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(54) **Title:** PYRIMIDINE, PYRIDINE, PTERIDINONE AND INDAZOLE DERIVATIVES AS ENZYME INHIBITORS

(57) **Abstract**

The use of a compound which binds at the tetrahydrobiopterin site of NO synthase for the treatment of conditions where there is an advantage in inhibiting neuronal NO synthase with little or no inhibition of endothelial NO synthase is disclosed. Pharmaceutical formulations comprising such compounds, and processes, including a novel process, for their preparation are also disclosed.

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PYRIMIDINE, PYRIDINE, PTERIDINONE AND INDAZOLE DERIVATIVES AS ENZYME INHIBITORS

The present invention relates to neuronal nitric oxide (NO) synthase inhibitors, to methods for their manufacture, to pharmaceutical compositions containing them and to their use in therapy, in particular their use in diseases of the nervous system in which NO plays a part.

It has been known since the early 1980's that the vascular relaxation brought about by acetylcholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years and NO is the active component of amyl nitrite, glyceryl trinitrite and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesised from the amino acid L-arginine by the enzyme NO synthase.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of biological actions in addition to endothelium-dependent relaxation including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al, Biochemical Pharmacology, 38, 1709-1715 (1989) and Moncada et al, Pharmacological Reviews, 43, 109-142 (1991)). It is now thought that excess NO production may be involved in a number of conditions, particularly conditions which involve systemic hypotension such as toxic shock and therapy with certain cytokines.

It has recently become apparent that the neuronal NO synthase is a distinct protein from the endothelial NO synthase (Sessa et al, J.Biol.Chem., 267, 15274-15276, 1992).

We believe that NO synthesis plays an important part in the pathology of a range of diseases of the nervous system, eg. ischemia. However, non-selective inhibitors of NO syntheses cause profound changes in blood pressure and blood flow, including cerebral blood flow. Unfortunately, ischemic injury inherently reduces the blood supply to the brain and any further decrease in blood flow caused by a non-selective NO synthase inhibitor would have a deleterious effect, potentially opposing any beneficial effect of decreased NO production within the brain. Nevertheless, studies of middle cerebral artery occlusion in both rats and mice have demonstrated a substantial protection effect of low doses of NO synthase inhibitors (see for example Nowicki et al, Eur. J.Pharmacol., 1991, 204, 339-340). At high doses, or in models of global ischemia, these inhibitors fail to provide protection. Thus,

there is a need for a potent inhibitor of neuronal NO synthase with preferably little or no activity against the vascular endothelial NO synthase.

The synthesis of NO from L-arginine can be inhibited by the L-arginine analogue L-N-monomethyl-arginine (L-NMMA) and the therapeutic use of L-NMMA for the treatment of toxic shock and other types of systemic hypotension has been proposed (WO 91/04024 and GB-A-2240041). The therapeutic use of certain other NO synthase inhibitors apart from L-NMMA for the same purpose has also been proposed in WO 91/04024 and in EP-A-0446699. Compounds like L-NMMA do not show selectivity for the neuronal NO synthase as opposed to the other NO synthases.

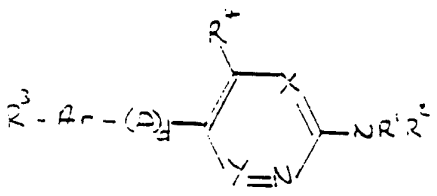
It is known that the presence of (6R)-5,6,7,8-tetrahydro-L-biopterin (hereinafter tetrahydrobiopterin) is necessary for activity of the NO synthase enzymes. We believe that tetrahydrobiopterin causes expression of the activity of the enzymes by binding to them. We have now found that compounds which competitively bind at the tetrahydrobiopterin sites of NO synthases inhibit neuronal NO synthase selectively over endothelial NO synthase.

Accordingly, the present invention provides the use of a compound which binds at the tetrahydrobiopterin site of NO synthase for the manufacture of a medicament for the treatment of a condition where there is an advantage in inhibiting neuronal NO synthase with little or no inhibition of endothelial NO synthase.

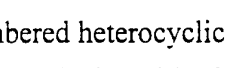
In another aspect, the present invention provides a method for the treatment or prophylaxis of a condition where there is an advantage in inhibiting neuronal NO synthase with little or no inhibition of endothelial NO synthase which comprises the administration of an effective amount of a compound which binds at the tetrahydrobiopterin site of NO synthase.

Suitable compounds which bind at the tetrahydrobiopterin site include those of formula (IA), formula (IC) or structural analogues of tetrahydrobiopterin and or salts thereof, as hereinafter defined.

1)

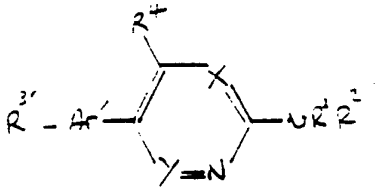


(IA)

Wherein R^1 and R^2 are the same or different and each is hydrogen or a C_{1-4} alkyl group or NR^1R^2 forms a 5- or 6-membered heterocyclic group  wherein T is oxygen, CH_2 or nitrogen substituted by hydrogen or C_{1-4} alkyl, and v and w are the same or different and each is 1 or 2 provided the sum of v and w is 3 or 4; X is nitrogen or CH; Y is nitrogen, CH or CNH_2; D is a group $S(O)_x$ wherein x is 0, 1 or 2, a C_{1-4} alkylene chain, or a C_{2-4} alkenylene or alkynylene chain; d is 0 or 1; Ar is a monocyclic or bicyclic ring system which may contain one or two heteroatoms and which contains at least one aromatic ring; R^3 represents hydrogen or one to three substituents on the ring system Ar which may be the same or different and are chosen from halo, NR^5R^6 wherein R^5 and R^6 are independently selected from hydrogen or $S(O)_{x'}$ R^7 wherein x' is 0, 1 or 2 and R^7 is C_{1-4} alkyl; nitro, cyano, a C_{1-4} carboxcylic acid group or an ester thereof, C_{1-4} alkyl optionally substituted by one to three halo atoms; phenyl or a group $-(A)_mR^8$ wherein A represents oxygen, $S(O)_n$ wherein n is 0, 1 or 2, or NR^9 wherein R^9 is hydrogen or C_{1-4} alkyl optionally substituted by halo and m is 0 or 1, and R^8 is hydrogen, or C_{1-4} alkyl or phenyl each optionally substituted by one to three halo atoms; R^4 is hydrogen, C_{1-4} alkyl, hydroxy, halo, trifluoromethyl or a group $NR^{10}R^{11}$ wherein R^{10} and R^{11} are the same or different and each is hydrogen or C_{1-4} alkyl, or $NR^{10}R^{11}$ forms a 5- or 6- membered heterocyclic group optionally substituted by a C_{1-4} alkyl group or R^4 represents a C_{1-2} alkylene group linking the heterocyclic ring to Ar.

Preferred heterocyclic groups include morpholino, piperidino and methylpiperazino.

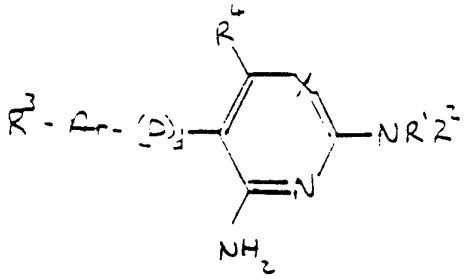
Formula (IA) includes compounds of formula (II)



(II)

or a salt thereof, wherein R^1,R^2,X,Y,R^4 are as hereinbefore defined, Ar' is a monocyclic or bicyclic ring system containing at least one aromatic ring, and $R^{3'}$ represents hydrogen or one to three substituents which may be the same or different and are chosen from halo, amino, nitro, cyano, a C_{1-4} carboxylic acid group or an ester thereof, a group $-(A)_mR^{8'}$ wherein A and m are as hereinbefore defined and $R^{8'}$ is C_{1-4} alkyl optionally substituted by halo;

Preferred compounds of the formula (IA) include those of the formula (III)



(III)

or a salt thereof

wherein D, d, Ar, R^3, R^1, R^2, X and R^4 are as hereinbefore defined.

For formulae (IA), (II) and (III):

Suitably d is 0;
Suitably Ar is phenyl, naphthyl, tetrahydronaphthyl, or benzothienyl.
Preferably Ar is phenyl.

Suitably R^3 is halo, most suitably chloro or bromo, C_{1-4} alkyl or C_{1-4} alkoxy, preferably methoxy. Preferably there are one or two substituents which are at the 3-, 4- or 5- positions of the phenyl ring (when Ar is phenyl) or at a position not α- to the linkage of the group Ar to the nitrogen containing aromatic ring when Ar is not phenyl. Preferably, when Ar is phenyl the, or one of the, subsituents is at the 4-position of the phenyl ring.

Suitably R^1 and R^2 are hydrogen, methyl, ethyl or NR^1R^2 is a methyl-piperazino group. Preferably R^1 and R^2 are hydrogen.

R^4 is most suitably hydrogen or NH_2 and preferably R^4 is hydrogen.

For formulae (IA) and (II) Y is preferably CNH_2

Suitable compounds of the formula (IA) include

2,4-diamino-6-(4-methoxyphenyl)pyrimidine
2,4-diamino-6-(3,4-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2-(4-methylphenyl)ethyl)pyrimidine
2,4-diamino-5-(4-methylphenylethynyl)pyrimidine
2,4-diamino-5-phenylethynylpyrimidine
2,6-diamino-3-(2,4,5-trichlorophenyl)pyridine

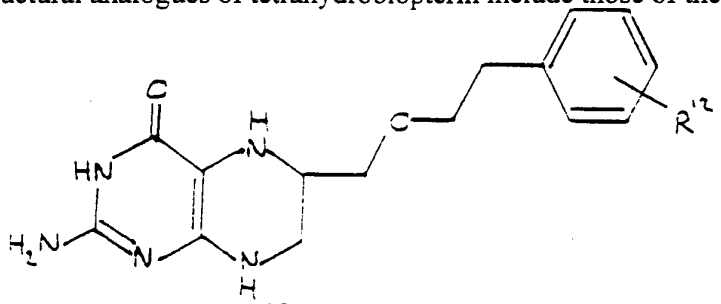
2,6-diamino-3-(4-methoxyphenyl)pyridine
2,6-diamino-3-(2-naphthyl)pyridine
2,6-bis(acetamido)-3-(3,4-dimethoxyphenyl)pyridine
2,6-diamino-3-(3,4-dimethoxyphenyl)pyridine
1-amino-2, 4-diaza-5, 6-dihydro-9-methoxy-3-(4-methyl-1-piperazinyl)phenanthrene
4-amino-9, 10-dihydro-7-methoxy-2-(4-methyl-1-piperazinyl)benzo [f] quinazaline
2-amino-5-((-naphthyl)pyrimidine
2-amino-5-(4-methoxyphenyl)pyrimidine
2-(4-methylpiperazinyl)-5-(2-naphthyl)pyrimidine
5-(3,4-dimethoxy)-2-(4-methyl-1-piperazinyl)pyrimidine
5-(1,3-benzo[d]dioxol-5-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(1,4-benzodioxan-6-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(3,4-dichlorophenyl)-2-(4-methylpiperazinyl)pyrimidine
2,4-diamino-5-(3-thienyl)pyrimidine
2,4-diamino-5-(3,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-biphenylpyrimidine
2,4-diamino-5-(3,5-bis(trifluoromethyl)phenyl)pyrimidine
2,4-diamino-5-(3,5-dichlorophenyl)pyrimidine
2,4-diamino-5-(2,5-dibromo-4-chlorophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-methanesulphonamidophenyl)pyrimidine
2,4-diamino-5-(4-methoxy-3-methylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethoxyphenyl)pyrimidine
2,4-diamino-5-(3-amino-4-chlorophenyl)pyrimidine
2,4-diamino-5-(3-aminophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-nitrophenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-hydroxyphenyl)pyrimidine
2,4-diamino-5-(3-fluorophenyl)pyrimidine
2,4-diamino-5-(3-trifluoromethoxyphenyl)pyrimidine
2,4-diamino-5-(3-bromo-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-fluoro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-fluorophenyl)pyrimidine
2,4-diamino-5-(4-chlorophenyl)pyrimidine
1,3-diamino-5, 6-dihydro-7-methoxy-2, 4-phenanthroline
1,3-diamino-5, 6-dihydro-8-methoxy-2, 4-phenanthroline

