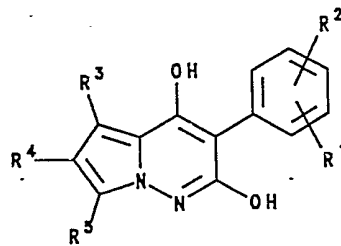
(A)



(B)



(C)



(D)

wherein R<sup>1</sup> to R<sup>5</sup> are as defined with reference to formula I above. It is to be understood that all tautomeric forms of the compounds of formula I, as well as all possible mixtures thereof, are included within the scope of the present invention.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>2-6</sub>)alkenyl and aryl(C<sub>2-6</sub>)alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and

conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C<sub>3-7</sub> heterocycloalkyl, C<sub>3-7</sub> heterocycloalkyl(C<sub>1-6</sub>)alkyl, heteroaryl and heteroaryl(C<sub>1-6</sub>)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Suitable aryl groups include phenyl and naphthyl groups.

A particular aryl(C<sub>1-6</sub>)alkyl group is benzyl.

A particular aryl(C<sub>2-6</sub>)alkenyl group is phenylethenyl.

A particular aryl(C<sub>2-6</sub>)alkynyl group is phenylethynyl.

Suitable heterocycloalkyl groups include piperidyl, piperazinyl and morpholinyl groups.

A particular heterocycloalkyl(C<sub>1-6</sub>)alkyl group is morpholinylethyl.



Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, indolyl, pyranyl, furyl, benzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups. Particular heteroaryl groups are pyridyl, pyrrolyl, indolyl, furyl, benzofuryl, thienyl, benzthienyl and oxadiazolyl.

Particular heteroaryl(C<sub>1-6</sub>)alkyl groups include pyridylmethyl, pyrrolylmethyl, indolylmethyl, furylmethyl and thienylmethyl.

Where R<sup>1</sup> and R<sup>2</sup> together represent the residue of a carbocyclic or heterocyclic ring, the ring may be saturated or unsaturated. The ring may suitably be a 4- to 9-membered ring, but will preferably be a 5- or 6-membered ring. Where R<sup>1</sup> and R<sup>2</sup> together represent the residue of a heterocyclic ring, this ring may contain up to four heteroatoms selected from oxygen, nitrogen and sulphur. Suitable carbocyclic rings of which R<sup>1</sup> and R<sup>2</sup> together represent the residue include cyclohexane, cyclohexene, cyclohexadiene and benzene rings. Suitable heterocyclic rings of which R<sup>1</sup> and R<sup>2</sup> together represent the residue include dioxolane, dioxane, pyridine, furan, thiophene, pyrrole, thiazole and thiadiazole rings.

The hydrocarbon and heterocyclic groups, as well as the carbocyclic or heterocyclic ring completed by R<sup>1</sup> and R<sup>2</sup>, may in turn be optionally substituted by one or more groups selected from C<sub>1-6</sub> alkyl, adamantyl, phenyl, halogen, C<sub>1-6</sub> haloalkyl, morpholinyl(C<sub>1-6</sub>)alkyl, trifluoromethyl, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkoxy, aryloxy, keto, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, carboxy, C<sub>2-6</sub> alkoxy-carbonyl, C<sub>2-6</sub> alkoxy-carbonyl(C<sub>1-6</sub>)alkyl, C<sub>2-6</sub> alkyl-carbonyloxy, aryl-carbonyloxy, C<sub>2-6</sub> alkyl-carbonyl, aryl-carbonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulphinyl, C<sub>1-6</sub>

alkylsulphonyl, amino, mono- or di(C<sub>1-6</sub>)alkylamino, C<sub>2-6</sub> alkylcarbonylamino and C<sub>2-6</sub> alkoxycarbonylamino.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

Suitable values for the substituents R<sup>1</sup> and R<sup>2</sup> include C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>2-6</sub>)alkenyl, aryl(C<sub>2-6</sub>)alkynyl, heteroaryl(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyloxy, aryloxy, aryl(C<sub>1-6</sub>)alkoxy, heteroaryloxy, arylthio, arylsulphonyl, arylamino, aryl(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, arylcarbonylamino, arylcarbonyl or heteroarylcarbonyl, any of which groups may be optionally substituted; and hydrogen, halogen, trifluoromethyl or nitro. Examples of optional substituents on the groups R<sup>1</sup> and/or R<sup>2</sup> include C<sub>1-6</sub> alkyl, morpholinyl(C<sub>1-6</sub>)alkyl, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkoxy, C<sub>1-6</sub> alkylthio and di(C<sub>1-6</sub>)alkylamino.