1,3-diamino-5, 6-dihydro-9-methoxy-2, 4-phenanthroline
3-(2, 4-diamino-5-pyrimidinyl)phenol
2.4-diamino-5-(3-methoxyphenyl)pyrimidine
2,4-diamino-6-(4-nitrophenyl)pyrimidine
2,4-diamino-5-(3,4-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(3,4,5-trimethoxyphenyl)pyrimidine
2,4-diamino-5-(4-fluorophenyl)pyrimidine
2,4-diamino-5-(4-methoxyphenylthio)pyrimidine
2,4-diamino-5-phenethylpyrimidine
2,4-diamino-5-(4-chlorophenylthio)pyrimidine
2,4-diamino-5-(4-chlorophenylsulphonyl)-6-methylpyrimidine
or a salt thereof.

Preferred compounds of the formula (IA) include:

2, 4-diamino-5-(3, 4-dichlorophenyl)pyrimidine
2, 4-diamino-5-(4-methoxyphenyl)pyrimidine
2, 4-diamino-5-(4-methylphenyl)pyrimidine
2, 4-diamino-5-(4-chlorophenyl)pyrimidine
2, 4-diamino-5-(3-chlorophenyl)pyrimidine
2, 4-diamino-5-(2, 4-dichlorophenyl)pyrimidine
2,4-diamino-5-(3-trifluoromethylphenyl)pyrimidine
2.-4-diamino-5-(3-bromophenyl)pyrimidine
2,4-diamino-5-(3-methylphenyl)pyrimidine
2,4-diamino-5-(3,4-methylenedioxyphenyl)pyrimidine
2,4-diamino-5-(3,4-ethylenendioxyphenyl)pyrimidine
or a salt thereof

2) Structural analogues of tetrahydrobiopterin include those of the formula (IB):

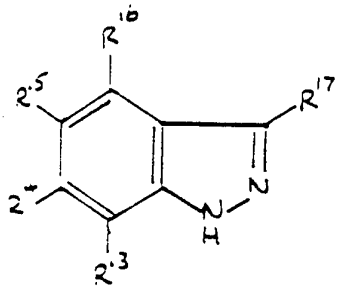


(IB)

and salts thereof wherein R^{12} is hydrogen, halo, C_{1-4} alkyl optionally substituted by halo or alkoxy and preferably R^{12} is a substituent at 3, 4 or 5 position. (+-)-2-Amino-6-[[(4-

chlorophenethyl)oxy]methyl]-5, 6, 7, 8-tetrahydro-4(3H)-pteridinone is an example of a compound of the formula (IB). These compounds bind less strongly than those of formula (IA).

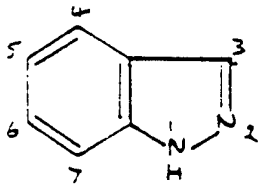
3)



(IC)

wherein R^{13}, R^{14}, R^{15} and R^{16} are each separately selected from hydrogen, halo, haloalkyl, formyl, carboxy, sulpho, cyano, nitro, COR^{18} and $^{+}NR^{18}R^{19}R^{20}$, wherein R^{18}, R^{19} and R^{20} are each separately alkyl, aralkyl or aryl groups and R^{17} is selected form hydrogen, halo, haloalkyl, formyl, carboxy, sulpho, cyano, nitro, hydroxy, alkoxy, alkyl, COR^{18}, $NHCOR^{18}$ and $^{+}NR^{18}R^{19}R^{20}$ groups, wherein R^{18}, R^{19} and R^{20} are each separately alkyl aralkyl or aryl groups.

The standard system of numbering is used herein for the indazole ring system as shown below



As regards the groups R^{13}, R^{14}, R^{15} and R^{16}, the halo and haloalkyl groups may for example be a fluoro, bromo, iodo or particularly a chloro group or a C_{1-12}, particularly C_{1-6}, straight or branched chain alkyl group, for example an ethyl or especially a methyl group, substituted by one or more, for example three, such halo groups. Aralkyl and aryl groups R^{18}, R^{19} and R^{20}, may conveniently be or contain various forms of aromatic hydrocarbyl group but 1- or 2-naphthyl and particularly phenyl groups are of most interest. Alkyl and aralkyl group R^{18}, R^{19} and R^{20} may conveniently be or contain alkyl group such as are described above in relation to the haloalkyl groups R^{13}, R^{14}, R^{15}, R^{16}. Particular examples of groups COR^{18} and $^{+}NR^{18}R^{19}R^{20}$ are thus propionyl and especially acetyl, and triethylamino and especially trimethylamino.

As regards the group R^{17}, similar comments apply to halo, haloalkyl, COR^{18} and $^{+}NR^{18}R^{19}R^{20}$ groups as for R^{13}, R^{14}, R^{15} and R^{16} whilst the alkyl groups R^{17} may conveniently be selected similarly to the alkyl portion of the halo alkyl groups R^{13}, R^{14}, R^{15}, R^{16} and R^{17} and the groups R^{18} in $NHCOR^{18}$ may conveniently be selected as for the groups R^{18} in COR^{18} and $^{+}NR^{18}R^{19}R^{20}$, the group $NHCOR^{18}$ being for example propionamido or acetamido.

Although each of the groups R^{13}, R^{14}, R^{15} and R^{16} may be hydrogen it is preferred that at least one is other than hydrogen, particularly the group R^{14} or R^{15} or especially R^{13}, although preferably two or three of R^{13}, R^{14}, R^{15} and R^{16} are hydrogen. As regards the groups which are other than hydrogen, the groups which are preferred are those which effect a significant degree of electron withdrawal from the benzene ring. Accordingly a nitro group is of particular interest. Other groups of interest, possibly together with another type of group such as nitro, are haloalkyl and especially halo groups.

Although groups $^{+}NR^{18}R^{19}R^{20}$, for example trialkylamino groups such as trimethylamino, also possess this ability their charged nature is a disadvantage in terms of entry into the brain across the blood/brain barrier.

It will be appreciated that where more than one of R^{13}, R^{14}, R^{15} and R^{16} is other than hydrogen the two or more substituents may differ from each other. Conveniently however at least one, for example R^{13}, is one of the groups just indicated as being of interest.

Although R^{17} may be other than hydrogen, for example a halo group such as chloro, it is preferably hydrogen.

Moreover, when one or more of R^{13}, R^{14}, R^{15} or R^{16} is a group $^{+}NR^{18}R^{19}R^{20}$ the compounds will be a quaternary ammonium salt which contains one or more physiologically acceptable anions. Such anions may for example correspond to those present in the acid addition salts hereinafter described but halo groups such as chloro and bromo are preferred.

Furthermore, when an acid substituent R^{13}, R^{14}, R^{15}, R^{16} or R^{17} such as carboxy or sulpho is present then the physiologically acceptable salt may be one formed with a suitable base, examples of which are the alkali metal hydroxides, for example sodium hydroxide, quaternary ammonium hydroxides and amines such as tris (tris representing 2-amino-2-hydroxymethyl propane 1,3-diol).

When a carboxy or sulpho substituent is present or when a hydroxy group is present the indazoles (IC) can be used in the form of physiologically acceptable ester. Such esters may be formed respectively with a suitable phenol or alcohol or with a suitable organic acid or even inorganic acid. Of particular interest are esters formed with a C_{1-12}, particularly C_{1-6} alkanol, for example ethyl and especially methyl esters.

Examples of specific indazoles (IC) of use in the present invention are indazole and its 4-, 5-, 6- and 7-nitro derivatives together with their halogeno, for example chloro or bromo, analogues. Of these indazole and the last three mentioned nitro derivatives, especially 7-nitroindazole, are of particular interest.

The compounds of formula (IA) (IB) and (IC) may include a number of asymmetric centres in the molecule depending on the precise meaning of the various groups and formula (IA) (IB) and (IC) are intended to include all possible isomers.

The activity of a compound as a tetrahydrobiopterin-site inhibitor of neuronal NO synthase can be determined by an assay in which L-[^{14}C]-arginine is converted to [U^{14}C]-citrulline by brain cytosol NO synthase (as described by Salter et al., FEBS Lett. 291, 1991, 145-149) following a preincubation with the compound in the absence or presence of a saturating concentration (typically 10μM) of tetrahydrobiopterin). Such inhibitors also show activity in an intact cell system in which conversion of [^{14}C]-L-arginine to [^{14}C]-citrulline is measured in brain slices stimulated with veratrine. In these experiments, single coronal slices of adult rat forebrain are preincubated in Krebs-Henseleit buffer before transfer to fresh buffer containing L-[U-^{14}C]-arginine, 10μg/ml veratrine and various concentrations of test compound (routinely 1- 100μM). The mixture of test compound and coronal slices is then incubated and the level of [U-^{14}C]-citrulline formed, then determined (essentially as described previously, Salter et al. 1991). Selectively for the neuronal NO synthase can be determined by comparison with enzyme assays for other forms of NO synthase or by comparisons with intact cell preparation NO synthesis such as in rat aortic rings in which the basal tone of the tissue is used as an indication of the activity of the constitutive NO synthase.

Alternatively, the activity of the compounds can be determined by the method of Dwyer et al., Biochem. Biophys. Res. Commun. 1991, 176, 1136-1141.