Particular values for the substituents R<sup>1</sup> and R<sup>2</sup> include hydrogen, methyl, phenyl, benzyl, methoxymethyl-benzyl, morpholinylethyl-benzyl, hydroxybenzyl, methoxybenzyl, methoxymethoxy-benzyl, methylthio-benzyl, phenylethenyl, phenylethynyl, thienylmethyl, pyrrolylmethyl, indolylmethyl, fluoro, chloro, bromo, iodo, trifluoromethyl, nitro, methoxy, ethoxy, allyloxy, methyl-allyloxy, phenoxy, methyl-phenoxy, methoxy-phenoxy, dimethylamino-phenoxy, benzyloxy, furyloxy, thienyloxy, pyridyloxy, phenylthio, phenylsulphonyl, phenylamino, benzylamino, dimethylamino, phenylcarbonylamino, phenylcarbonyl, furylcarbonyl and thienylcarbonyl.

Suitably, at least one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen.

Where R<sup>1</sup> and R<sup>2</sup> together represent the residue of a carbocyclic or heterocyclic ring, this may be, in

particular, a dioxolane or optionally substituted benzene ring.

The pyrrolo moiety of the 4-hydroxy-pyrrolo[1,2-b]pyridazin-2(1H)-one ring system shown in formula I above may be substituted or unsubstituted. Particular substituents include halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio and C<sub>2-7</sub> alkoxy-carbonyl. Suitably R<sup>3</sup> is hydrogen and R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, halogen, cyano, trifluoromethyl, nitro, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl, at least one of R<sup>4</sup> and R<sup>5</sup> desirably being other than hydrogen. Preferably, R<sup>3</sup> is hydrogen and R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, cyano, trifluoromethyl, nitro, methyl, ethyl, vinyl or halogen, especially chlorine or iodine. In a particular embodiment, R<sup>3</sup> is hydrogen, one of R<sup>4</sup> and R<sup>5</sup> is hydrogen and the other of R<sup>4</sup> and R<sup>5</sup> represents hydrogen, cyano, trifluoromethyl, nitro or halogen, especially chlorine.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts of the compounds of formula I above include alkali metal salts, e.g. lithium, sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts. Where appropriate, acid addition salts may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic

acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

5 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in 10 "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to 15 the invention possess two or more asymmetric centres, 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.

20 Specific compounds within the scope of the present invention include:

4-hydroxy-3-phenylpyrrolo[1,2-b]pyridazin-2(1H)-one; and salts and prodrugs thereof.

25 The pharmaceutical compositions of this invention are preferably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, or suppositories, for oral, intravenous, parenteral or rectal administration. For preparing solid compositions such as tablets, the 30 principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical

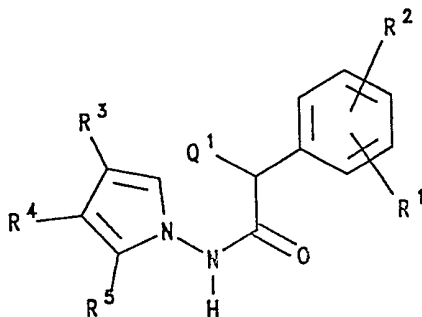
diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical

vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

5 In the treatment of neurodegeneration, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day. 10 In a particular embodiment, the compounds may be conveniently administered by intravenous infusion.

The compounds of formula I above may be prepared by a process which comprises cyclising a 15 compound of formula II:



(II)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above; and Q<sup>1</sup> represents a reactive carboxylate moiety.

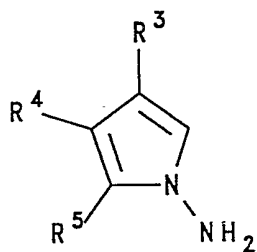
The reaction is conveniently carried out by heating a solution of compound II in a suitable hydrocarbon solvent, for example mesitylene, preferably 30 at the reflux temperature of the solvent.

Suitable values for the reactive carboxylate moiety Q<sup>1</sup> include esters, for example C<sub>1-4</sub> alkyl esters; acid anhydrides, for example mixed anhydrides with C<sub>1-4</sub>

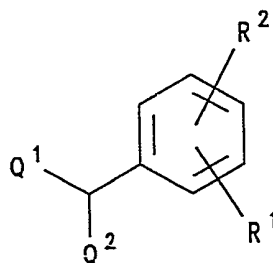
alkanoic acids; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

Preferably, the group  $Q^1$  represents methoxycarbonyl or ethoxycarbonyl.

5 The intermediates of formula II above may conveniently be prepared by reacting a compound of formula III with a compound of formula IV:



(III)



(IV)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $Q^1$  are as defined above; and  $Q^2$  represents a reactive carboxylate moiety.

20 The reaction is conveniently effected by mixing the reagents in an inert solvent, such as dichloromethane or 1,2-dichloroethane, and stirring the reaction mixture for several hours at ambient temperature.

25 It will be understood that the reactive carboxylate moieties  $Q^1$  and  $Q^2$  will be different in order to permit isolation of a stable intermediate of formula III before the subsequent cyclisation step is performed. As depicted, the moiety  $Q^2$  will be the most reactive of the two groups  $Q^1$  and  $Q^2$  with the primary amino functionality attached to the pyrrole nucleus in  
30 structure III. Preferably, the group  $Q^2$  is an acid halide group, in particular an acid chloride group. A compound of formula IV wherein  $Q^2$  represents an acid chloride group may conveniently be prepared from the corresponding compound of formula IV wherein  $Q^2$

represents a carboxy group  $-CO_2H$  by treatment with oxalyl chloride or thionyl chloride under standard conditions well known from the art.

5 Where they are not commercially available, the 1-aminopyrrole derivatives of formula III above may be prepared by methods known from the art, in particular by procedures analogous to those described in Chem. Ber., 1969, 102, 3268.

10 The aromatic intermediates of formula IV above, including the precursors of formula IV wherein  $Q^2$  represents  $-CO_2H$ , where they are not commercially available, may be prepared by methods which will be readily apparent to those skilled in the art.

15 It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art.

20 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may  
25 be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-  
30 p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides,



followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This  
5 may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wutts, Protective Groups in  
10 Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Example illustrates the preparation of compounds according to the invention.

15 The compounds useful in this invention potently and selectively block responses to NMDA and/or AMPA in a brain slice from rat cortex, and inhibit the binding of agonists and antagonists to the strychnine-insensitive site present on the NMDA receptor and/or AMPA binding to  
20 rat forebrain membranes.

#### Cortical Slice Studies

The effects of compounds of the invention on responses to NMDA and AMPA can be assessed using the rat  
25 cortical slice as described by Wong et al., Proc. Natl. Acad. Sci. USA, 1986, 83, 7104. The apparent equilibrium constant ( $K_b$ ) is calculated from the righthand shift in the NMDA or AMPA concentration-response curves produced by the compound under test. The compound of the  
30 accompanying Example was tested and was found to possess a  $K_b$  value in response to NMDA of below 150  $\mu$ M.

Binding Studies

The ability of test compounds to displace <sup>3</sup>H-L-689,560 (trans-2-carboxy-5,7-dichloro-4-phenyl-aminocarbonylamino-1,2,3,4-tetrahydroquinoline) binding to the strychnine-insensitive site present on the NMDA receptor of rat forebrain membranes can be determined by the method of Grimwood et al., Proceedings of The British Pharmacological Society, July 1991, Abstract C78. The concentration of the compound of the accompanying Example required to displace 50% of the specific binding (IC<sub>50</sub>) is below 50 μM.