Conditions in which there is an advantage in selectively inhibiting neuronal NO production include cerebral ischemia, CNS trauma, epilepsy, AIDS dementia, chronic neurodegenerative disease (eg Parkinson's disease), schizophrenia and chronic pain, and conditions in which non-adreneric non-cholinergic nerve may be implicated such as priapism, obesity and hyperphagia. They are also suitable for use as analgesics and in the treatment of acute neurodegenerative diseases, for example in the treatment of convulsions or particularly for prophylactic use in the prevention of an ischemic incident and possibly also in memory enhancement.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

The present invention includes neuronal NO inhibitors in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric, citric, tartaric, phosphoric, phosphonic, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Salts of neuronal NO inhibitors can be made by reacting the appropriate compound in the form of the free base with the appropriate acid. Esters are pharmaceutically acceptable esters, for example C_{1-4} alkyl esters.

A further aspect of the present invention provides a compound of formula (IA), (IB) or (IC) or a salt thereof for use in medicine, with the proviso that R^{12} is not hydrogen, and that R^{14} and R^{15} are not independently selected from hydrogen, nitro or carboxy when R^{13}, R^{16} and R^{17} are each hydrogen.

Many compounds of formula (IA), (IB) or (IC) or salts thereof are novel, and accordingly the invention also provides:

(i) novel compounds of formula (IA) and salts thereof. Such compounds include:

2,4-diamino-5-(3-trifluoromethylphenyl)pyrimidine
2,-4-diamino-5-(3-bromophenyl)pyrimidine
2,4-diamino-5-(3-methylphenyl)pyrimidine
2,4-diamino-5-(3,4-methylenedioxyphenyl)pyrimidine

2,4-diamino-5-(3,4-ethylenendioxyphenyl)pyrimidine
2,4-diamino-6-(4-methoxyphenyl)pyrimidine
2,4-diamino-6-(3,4-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2-(4-methylphenyl)ethyl)pyrimidine
2,4-diamino-5-(4-methylphenylethynyl)pyrimidine
2,4-diamino-5-phenylethynylpyrimidine
2,6-diamino-3-(2,4,5-trichlorophenyl)pyridine
2,6-diamino-3-(4-methoxyphenyl)pyridine
2,6-diamino-3-(2-naphthyl)pyridine
2,6-bis(acetamido)-3-(3,4-dimethoxyphenyl)pyridine
2,6-diamino-3-(3,4-dimethoxyphenyl)pyridine
1-amino-2, 4-diaza-5, 6-dihydro-9-methoxy-3-(4-methyl-1-piperazinyl)phenanthrene
4-amino-9, 10-dihydro-7-methoxy-2-(4-methyl-1-piperazinyl)benzo[f]quinazoline
2-amino-5-((-naphthyl)pyrimidine
2-amino-5-(4-methoxyphenyl)pyrimidine
2-(4-methylpiperazinyl)-5-(2-naphthyl)pyrimidine
5-(3,4-dimethoxy)-2-(4-methyl-1-piperazinyl)pyrimidine
5-(1,3-benzo[d]dioxol-5-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(1,4-benzodioxan-6-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(3,4-dichlorophenyl)-2-(4-methylpiperazinyl)pyrimidine
2,4-diamino-5-(3-thienyl)pyrimidine
2,4-diamino-5-(3,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-biphenylpyrimidine
2,4-diamino-5-(3,5-bis(trifluoromethyl)phenyl)pyrimidine
2,4-diamino-5-(3,5-dichlorophenyl)pyrimidine
2,4-diamino-5-(2,5-dibromo-4-chlorophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-methanesulphonamidophenyl)pyrimidine
2,4-diamino-5-(4-methoxy-3-methylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethoxyphenyl)pyrimidine
2,4-diamino-5-(3-amino-4-chlorophenyl)pyrimidine
2,4-diamino-5-(3-aminophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-nitrophenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-hydroxyphenyl)pyrimidine
2,4-diamino-5-(3-fluorophenyl)pyrimidine
2,4-diamino-5-(3-trifluoromethoxyphenyl)pyrimidine

2,4-diamino-5-(3-bromo-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-fluoro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-fluorophenyl)pyrimidine
2,4-diamino-5-(4-chlorophenyl)pyrimidine

(ii) compounds of formula (IB) and salts thereof with the proviso that R^{12} is not hydrogen; and

(iii) novel compounds of formula (IC) and salts thereof.

Whilst it may be possible for the neuronal NO synthase inhibitors of the present invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a compound which binds at the tetrahydrobiopterin site of NO Synthase in combination with a pharmaceutically acceptable carrier therefor and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (IA), (IB) or (IC) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration my be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.
Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The neuronal NO synthase inhibitors of the invention may be administered orally or via injection at a dose of from 0.1 to 500mg/kg per day. The dose range for adult humans is generally from 5mg to 35g/day and preferably 5mg to 2g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 200mg.

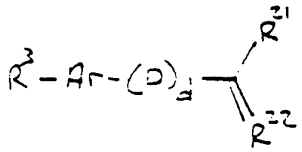
The neuronal NO synthase inhibitors of the invention are preferably administered orally or by injection (intramuscular, intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also the route of administration may vary depending on the condition and its severity.

The present invention also provides a process for the preparation of the novel compounds of formula (IA), (IB) and (IC) as hereinbefore defined

Compounds of the present invention are commercially available or may be made by analogous methods to those known in the art. More specifically:

(a) Compounds of formula (IA) may be prepared

(i) when X is nitrogen, by the cyclisation of a compound of the formula (IV)



(IV)

wherein R^{21} is cyano or COR^{23} wherein R^{23} is hydroxy, C_{1-4} alkoxy or hydrogen and R^{22} is oxo or a group $C<^{L}_{H}$ wherein L is a leaving group; with amino guanidine or guanidine respectively. Suitable leaving groups include alkoxy and substituted secondary amino groups, eg. aniline and substituted aniline groups and heterocyclic amines such as morpholine.

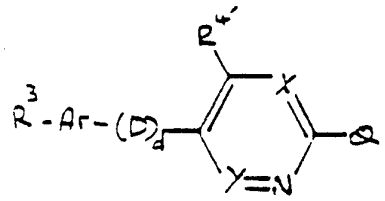
The reaction conveniently takes place in a polar solvent, for example an alkanol, e.g. a C_{1-4} alkanol such as ethanol, or a dipolar aprotic solvent such as

dimethylsulphoxide at a non-extreme temperature, e.g. 20° to 150°C and conveniently 25° to 90°C, with the guanidine or aminoguanidine present in the form of a salt. The free guanidine or aminoguanidine can then conveniently be liberated in-situ by the presence of base, for example an alkoxide such as sodium methoxide. When the guanidine or aminoguanidine is in the form of its carbonate/bicarbonate, base is not required.

These reactions are analagous to those described in UK patent 1261455, UK patent 002121 and European patent application EP 0372934 for the preparation of benzyl pyrimidines, trizines and phenyl pyrimidines respectively

(ii) when R^1 and R^2 are hydrogen the removal of one or more protecting groups from NR^1R^2 and optionally from R^4, when it is desired that R^4 is NH_2. Suitable protecting groups are derived from carboxylic acids, for example acetic or benzoic acids.

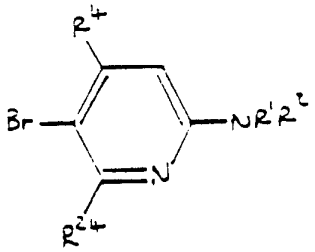
(iii) by the conversion of one compound of the formula (IA) to a further compound of the formula (IA), for example when R^1 and/or R^2 are C_{1-4} alkyl the alkylation of the corresponding compound wherein R^1 and/or R^2 are hydrogen; or when R^1 and R^2 are hydrogen, the amination, or chlorination and subsequent amination, of a compound of the formula (V):



(V)

wherein Q is chloro or bromo, preferably chloro, or hydroxy respectively and $R^{4'}$ is hydrogen, methyl, hydroxy, trifluoromethyl or halo. Suitable chlorinating agents include phosphorous oxychloride which can also be used as solvent. The amination is conveniently carried out by reaction with ammonia in a suitable solvent such as a C_{1-4} alkanol, e.g. ethanol. The reaction is suitably carried out at an elevated temperature, for example 50-200°C, in a sealed system, and preferably under pressure.

(iv) when X is CH and Y is a group CH or CNH_2 the reaction of a compound of the formula (VI):



(VI)

or a suitably protected derivative thereof, wherein R^{24} is hydrogen or NH_2 with benzene boronic acid or benzene boronic acid substituted so as to give the desired substituent R^{11} in the compound of the formula (IA) so formed, followed by the removal of any protecting groups.

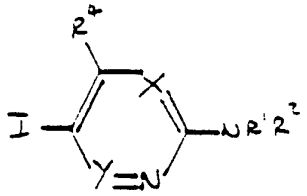
This reaction is conveniently carried out in the presence of a catalyst, for example a palladium catalyst. We have found that tetrakistriphenylphosphine palladium is a suitable catalyst for this reaction. The reaction is conveniently carried out at a non-extreme temperature, for example 20° to 100°C and preferably 50° to 90°C in a solvent, for example a mixture of an aromatic hydrocarbon such as benzene and an alkanol such as ethanol under an inert atmosphere. Acyl groups, for example acetyl groups, are suitable protecting groups when R^{1b} and/or R^{2b} are hydrogen.

(b) Compounds of the formula (IB) may be prepared by the reduction of the corresponding 8-oxide. This is conveniently accomplished by hydrogenation in the presence of a suitable catalyst. The catalyst will normally be a transition metal catalyst, for example containing palladium or platinum, and will be chosen so that it reduces the 8-N-oxide function without affecting any of the other groups in the molecule, unless it is desired to also reduce these. We have found that palladium (as a 5% of a mixture with barium sulphate) is a suitable selective catalyst. The reaction is conveniently carried out in a solvent, for example a glacial acetic acid/trifluoroacetic acid mixture, at a non-extreme temperature, for example between 0° and 80°C and suitably at room temperature.

(c) Compounds of formula (IC) can be prepared using various routes to indazoles described in the literature, for example the process of U.S. Patent 3, 988, 347 which involves reaction of o-methylacetanilide containing the appropriate substituents R^{13}, R^{14}, R^{15} and R^{16} or substitutents convertible thereto. Indazoles (IC) having a substituent at the 3-position, i.e. containing a group R^{17} other than hydrogen may be prepared by other procedures described in the art of indazole chemistry or by modification of those procedures.

The compounds may be prepared directly in salt form or converted thereto by reaction of the indazole with the appropriate acid or base. Esters may similarly be prepared directly or through acid or base. Esters may similarly be prepared directly or through reaction of the corresponding indazole containing a carboxy or sulpho group with the appropriate alcohol or of the corresponding indazole containing a hydroxy group with the appropriate acid.

The present invention also provides a novel process for the preparation of a compound of formula (IA) as hereinbefore defined, which comprises the reaction of a compound of formula (VII).



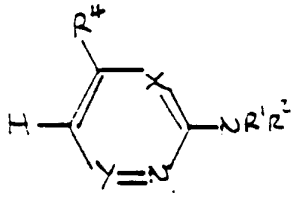
(VII)

or a suitably protected derivative thereof with a compound of formula R^3-Ar-$(D)_d$-$B(OH)_2$ wherein R^1, R^2, R^3, R^4, Ar, D, d, X and Y are as hereinbefore defined, followed by deprotection if necessary.

Preferably d is 0 and/or Ar is phenyl.

The reaction is conveniently carried out in a polar solvent, for example toluene, in the presence of aqueous sodium carbonate and tetrakistriphenylphosphine palladium, under an inert atmosphere, for example nitrogen. The reaction is preferably carried out at a non-extreme temperature of 20°C to 150°C, suitably 80°C to 120°C.

Compounds of formula (VII) may be prepared from a compound of formula (VIII)



(VIII)

or a suitably protected derivative thereof wherein R^1, R^2, R^4, X and Y are as hereinbefore defined, by reaction with iodine monochloride. The reaction is carried out in a suitable solvent, such as glacial acetic acid, at non-extreme temperature for example room temperature.

The present invention will now be described by way of example only, and is not intended to be limiting thereof.

Example 1

Preparation of 5-(Benzo-[B]-thien-3-yl)-2,4-diaminopyrimidine

(a) 2-(Benzo-[B]-thien-3-yl)-3-methoxyacrylonitrile

To a solution of sodium ethoxide (from 1.1gms of Na) in ethanol (60ml) at room temperature was added benzo-[B]-thien-3-yl acetonitrile (7.79gms, Maybridge Chemicals Ltd) in a single portion. Stirring was continued for 15 minutes, ethylformate (6.66gms) added, and the mixture left to stir overnight at room temperature. The suspension was then refluxed for 3 hours during which time the solid completely dissolved. After cooling, the solvent was removed in vacuo and the residue triturated with diethyl ether. The solid was filtered off and dried in vacuo to leave the crude product as a tan coloured solid (6.93gms).

The above product was divided into three equal portions. These were placed in separate Young tubes, methyl iodide (1.8gms) and DMF/18mls) added to each, and the tubes sealed. After stirring at 50 ^{0}C for 4 hours the contents were cooled, combined, and the solvent removed in vacuo. The residue was then partitioned between ethyl acetate and water, and the organic phase again washed with water before drying over $MgSO_4$. After treating with activated charcoal, the solvent was evaporated to leave the desired product as a pale yellow waxy solid. (4.8 gms, 50% yield)

(b) 5-(Benzo-[B]-thien-3-yl)-2,4-diaminopyrimidine

To a solution of sodium ethoxide (from 1.03gms of Na) in ethanol (40ml) at room temperature was added guanidine HCl (4.26gms). After stirring for a further 5 minutes, the above intermediate was added in ethanol (40ml) and the resulting suspension refluxed for 5 hours. After cooling, the solvent was removed in vacuo and the residue partitioned between chloroform and water. After washing the organic phase with water and drying over $MgSO_4$, the solvent was removed in vacuo. The crude product was then purified by column chromatography (SiO_2)

eluting with $CHCl_3$ to 4% MeOH-$CHCl_3$. Recrystallization from ethanol gave the product as a white crystalline solid. (2.7gms. 50% yield, mp 193-4 °C)

The following compounds were made by an analogous method:

2,4-diamino-5-(4-methoxy-3-methylphenyl)pyrimidine; mpt = 229-230°C
2,4-diamino-5-(4-trifluoromethylphenyl)pyrimidine; mpt = 218-219°C
2,4-diamino-5-(4-trifluoromethoxyphenyl)pyrimidine; mpt = 174-175°C
2,4-diamino-5-(3-fluorophenyl)pyrimidine; mpt = 215-217°C
2,4-diamino-5-(3-trifluoromethoxyphenyl)pyrimidine; mpt = 197.7-199.6°C
2,4-diamino-5-(3-bromo-4-methoxyphenyl)pyrimidine; mpt = 269.3-271.8°C
2,4-diamino-5-(3-fluoro-4-methoxyphenyl)pyrimidine; mpt = 243-245°C
2,4-diamino-5-(3-chloro-4-methoxyphenyl)pyrimidine; mpt = 337-339°C
2,4-diamino-5-(3-chloro-4-fluorophenyl)pyrimidine; mpt = 233-235°C
2,4-diamino-5-(3-methylphenyl)pyrimidine; mpt = 167-169°C
2,4-diamino-5-(3-bromophenyl)pyrimdine; mpt = 215.7-218.5°C
2,4-diamino-5-(3-trifluoromethylphenyl)pyrimidine; mpt = 260-261°C
2,4-diamino-5-(3-bromo-4-chloro)pyrimidine; mpt = 221-222°C
2,4-diamino-5-(3-chloro-4-methyl)pyrimidine; mpt = 281-282°C

Example 2

Preparation of 2,6-Diamino-3-(3,5-dichlorophenyl)pyridine

(a) 2,6-Diacetamido-3-(3,5-dichlorophenyl)pyridine

To a mixture of 3-bromo-2,6-diacetamidopyridine (2.00g, Alfred Bader Library of Rare Chemicals; Div. of Aldrich Chemical Company, INC.) in benzene (15ml), 2M aqueous sodium carbonate (7.36ml) and tetrakistriphenylphosphine palladium (0.25g), a solution of 3,5-dichlorobenzene boronic acid (1.52g) in absolute ethanol (3ml) was slowly added. The yellow biphasic reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was partitioned between water and chloroform. The chloroform layer was washed once with saturated sodium bicarbonate, twice with water and dried over anhydrous magnesium sulphate. The solvent was removed under vacuo and the crude product was purified by column chromatography (SiO_2) eluting with chloroform to 2% methanol-chloroform. The

product was triturated with ether, filtered and dried under vacuo at 60°C to give a white solid. (0.738g, mp 200-204°C.)

(b) 2,6-Diamino-3-(3,5-dichlorophenyl)pyridine

2,6-Diacetamido-3-(3,5-dichlorophenyl)pyridine was suspended in dilute hydrochloric acid (0.40ml, 12M HCl/1ml H_2O) and refluxed at 120°C for 1.50 hours. The reaction mixture was cooled in an ice-bath and basified with 0.880 ammonia. The white solid which precipitated was filtered, washed with water and dried under vacuo at room temperature. The crude product was purified by column chromatography [SiO_2] eluting with ether. The product was triturated with petroleum ether, filtered and dried under vacuo at 70°C to give a cream solid. (0.107g, mp 114-116°C.)

Example 3

Preparation of 2, 4-diamino-5-(4-phenoxyphenyl)pyrimidine

(a) 2,4-diamino-5-iodopyrimidine

A soloution of iodine monochloride (16.24g, 0.1mol) in glacial acetic acid (5ml.) was added dropwise with stirring during 30 minutes to a mixture of 2,4-diaminopyrimidine (11g. 0.1mol) and glacial acetic acid (150ml). The mixture became homogeneous towards the end of the addition and then the product hydrochloride began to separate. The thick slurry was vigorously stirred for 4 hours then filtered. The filter cake was sucked as dry as possible then dissolved in hot water (400ml). Solid sodium sulphite was added in small portions until the iodine colour was completely discharged. The solution was filtered and the filtrate was basified with 10N.NaOH. Cooling in the refrigerator overnight gave the product as a cream cystalline solid (18.9g. 80% yield, m.p. 229-230).

(b) 2,4-diamino-5-(4-phenoxyphenyl)pyrimidine

A mixture of 2,4-diamino-5-iodopyrimidine (1.18g. 5mmol), 4-phenoxy-benzeneboronic acid (1.28g. 6mmol), toluene (40 ml), 2M aqueous sodium carbonate (10ml. 20mmol) and tetrakistriphenylphosphine palladium (400 mg. 0.35 mmol) was stirred and heated at 110°C under nitrogen for 6 hours. The reaction

mixture was evaporated to dryness in vacuo and the residue was washed with warm water and taken up in dichloromethane. The organic extract was dried ($MgSO_4$) and evaporated to drynes in vacuo. The residue was purified by flash column chromatography (SiO_2). Elution with CH_2Cl_2 to 5% EtOH-CH_2Cl_2 gave a solid which after recrystallisation form EtOH afforded the product as a cream crystalline solid (860mg 62% yield, m.p. 149).

The following compounds were prepared by an analgous method:

2,4-diamino-6-(4-methoxyphenyl)pyrimidine; mpt. 220-222°C
2,4-diamino-6-[3,4-dimethoxyphenyl]pyrimidine; mpt 202-204°C
2.4-diamino-5-[2-(4-methylphenyl)ethyl]pyrimidine; mpt 187°C
2,4-diamino-5-(4-methylphenylethynyl)pyrimidine; mpt 197-199°C
2,4-diamino-5-phenylethynylpyrimidine; mpt 190°C
2,6-diamino-3-(2,4,5-trichlorophenyl)pyridine; mpt 173-175° C
2,6-diamino-3-(4-methoxyphenyl)pyridine; mpt 131°
2,6-diamino-3-(2-naphthyl)pyridine; mpt 193-194°C
2,6-Bis(acetamido)-3-(3,4-dimethoxyphenyl)pyridine; mpt 231-233°C
2,6-diamino-3-(3,4-dimethoxyphenyl)pyridine; mpt 190° C
2,4-diamino-5-[3,4-ethylenedioxyphenyl]pyrimidine; mpt 222-224°C
2,4-diamino-5-[3,4-methylenedioxyphenyl]pyrimidine; mpt 225-227°C
2-amino-5-(1-naphthyl)pyrimidine; mpt 155°C
2-amino-5-(4-methoxyphenyl)pyrimidine; mpt 183-184°C
2,4-diamino-5-(3-thienyl)pyrimidine; mpt 171-172°C
2,4-diamino-5-(3,5-dimethoxyphenyl)pyrimidine;
2,4-diamino-5-(2,5-dimethoxyphenyl)pyrimidine; mpt 157°C
2,4-diamino-5-biphenylpyrimidine; mpt 204-206°C
2,4-diamino-5-[3,5-bis(trifluoromethyl)phenyl]pyrimidine; mpt 201-203°C
2,4-diamino-5-(3,5-dichlorophenyl)pyrimidine; mpt 289-292°C

Example 4

The following compounds were made by conversion of a compound of formula (IA) according to the reaction scheme shown in Fig. 1.