EXAMPLE 1

Step 1: Ethyl  $\alpha$ -(1-pyrroleaminocarbonyl)phenyl acetate

5 Oxalyl chloride (1.05ml, 1.52g, 12mmol) was added to a solution of phenylmalonate monoethyl ester (2.08g, 10mmol) in dry dichloromethane (50ml) containing DMF (3 drops). After stirring for 2h, the solution was evaporated, the residue co-  
10 evaporated with carbon tetrachloride and then redissolved in dichloromethane (40ml). A solution of 1-aminopyrrole (0.72g, 8.8mmol) in dry pyridine (5ml) was added and the mixture stirred overnight and then washed with 1M HCl (2 x 40ml), dried (MgSO<sub>4</sub>) and evaporated. The residue was subjected to column chromatography, eluting with 35% ethyl acetate in  
15 hexanes, to afford the title compound as a gum (1.82g, 76%).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.24-1.32 (3H, m, CH<sub>3</sub>), 4.11-4.32 (2H, m, -OCH<sub>2</sub>CH<sub>3</sub>), 4.67 (1H, s, -CH-), 6.15 (2H, t, J 2.2Hz, pyrrole-3,4-H), 6.60 (2H, t, J 2.2Hz, pyrrole-2,5-H), 7.37-7.46 (5H, m, ArH) and 9.52 (1H, s, NH).

20

Step 2: 4-Hydroxy-3-phenylpyrrolo[1,2-b]pyridazin-2(1H)-one

25 A solution of the above compound (0.5g, 2.1mmol) in mesitylene (25ml) was stirred at reflux under an atmosphere of nitrogen for 3h. On cooling, the product was collected by filtration, washed with hexanes and dried to leave a pale brown

solid (0.28g, 56%), m.p. 270°C (dec.). (Found: C, 69.37; H, 4.46; N, 12.10.  $C_{13}H_{10}N_2O_2$  requires: C, 69.02; H, 4.46; N, 12.38%).  $\delta_H$  (DMSO- $d_6$ ) 6.51 (1H, dd, J 4.3, 2.6Hz, 6H), 6.72 (1H, dd, J 4.3, 1.7Hz, 5-H), 7.24-7.30 (1H, m, ArH), 7.34-7.37 (4H, m, ArH), 7.43 (1H, dd, J 2.6, 1.7Hz, 7-H), 10.61 (1H, br s, NH), 10.77 (1H, br s, OH).

### EXAMPLE 2

#### Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compound are prepared as illustrated below:

4-Hydroxy-3-phenylpyrrolo[1,2-b]pyridazin-2(1H)-one

TABLE FOR DOSES CONTAINING FROM  
1-25MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

TABLE FOR DOSES CONTAINING FROM  
26-100MG OF THE ACTIVE COMPOUND

	Amount-mg			
5				
	Active Compound	26.0	50.0	100.0
	Microcrystalline cellulose	52.0	100.0	200.0
	Modified food corn starch	2.21	4.25	8.5
	Magnesium stearate	0.39	0.75	1.5

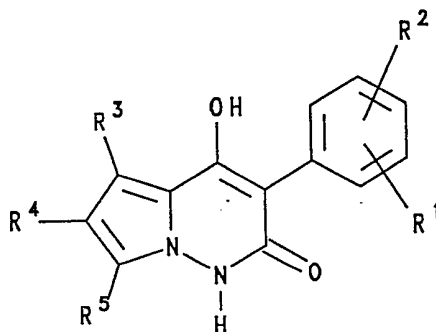
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All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The

15 resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

CLAIMS:

1. A compound of formula I, or a salt or  
5 prodrug thereof:



(1)

wherein

R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen,  
hydrocarbon, a heterocyclic group, halogen, cyano,  
trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>,  
20 -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or  
-CONR<sup>a</sup>R<sup>b</sup>; or R<sup>1</sup> and R<sup>2</sup> together represent the residue of a  
carbocyclic or heterocyclic ring;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen,  
hydrocarbon, a heterocyclic group, halogen, cyano,  
25 trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>,  
-SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or  
-CONR<sup>a</sup>R<sup>b</sup>; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen,  
hydrocarbon or a heterocyclic group.