(1) 2,4-diamino-5-(3-chloro-4-hydroxyphenyl)pyrimidine; mpt = 165-167°C
(2) 2,4-diamino-5-(4-chloro-3-nitrophenyl)pyrimidine; mpt = 245-246°C

(3) 2,4-diamino-5-(3-aminophenyl)pyrimidine; mpt = 156-157°C

(4) 2,4-diamino-5-(3-amino-4-chlorophenyl)pyrimidine; mpt = 189-190°C

(5) 2,4-diamino-5-(2,5-dibromo-4-chlorophenyl)pyrimidine; mpt = 245-248°C

(6) 2,4-diamino-5-(4-chloro-3-methanesulphonamidophenyl)pyrimidine; mpt = 234-235°C

(7) 2,4-diamino-5-(4-chloro-3-cyanophenyl)pyrimidine; mpt > 300°C

Example 5

Preparation of (+-)-2-Amino-6-[[(4-chlorophenethyl)oxy]methyl]-5,6,7,8-tetrahy-dro-4(3H)-pteridinone

a) 2-Amino-6-[[(4-chlorophenethyl)oxy]methyl]-4(3H)-pteridinone 8-oxide

The title compound was prepared from 3-amino-6-chloromethyl-2-pyrazinecarbonitrile 4-oxide and 4-chlorophenethanol by the method of Bigham et al, J.Med.Chem. 1987, 30, 40-45.

b) (+-)-2-Amino-6-[[(4-chlorophenethyl)oxy]methyl]-5,6,7,8-tetrahydro-4(3H)-pteridinone

A mixture of 2-amino-6-[[(4-chlorophenethyl)oxy]methyl]-4(3H)-pteridinone 8-oxide monohydrate (0.600g), 5%Pd/$BaSO_4$ (0.200-0.300g), glacial acetic acid (40ml), and trifluoroacetic acid (20ml) was hydrogenated a total of three times for a total of 1h 23min. The total uptake of hydrogen was 111 ml. 6N HCl (10ml) was added. After 3h, the mixture was filtered, and the yellow filtrate was evaporated to dryness. The crude product was dissolved almost completely in hot 6N HCl (100ml), and the solution was treated with charcoal, filtered, and cooled. The resulting mixture was concentrated under vacuum to a solid that was dissolved in hot 6N HCl (70ml). The solution was allowed to cool, and the crystallized white solid was filtered, washed with 6N HCl (2x10 ml), and dried under vacuum at 50°C; yield 0.474g = mp 232-237°C (dec); IR(KBr) 1663 (CO) overlapping less intense 1700 cm^{-1}; NMR(Me_2SO-δ_6) d 2.81(t,2H,CH_2 Cl); 3.1-3.2(m,1H,C-6H); 3.3-3.5(br d,2H,c-7 H_2); 3.5-3.8(m, 4H, CH_2OCH_2); 5.6(br); 6.78(br s, 2H, NH_2); 7.24-7.35 (AA'XX', 4H, ArH); 7.42 (br s, 1H, NH); 1 10.0 (very br); 10.75 (br s, 1H, NH); UV(0.1N HCl) λ max 265.5 nm (e 13800); Anal.$C_{15}H_{18}ClN_5O_2$;2HCl.H_2O (C,H,N,Cl).

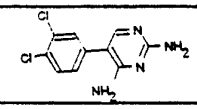
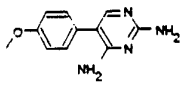
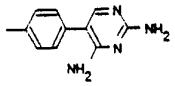
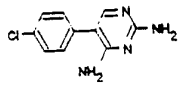
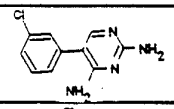
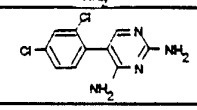
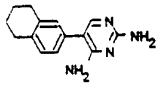
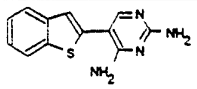
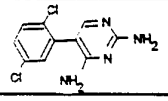
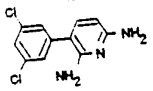
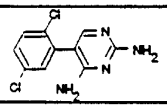
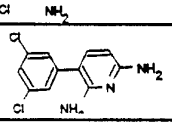
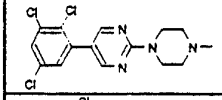
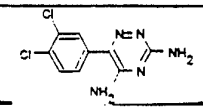
Example 6

Biological Activity of Compounds of the Present Invention

The activity of a compound as a tetrahydrobiopterin-site inhibitor of neuronal NO synthase was determined by an assay in which L-[U^{14}C]-arginine is converted to [U^{14}C]-citrulline by brain cytosol NO synthase (as described by Salter M. Knowles, R.G. and Moncada, S. (1991) FEBS Lett. 291, 145-149. following a 5 min preincubation with the compound in the absence or presence of a saturating concentration (typically 10μM) of tetrahydrobiopterin). Compounds were initially tested at a concentration of 10μM and the inhibition expressed as % control value at this concentration (see Table 1, column 2). Subsequent determinations of the effects of 0.01-30 μM compound permitted estimation of the maximum inhibition attainable under these conditions (see Table 1, column 3); maximal inhibition close to 100% could be achieved following longer incubation with the compounds. Such inhibitors also show activity in an intact cell system in which conversion of [^{14}C]-L-arginine to [^{14}C]-citrulline is measured in brain slices stimulated with veratrine.

TABLE 1

Pterin-site Inhibitors of Neuronal NO Synthase

Structure	Inhib^{n} at 10μM (%)	IC_{50} (μM)	Max. Inhib^{n} (%)
	75	0.09 ± 0.03(3)	80
	70	0.09	70
	70	0.22	70
	55	0.25	70
	67	0.26	70
	52	0.4	60
	68	0.5	70
	68	0.7	70
	73	0.8	70
	65	0.8	70
	61	1.0	80
	98	1.2	100
	71	5.0	100
	53	-	-

Example 7:

In vitro tests of 7-nitroindazole activity

Nitric oxide synthase (NOS) activity was determined in vitro by the method of Dwyer et al., Biochem. Biophys. Res. Commun. 1991, 176, 1136-1141. Mice (male, LACA, 28-32 g) were killed by cervical dislocation. Cerebella were removed, homogenized (1:10 w/v in 20mM tris buffer containing 2mM EDTA, pH. 7.4) and aliquots (25µl) incubated (37°C) with L-arginine (120nM) containing 0.5 µCi [^{3}H]-arginine (specific activity 62 Ci mmol^{-1}), NADPH (0.5mM) and $CaCl_2$ (0.75mM). Incubations also contained (a) 7-nitroindazole (MIM Research Chemicals Ltd.) in 0.5% w/v sodium carbonate solution (dissolution was effected by heating to 80°C and cooling when the 7-nitroindazole remained in solution), (b) for comparative puposes, L-N^G-nitoarginine methyl ester (L-NAME) or L-N^G-monomethyl arginine (L-NMMA) in distilled water, or, (c) as control, an equal volume (5µl) of 0.5% (w/v) sodium carbonate or distilled water. Final incubation volume was 105 µl. After 15 minutes the reaction was stopped by addition of 3 ml HEPES buffer (20mM containing 2 mM EDTA, pH 5.5. and [^{3}H]-citrulline produced was separated by cation exchange chromatography on 0.5 ml columns of Dowex AG50-W8 Na^+ form. [^{3}H]-Citrulline was quantitated by liquid scintillation spectroscopy of duplicate 1 ml aliquots of the flow-through.

In some experiments mice were injected i.p. with 7-nitroindazole (25 mg kg^{-1}) or L-NAME (50mg kg^{-1}) and killed 15 minutes thereafter. Cerebella were removed, homogenized and NOS activity determined as described above.

It was found the 7-nitroindazole potently inhibited mouse cerebellar NOS in vitro (IC_{50} 0.47 ± 0.01µM). For comparison, it was 1.8 times more potent than L-NAME (IC_{50} 0.87 ± 0.02µM) and 5 times more potent than L-NMMA (IC_{50} 2.37 ± 0.03µM), the detailed results being presented in Figure 2. The results shown give the mean ± s.e. mean, n = 6 (statistical anlaysis carried out by Student's unpaired t test). Where no error bar is indicated the error lies within the dimensions of the symbol. In separate experiments, administration of 7-nitroindazole (25 mg kg^{-1}, i.p.) decreased mouse cerebella NOS activity measured 15 minutes thereafter by over 55% (3.9 ± 0.06 nmol citrulline mg^{-1} protein 15 min^{-1}, cf. 9.1 ± 0.26 arachis oil-injected controls, n = 6, $P<0.01$). For comparison, a higher dose of L-NAME (50 mg kg^{-1}) produced only 46.2 ± 1.6% inhibition of this enzyme under indentical

condition (4.46 ± 0.012 pmol citrulline mg^{-1} protein 15 min^{-1}, cf. 8.33 ± 0.15, saline-injected controls, n = 6, P<0.01).

Example 8:

In vivo tests of 7-nitroindazole activity

Anti-nociceptive activity of 7-nitroindazole (10-50 mg kg^{-1}) administered i.p. to mice as a suspension in arachis oil produced by sonication was determined by the formalin-induced hindpaw licking assay as descrived by Moore et al., British Journal of Pharmacology, 1991, 102, 198-202. Control animals received 10ml kg^{-1} of arachis oil or saline (0.9% w/v NaCl). This test shows hindpaw licking time (seconds) in the early (0-5 minutes) and late (15-30 minutes) phases on injection of 10µl formalin (5% v/v) administered 15 minutes after the 7-nitroindazole.

In separate experiments, again described by Moore et al. (ibid), the blood pressure of urethane-anaesthetized (10 g kg^{-1}) mice was monitored for 45 minutes after i.p. administration of 7-nitroindazole.

7-Nitroindazole (10, 25 and 50 mg kg^{-1}) produced a dose-related inhibition of late phase formalin-induced hindpaw licking without influencing the early phase response. The detailed results are presented in Figure 3 where open columns indicate the early phase (0.5 minutes) and hatched columns the late phase (15-30 minutes) hindpaw licking times. The mean ± s.e. mean is shown (statistical analysis by Student's unpaired t test), n = 6-12, **P<0.01. The control animals, identified by C, are those which received 10 ml kg^{-1} arachis oil which, alone, did not influence hindpaw licking time. (The saline-injected mice gave an early phase value of 89.8 ± 7.0 seconds and a late phase value of 150.7 ± 11.5 seconds, n =15). The ED_{50} for the anti-nociceptive effect was 26 mg kg^{-1} (equivalent to 159.5 µmol kg^{-1}).

Administration of 7-nitroindazole (25 and 80 mg kg^{-1}) did not increase mean arterial pressure (MAP) over the 45 minute experimental period (e.g. 25 mg kg^{-1}, 47.4 ± 5.1 mmHg, cf. 51.6 ± 4.4 mmHg, n = 4, before 7-nitroindazole administration, 80 mg kg^{-1}, 43.9 ± 5.3 mmHg, cf. 49.5 ± 2.9 mmHg, n = 4, before 7-nitroindazole administration). In control experiments, i.p. administration of arachis oil failed to alter MAP.

Example 9:

In vitro and in vivo tests of other indazoles

The procedure of Example 7 was repeated for 7-nitroindazole and other indazoles but using rat cerebella. The IC_{50} values so obtained for inhibition of rat cerebella nitric oxide synthase (NOS) for various indazoles are shown in Table 2 below.

The procedure of Example 8 was repeated for 7-nitroindazole and other indazoles. The percentage inhibition of formalin-induced licking in the late phase following the administration of 50 mg kg^{-1} i.p. of the indazoles is shown in Table 2 below. For the compound 5-nitroindazole, where an asterisk is shown, a pronounced sedative effect was produced which interfered with the determination of the anti-nociceptive effect so that it could not be quantitated. The other indazoles did not exhibit an overtly sedative effect.

Table 2

Compound	**IC_{50} NOS μM**	**Inhibition of licking (%)**
indazole	232	83.2 ± 12.2
5-nitroindazole	56	*
6-nitroindazole	32	67.0 ± 12.0
7-nitroindazole	1	100
3-chloroindazole	100	not tested
3-chloro-5-nitroindazole	177	not tested
3-bromo-7-nitroindazole	0.17	not tested
2,7-dinitroindazole	0.62	not tested

Example 10:
Formulation of medicaments

(A) Tablets of the following composition are prepared:

	mg/tablet
7-nitroindazole (micronised)	250
'Avicel' (microcrystalline cellulose)	38
polyvinylpyrrolidone	3

alginic acid	6
magnesium stearate	3

The 7-nitroindazole is mixed with 'Avicel' and polyvinylpyrrolidone is added, dissolved in sufficient industrial methylated spirits (74° OP) to produce a mass suitable for granulating. The mass is granulated through a 20 mesh sieve and the resultant granules are dried at a temperature not exceeding 50°C. The dried granules are passed through a 20 mesh sieve and the alginic acid and magnesium stearate are then added and mixed with the granules. The produce is compressed into tablets each weighing 300 mg on 3/8 inch flat bevelled edge divided punches.

(B) Tablets of the following composition are prepared:

	mg/tablet
7-nitroindazole (micronised)	250
lactose (300 mesh)	134
maize starch	4
gelatine	8
magnesium stearate	4

The tablets are prepared by essentially the same procedure as described in (A) and are compressed at a tablet weight of 400mg on 7/16 inch falt bevelled punches.

(C) Tablets of the following composition are prepared:

	mg/tablet
7-nitroindazole (micronised)	250
lactose (300 mesh)	19
maize starch	15
gelatine	10
magnesium stearate	6

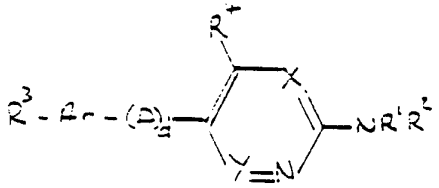
The 7-nitroindazole is mixed with lactose and half the total quantity of maize starch required. and a 5% solution of gelatine in water is added to the mass. The product is granulated through a 16 mesh sieve. and the resultant granules are dried to constant weight

at a temperature not exceeding 50°C. The dried granules are passed through a 20 mesh sieve and mixed with magnesium stearate and the remainder of the maize starch. The product is compressed at a 300 mg tablet weight on 3/8 inch flat bevelled edge divided punches.

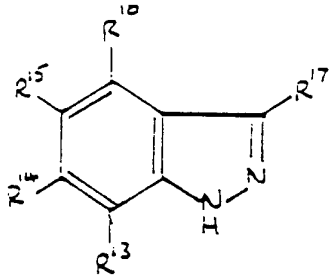
CLAIMS

1. Use of a compound which binds at the tetrahydrobiopterin site of NO synthase for the manufacture of a medicament for the treatment of a condition where there is an advantage in inhibiting neuronal NO synthase with little or no inhibition of endothelial NO synthase.

2. Use of a compound according to Claim 1, wherein the compound is one of formula (IA), formula (IC) or a structural analogue of tetrahydrobiopterin or salts thereof



(IA)

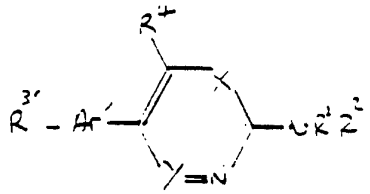


(IC)

Wherein R^1 and R^2 are the same or different and each is hydrogen or a C_{1-4} alkyl group or NR^1R^2 forms a 5- or 6-membered heterocyclic group $-N\langle^{(CH_2)_v}_{(CH_2)_w}\rangle T$ wherein T is oxygen, CH_2 or nitrogen substituted by hydrogen or C_{1-4} alkyl, and v and w are the same or different and each is 1 or 2 provided the sum of v and w is 3 or 4; X is nitrogen or CH; Y is nitrogen, CH or CNH_2; D is a group $S(O)_x$ wherein x is 0, 1 or 2, a C_{1-4} alkylene chain, or a C_{2-4} alkenylene or alkynylene chain; d is 0 or 1; Ar is a monocyclic or bicyclic ring system which may contain one or two heteroatoms and which contains at least one aromatic ring; R^3 represents hydrogen or one to three substituents on the ring system Ar which may be the same or different and are chosen from halo, NR^5R^6 wherein R^5 and R^6 are independently selected from hydrogen or $S(O)_{x'}$ R^7 wherein x' is 0, 1 or 2 and R^7 is C_{1-4} alkyl; nitro, cyano, a C_{1-4} carboxcylic acid group or an ester thereof, C_{1-4} alkyl optionally substituted by one to three halo atoms; phenyl or a group $-(A)_mR^8$ wherein A represents oxygen, $S(O)_n$ wherein n is 0, 1 or 2, or NR^9 wherein R^9 is hydrogen or C_{1-4} alkyl optionally substituted by halo and m is 0 or 1, and R^8 is hydrogen, or C_{1-4} alkyl or phenyl each optionally substituted by one to three halo

atoms; R^4 is hydrogen, C_{1-4} alkyl, hydroxy, halo, trifluoromethyl or a group $NR^{10}R^{11}$ wherein R^{10} and R^{11} are the same or different and each is hydrogen or C_{1-4} alkyl, or $NR^{10}R^{11}$ forms a 5- or 6- membered heterocyclic group optionally substituted by a C_{1-4} alkyl group or R^4 represents a C_{1-2} alkylene group linking the heterocyclic ring to Ar; R^{13}, R^{14}, R^{15} and R^{16} are each separately selected from hydrogen, halo, haloalkyl, formyl, carboxy, sulpho, cyano, nitro, COR^{18} and $^+NR^{18}R^{19}R^{20}$, wherein R^{18}, R^{19} and R^{20} are each separately alkyl, aralkyl or aryl groups and R^{17} is selected form hydrogen, halo, haloalkyl, formyl, carboxy, sulpho, cyano, nitro, hydroxy, alkoxy, alkyl, COR^{18}, $NHCOR^{18}$ and $^+NR^{18}R^{19}R^{20}$ groups, wherein R^{18}, R^{19} and R^{20} are each separately alkyl aralkyl or aryl groups.

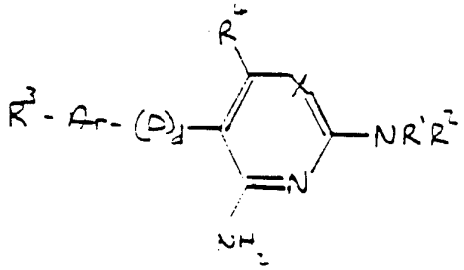
3) Use of a compound of formula (IA) according to Claim 2, which is a compound of formula (II)



(II)

or a salt thereof, wherein R^1,R^2,X,Y,R^4 are as hereinbefore defined, Ar' is a monocyclic or bicyclic ring system containing at least one aromatic ring, and $R^{3'}$ represents hydrogen or one to three substituents which may be the same or different and are chosen from halo, amino, nitro, cyano, a C_{1-4} carboxylic acid group or an ester thereof, a group $-(A)_mR^{8'}$ wherein A and m are as hereinbefore defined and $R^{8'}$ is C_{1-4} alkyl optionally substituted by halo.

4) Use of a compound of formula (IA) according to Claim 2, which is a compound of formula (III)



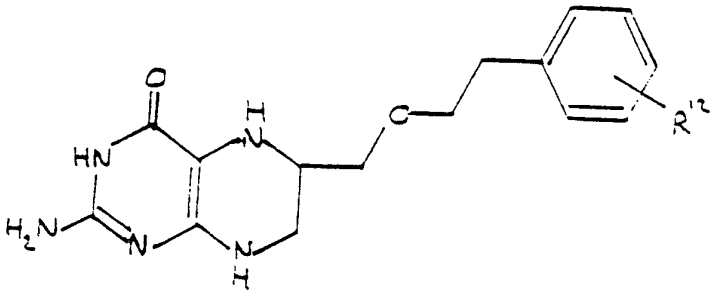
(III)

or a salt thereof wherein D, d, Ar, R^3, R^1, R^2, X and R^4 are as hereinbefore defined.

5. Use of a compound according to Claim 4, wherein the compound is selected from

2, 4-diamino-5-(3, 4-dichlorophenyl)pyrimidine
2, 4-diamino-5-(4-methoxyphenyl)pyrimidine
2, 4-diamino-5-(4-methylphenyl)pyrimidine
2, 4-diamino-5-(4-chlorophenyl)pyrimidine
2, 4-diamino-5-(3-chlorophenyl)pyrimidine
2, 4-diamino-5-(2, 4-dichlorophenyl)pyrimidine
2,4-diamino-5-(3-trifluoromethylphenyl)pyrimidine
2,-4-diamino-5-(3-bromophenyl)pyrimidine
2,4-diamino-5-(3-methylphenyl)pyrimidine
2,4-diamino-5-(3,4-methylenedioxyphenyl)pyrimidine
2,4-diamino-5-(3,4-ethylenendioxyphenyl)pyrimidine
or a salt thereof.

6. Use of a tetrahydrobiopterin analogue according to Claim 2 which is a compound of formula (IB)



(IB)

wherein R^{12} is hydrogen, halo, C_{1-4} alkyl optionally substituted by halo or alkoxy.

7. Use of a compound of formula (IC) according to Claim 2, wherein R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from hydrogen, nitro or halo.

8. Use according to Claim 1 for the treament of cerebral ischemia.

9. Use according to Claim 1 for the treatment of CNS trauma.

10. Use according to Claim 1 for the treatment of AIDS dementia.

11. Use according to Claim 1 for the treatment of epilepsy.

12. Use according to Claim 1 for the treatment of chronic neurogenerative disease or chronic pain.

13. Use according to Claim 1 for the treatment of schizophrenia.

14 Use according to Claim 1 for the treatment of conditions in which non-adrenegic non-cholinergic nerve may be implicated.

15. Use according to Claim 1 as an analgesic.

16. Use according to Claim 1 for the treatment of acute neurodegenerative diseases.

17. A compound of formula (IA), (IB) or (IC) or a salt thereof for use in medicine, with the proviso that R^{12} is not hydrogen, and that R^{14} and R^{15} are not independently selected from hydrogen, nitro or carboxy when R^{13}, R^{16} and R^{17} are each hydrogen.