30

2. A compound as claimed in claim 1 wherein  
R<sup>1</sup> and R<sup>2</sup> are independently selected from the group  
consisting of hydrogen, methyl, phenyl, benzyl,  
methoxymethyl-benzyl, morpholinylethyl-benzyl,

hydroxybenzyl, methoxybenzyl, methoxymethoxy-benzyl,  
methylthio-benzyl, phenylethenyl, phenylethynyl,  
thienylmethyl, pyrrolylmethyl, indolylmethyl, fluoro,  
chloro, bromo, iodo, trifluoromethyl, nitro, methoxy,  
5 ethoxy, allyloxy, methyl-allyloxy, phenoxy, methyl-  
phenoxy, methoxy-phenoxy, dimethylamino-phenoxy,  
benzyloxy, furyloxy, thienyloxy, pyridyloxy, phenylthio,  
phenylsulphonyl, phenylamino, benzylamino, dimethylamino,  
phenylcarbonylamino, phenylcarbonyl, furylcarbonyl and  
10 thienylcarbonyl.

3. A compound as claimed in claim 1 or claim  
2 wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from  
the group consisting of hydrogen, halogen, cyano,  
15 trifluoromethyl, nitro, hydroxy, amino, carboxy, C<sub>1-6</sub>  
alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio and C<sub>2-7</sub>  
alkoxycarbonyl.

4. A compound as claimed in claim 3 wherein  
20 R<sup>3</sup> is hydrogen, one of R<sup>4</sup> and R<sup>5</sup> is hydrogen and the other  
of R<sup>4</sup> and R<sup>5</sup> is selected from the group consisting of  
hydrogen, cyano, trifluoromethyl, nitro and halogen.

5. A compound selected from:  
25 4-hydroxy-3-phenylpyrrolo[1,2-b]pyridazin-2(1H)-one;  
and salts and prodrugs thereof.

6. A compound as claimed in any one of the  
preceding claims as herein specifically disclosed.

30 7. A pharmaceutical composition comprising a  
compound of formula I as defined in claim 1 or a  
pharmaceutically acceptable salt thereof or a prodrug

thereof in association with one or more pharmaceutically acceptable carriers and/or excipients.

5           8.    A pharmaceutical composition substantially as herein described.

          9.    A compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for use in therapy.

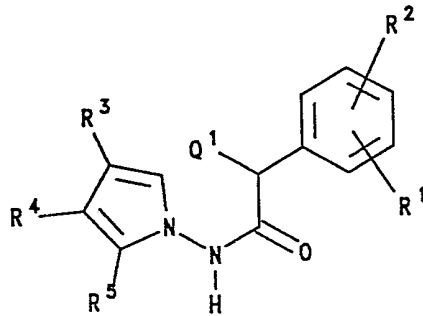
10           10. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of  
15           conditions which require the administration of a selective non-competitive antagonist of NMDA receptors.

          11. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt  
20           thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of conditions which require the administration of an antagonist of AMPA receptors.

25           12. A process for the preparation of a compound as claimed in any one of claims 1 to 6, which comprises cyclising a compound of formula II:

30





(11)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in claim 1;  
and Q<sup>1</sup> represents a reactive carboxylate moiety.

15 13. A process as claimed in claim 12  
substantially as herein described.

20 14. A compound as claimed in any one of claims  
1 to 6 whenever prepared by a process as claimed in claim  
12 or claim 13.

**Patents Act 1977  
Examiner's report to the Comptroller under  
Section 17 (The Search Report)**

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GB 9305306.4

**Relevant Technical fields**

- (i) UK Cl (Edition L ) C2C (CTN)
- (ii) Int Cl (Edition 5 ) C07D 487/04

**Search Examiner**

S I AHMAD

**Databases (see over)**

- (i) UK Patent Office
- (ii) ONLINE DATABASE: CAS ONLINE

**Date of Search**

14 JUNE 1993

Documents considered relevant following a search in respect of claims 1-14

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
	NONE	



Category	Identity of document and relevant passages	Relevant to claim(s)

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