18. A novel compound of formula (IA), (IB) or (IC) or a salt thereof as hereinbefore defined.

19. A compound according to Claim 18 which is selected from:

2,4-diamino-5-(3-trifluoromethylphenyl)pyrimidine
2,-4-diamino-5-(3-bromophenyl)pyrimidine
2,4-diamino-5-(3-methylphenyl)pyrimidine
2,4-diamino-5-(3,4-methylenedioxyphenyl)pyrimidine
2,4-diamino-5-(3,4-ethylenendioxyphenyl)pyrimidine
2,4-diamino-6-(4-methoxyphenyl)pyrimidine
2,4-diamino-6-(3,4-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2-(4-methylphenyl)ethyl)pyrimidine
2,4-diamino-5-(4-methylphenylethynyl)pyrimidine
2,4-diamino-5-phenylethynylpyrimidine
2,6-diamino-3-(2,4,5-trichlorophenyl)pyridine
2,6-diamino-3-(4-methoxyphenyl)pyridine
2,6-diamino-3-(2-naphthyl)pyridine

2,6-bis(acetamido)-3-(3,4-dimethoxyphenyl)pyridine
2,6-diamino-3-(3,4-dimethoxyphenyl)pyridine
1-amino-2, 4-diaza-5, 6-dihydro-9-methoxy-3-(4-methyl-1-piperazinyl)phenanthrene
4-amino-9, 10-dihydro-7-methoxy-2-(4-methyl-1-piperazinyl)benzo[f]quinazoline
2-amino-5-((-naphthyl)pyrimidine
2-amino-5-(4-methoxyphenyl)pyrimidine
2-(4-methylpiperazinyl)-5-(2-naphthyl)pyrimidine
5-(3,4-dimethoxy)-2-(4-methyl-1-piperazinyl)pyrimidine
5-(1,3-benzo[d]dioxol-5-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(1,4-benzodioxan-6-yl)-2-(4-methylpiperazin-1-yl)pyrimidine
5-(3,4-dichlorophenyl)-2-(4-methylpiperazinyl)pyrimidine
2,4-diamino-5-(3-thienyl)pyrimidine
2,4-diamino-5-(3,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-(2,5-dimethoxyphenyl)pyrimidine
2,4-diamino-5-biphenylpyrimidine
2,4-diamino-5-(3,5-bis(trifluoromethyl)phenyl)pyrimidine
2,4-diamino-5-(3,5-dichlorophenyl)pyrimidine
2,4-diamino-5-(2,5-dibromo-4-chlorophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-methanesulphonamidophenyl)pyrimidine
2,4-diamino-5-(4-methoxy-3-methylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethylphenyl)pyrimidine
2,4-diamino-5-(4-trifluoromethoxyphenyl)pyrimidine
2,4-diamino-5-(3-amino-4-chlorophenyl)pyrimidine
2,4-diamino-5-(3-aminophenyl)pyrimidine
2,4-diamino-5-(4-chloro-3-nitrophenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-hydroxyphenyl)pyrimidine
2,4-diamino-5-(3-fluorophenyl)pyrimidine
2,4-diamino-5-(3-trifluoromethoxyphenyl)pyrimidine
2,4-diamino-5-(3-bromo-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-fluoro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-methoxyphenyl)pyrimidine
2,4-diamino-5-(3-chloro-4-fluorophenyl)pyrimidine
2,4-diamino-5-(4-chlorophenyl)pyrimidine

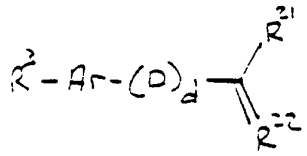
20. A pharmaceutical formulation which comprises a compound which binds at the tetrahydrobiopterin site of NO synthase according to Claim 1, together with one or

more pharmaceutically acceptable carriers therefor and optionally one or more other therapeutic ingredients.

21. A process for the preparation of the novel compounds according to Claim 17, which comprises:

(a) for a compound of formula (IA)

(i) when X is nitrogen, by the cyclisation of a compound of the formula (IV)

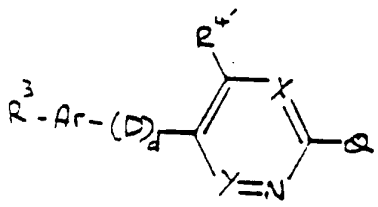


(IV)

wherein R^{21} is cyano or COR^{23} wherein R^{23} is hydroxy, C_{1-4} alkoxy or hydrogen and R^{22} is oxo or a group $C<^{L}_{H}$ wherein L is a leaving group; with amino guanidine or guanidine respectively.

(ii) when R^1 and R^2 are hydrogen the removal of one or more protecting groups from NR^1R^2 and optionally from R^4, when it is desired that R^4 is NH_2.

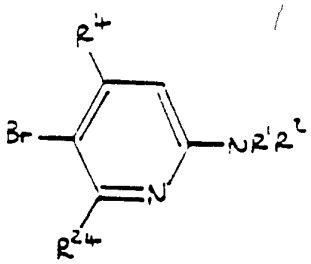
(iii) by the conversion of one compound of the formula (IA) to a further compound of the formula (IA), for example when R^1 and/or R^2 are C_{1-4} alkyl the alkylation of the corresponding compound wherein R^1 and/or R^2 are hydrogen; or when R^1 and R^2 are hydrogen, the amination, or chlorination and subsequent amination, of a compound of the formula (V):



(V)

wherein Q is chloro or bromo, preferably chloro, or hydroxy respectively and $R^{4'}$ is hydrogen, methyl, hydroxy, trifluoromethyl or halo.

(iv) when X is CH and Y is a group CH or CNH_2 the reaction of a compound of the formula (VI):



(VI)

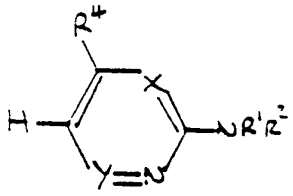
or a suitably protected derivative thereof, wherein R^{24} is hydrogen or NH_2 with benzene boronic acid or benzene boronic acid substituted so as to give the desired substituent R^{11} in the compound of the formula (IA) so formed, followed by the removal of any protecting groups;

(b) for a compound of formula (IB), the reduction of the corresponding 8-oxide; and

(c) for a compound of formula (IC), the reaction of O-methylacetanilide containing the appropriate substituents or substituents covertible thereto.

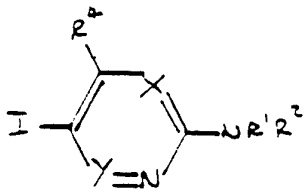
22. A process which comprises:-

(i) the reaction of a compound of formula (VIII)



(VIII)

or a suitably protected derivative thereof wherein R^1, R^2, R^4, X and Y are as hereinbefore defined, with iodine monochloride, to give a compound of formula (VII)



(VII)

(ii) the reaction of a compound of formula (VII) as hereinbefore defined with a compound of formula R^3-Ar-$(D)_d$-$B(OH)_2$ wherein R^3, Ar, D and d are as hereinbefore defined to give a compound of formula (IA) as hereinbefore defined.

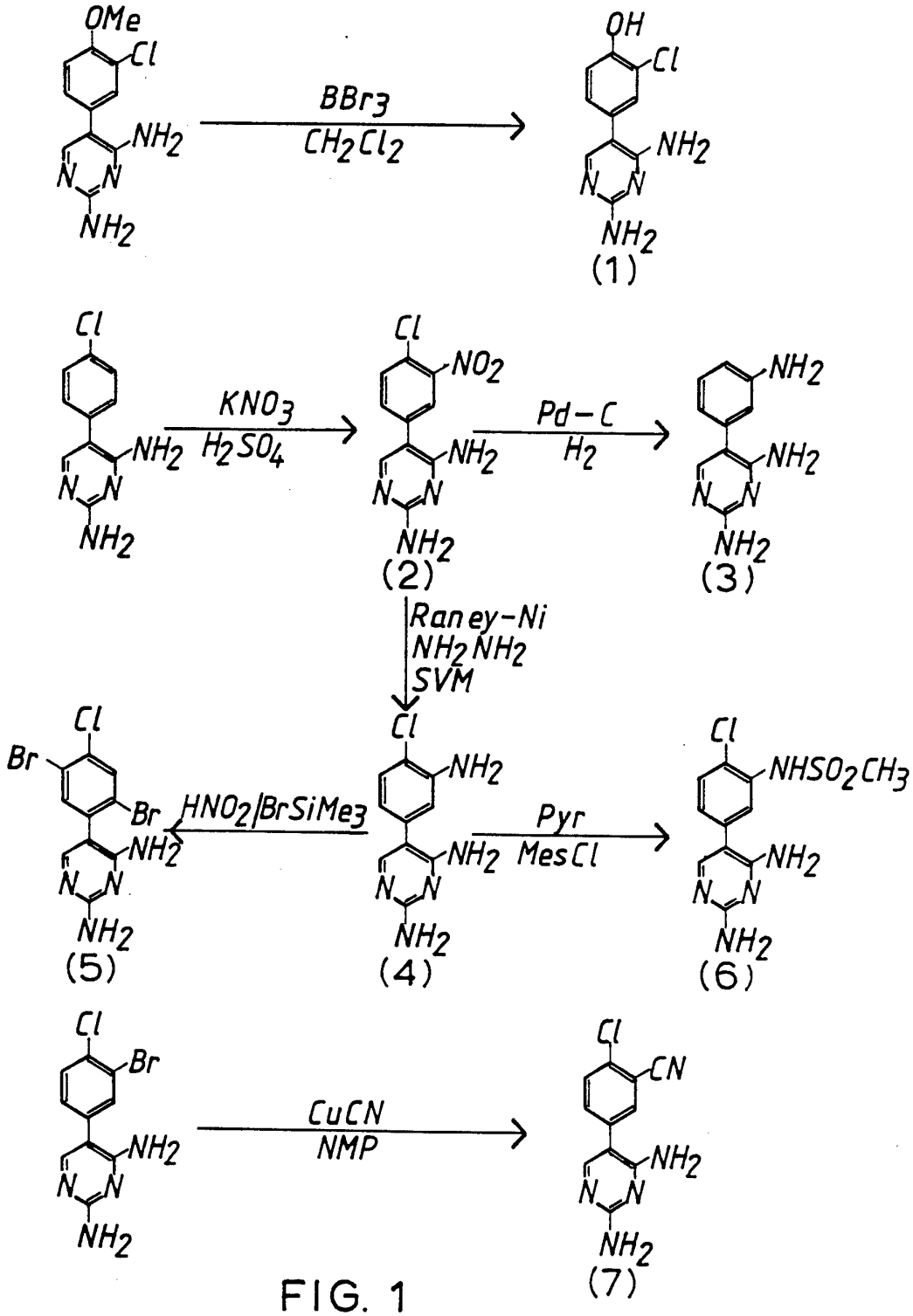

OMe
Cl
NH2
N
N
NH2
BBr3
CH2Cl2
OH
Cl
NH2
N
N
NH2
(1)
Cl
NH2
N
N
NH2
KNO3
H2SO4
Cl
NO2
NH2
N
N
NH2
(2)
Pd-C
H2
NH2
NH2
N
N
NH2
(3)
Raney-Ni
NH2NH2
SVM
Cl
Br
Br
NH2
N
N
NH2
(5)
HNO2/BrSiMe3
Cl
NH2
NH2
N
N
NH2
(4)
Pyr
MesCl
Cl
NHSO2CH3
NH2
N
N
NH2
(6)
Cl
Br
NH2
N
N
NH2
CuCN
NMP
Cl
CN
NH2
N
N
NH2
(7)

FIG. 1

FIG. 2

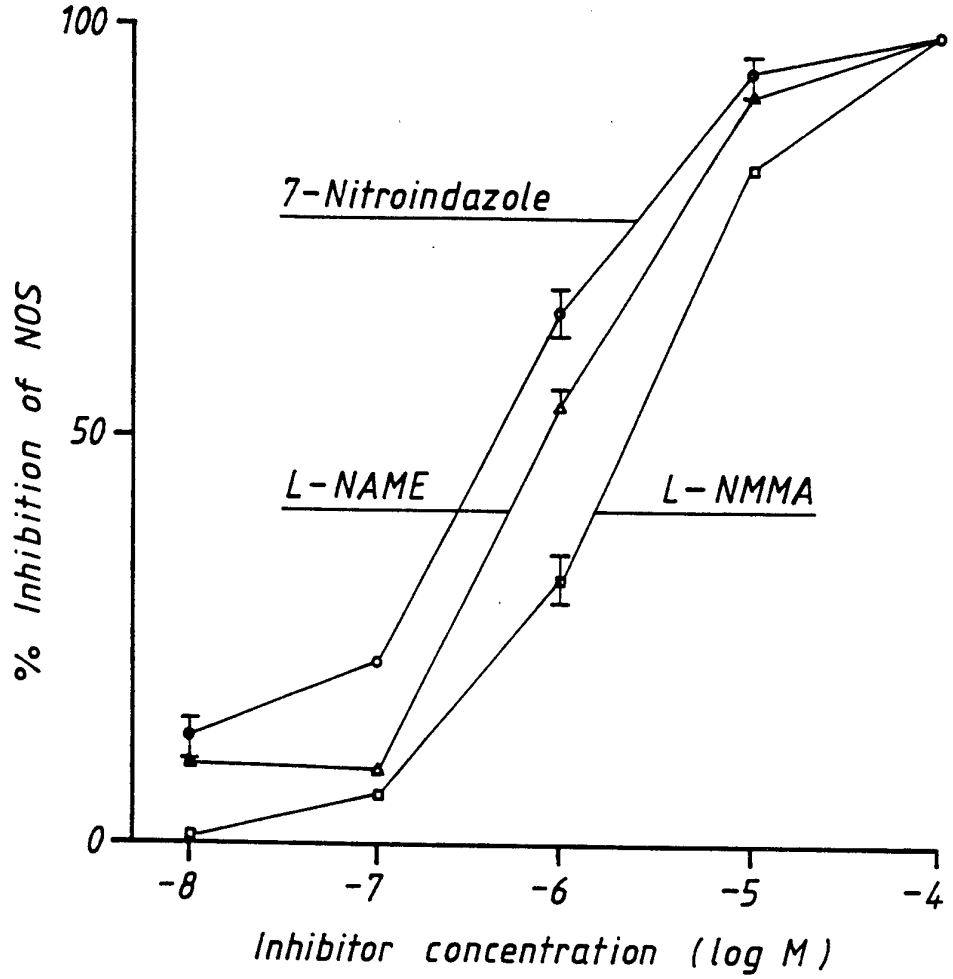
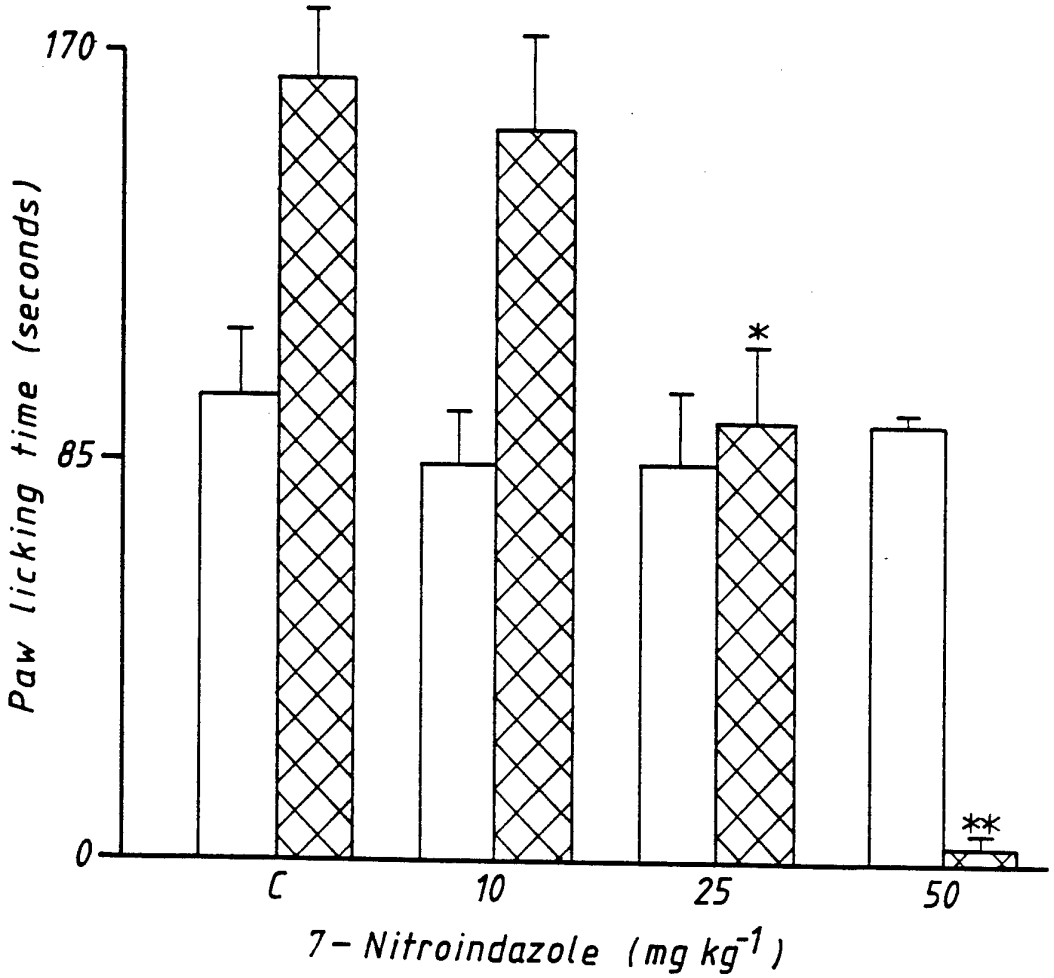

100
50
0
% Inhibition of NOS
7-Nitroindazole
L-NAME
L-NMMA
-8
-7
-6
-5
-4
Inhibitor concentration (log M)

FIG. 3


170
85
0
Paw licking time (seconds)
*
**
C
10
25
50
7-Nitroindazole (mg kg-1)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 93/02556

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D239/48 C07D239/42 C07D213/75 C07D409/04 C07D475/04
C07D231/56 A61K31/505 A61K31/44 A61K31/495 A61K31/415
C07D213/73

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)
IPC 5 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 459 819 (THE WELLCOME FOUNDATION LTD.) 4 December 1991 see claims	1-5,8-22
X	EP,A,0 372 934 (THE WELLCOME FOUNDATION LTD.) 13 June 1990 see claims	1-5,8-22
X	WO,A,88 04293 (STEVENS) 16 June 1988 see claims	1-5,8-22
X	BE,A,518 622 (THE WELLCOME FOUNDATION LTD.) 15 April 1953 see the whole document	1-5,8-22
X	FR,M,7 631 (I.R.S.) 26 January 1970 see claims	1,2,17, 18,20,21

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 1994	23. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	BIOCHEMICAL PHARMACOLOGY vol. 31, no. 18 , 1982 , G.B. pages 3002 - 3005 M. MURRAY 'Inhibition and enhancement of mixed-function oxidases by nitrogen heterocycles' see the whole article,especially page 3003, table 1, compound VII and column 2, last paragraph; page 3004 (C) and page 3005, first paragraph.	1,2,17, 18,20,21
X	CHEMICAL ABSTRACTS, vol. 102, no. 13, 1985, Columbus, Ohio, US; abstract no. 113361m, B. BEYER 'Antiallergic activity of some indazole derivatives' see abstract & ACTA CLIENT. VENEZ. vol. 35, no. 2 , 1984 pages 103 - 106	1,2,17, 18,20,21
X	JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 22, no. 4 , 1985 pages 985 - 991 J.W. STREEF AND AL. 'Reactivity of some 3-substituted derivatives of 2,6-dihalogenopyridines towards potassium amide in liquid ammonia.' see the whole document	1-5,8-22
X	CHEMICAL ABSTRACTS, vol. 91, no. 7, 1979, Columbus, Ohio, US; abstract no. 56787h, C. WLADYSLAW ET AL. 'Rearrangements of N-mono- and N,N-disubstituted 2,6-diaminopyridines in the presence of aluminium chloride.' see abstract & POL. J. CHEM. vol. 53, no. 2 , 1979 pages 507 - 511	1-5,8-22
Y	EP,A,0 459 830 (THE WELLCOME FOUNDATION LTD.) 4 December 1991 see claims	1-22
Y	EP,A,0 108 890 (THE WELLCOME FOUNDATION LTD.) 23 May 1984 see claims	1-22

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Inte ɔnal Application No
PCT/GB 93/02556

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,3 843 678 (E.P. DIBELLA) 22 October 1974 see col.4, lines 65-68; col. 5, lines 1-10 and claims. ---	1-22
Y	US,A,3 988 347 (E.P. DI BELLA) 26 October 1976 see col.2, last paragraph; col. 5, lines 42-53 and claims. ---	1-22
P,X	CHEMICAL ABSTRACTS, vol. 118, no. 15, 12 April 1993, Columbus, Ohio, US; abstract no. 139709m, MOORE, P. K. '7-Nitro indazole, an inhibitor of nitric oxide synthase, exhibits anti-nociceptive activity in the mouse without increasing blood pressure.' see abstract & BR. J. PHARMACOL. vol. 108, no. 2 , 1993 pages 296 - 297 -----	1,2,17, 18,20,21

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ional Application No
PCT/GB 93/02556

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EP-A-0372934	13-06-90	AU-B-	639216	22-07-93
		AU-A-	4596489	14-06-90
		AU-B-	4915493	13-01-94
		CN-A-	1052306	19-06-91
		JP-A-	2202876	10-08-90
		OA-A-	9148	31-10-91
WO-A-8804293	16-06-88	DE-A-	3786256	22-07-93
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FR-M-7631	26-01-70	NONE		
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		BE-A-	827337	29-09-75
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		DE-A-	2513801	02-10-75
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		NL-A-	7503381	01-10-75
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		AU-A-	7809891	05-12-91
EP-A-0108890	23-05-84	AU-B-	572792	19-05-88
		AU-A-	1925683	29-03-84
		DE-A-	3378634	12-01-89
		JP-B-	5033229	19-05-93
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		US-A-	4665182	12-05-87
		US-A-	4701455	20-10-87
US-A-3843678	22-10-74	NONE		

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inte onal Application No
PCT/GB 93/02556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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