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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BOAR, Bernard, Robin [GB/GB]; 25 Meadow Way, Letchworth, Herts SG6 3JB (GB). CROSS, Alan, John [GB/GB]; 2 Sheerwater Road, Woodham, Woking, Surrey GU21 5TT (GB). GRAY, Duncan, Alastair [GB/GB]; Little Cefn Farm, Hyssington, Churchstoke, Powys SY15 6EQ (GB). GREEN, Alfred, Richard [GB/GB]; 22 Laurel Drive, Southmoor, Abingdon, Oxon OX13 5DG (GB).

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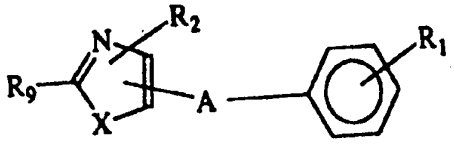
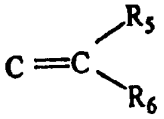
(54) Title: NOVEL (1-PHENYL-1-HETEROCYCLYL)ALKANE DERIVATIVES AND THEIR USE AS NEUROPROTECTIVE AGENTS



(1)

(a)



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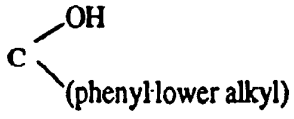

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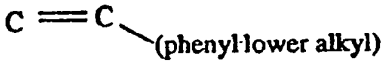

(d)

(57) Abstract

The present invention relates to novel heterocyclic compounds having general formula (1) wherein: X is O, S, Se, or NR_2; and A is (a) or (b) wherein W is O, S, NH or N-lower alkyl; with the proviso that when X is N-H or N-(aryl-methyl), then A is neither (c) or (d) and with the proviso that the following compound is excluded: 1-(1,2-dimethyl-4-imidazolyl)-1-phenylethanol; geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof having therapeutic activity, processes and intermediates for their preparation, pharmaceutical formulations containing said compounds and the medicinal use of said compounds.

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Novel (1-Phenyl-1-heterocyclyl)alkane Derivatives and their Use as Neuroprotective Agents

Field of the Invention

The present invention relates to novel heterocyclic compounds having therapeutic activity, processes and intermediates for their preparation, pharmaceutical formulations containing said compounds and the medicinal use of said compounds.

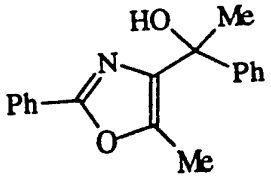
Background of the Invention

There exists a large group of acute and chronic neuropsychiatric disorders for which safe and clinically effective treatments are not currently available. This diverse group of disorders encompasses a broad spectrum of initial events which are characterised by the initiation of progressive processes that sooner or later lead to neuronal cell death and dysfunction. Stroke, cerebral ischaemia, trauma or a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease are all commonly occurring conditions that are associated with neurodegeneration of the brain and/or spinal cord.

The ongoing search for potential treatments of neurodegenerative disorders has involved investigation of excitatory amino acid antagonists, inhibitors of lipid peroxidation, calcium channel antagonists, inhibitors of specific pathways of the arachidonic acid cascade, kappa opioid agonists, adenosine agonists, PAF antagonists and diverse other agents. At the present time there is no consensus of the relative importance of the role played by compounds belonging to any of these general classes.

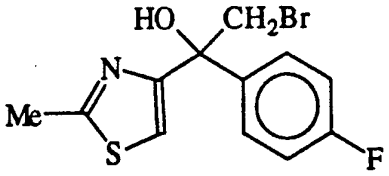
In a paper on the thermal and photochemical isomerisations of isoxazoles, A. Padwa et al (J. Amer. Chem. Soc., 1975, 97, 6484-6491) describe methylphenyl(2-

phenyl-5-methyloxazol-4-yl) carbinol:



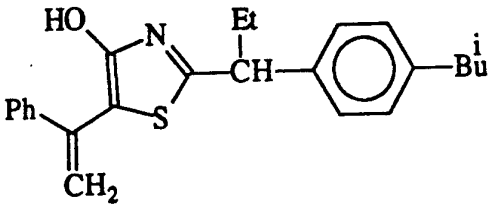
No pharmacological activity is ascribed to said compound.

In patent application EP 313 984, the bromo derivative:



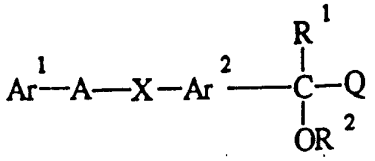
is described as an intermediate for the synthesis of imidazole or triazole based antifungal agents.

In patent application WO 91/08744, 4-hydroxythiazole derivatives are claimed which are 5-lipoxygenase inhibitors. One example of such compounds is:



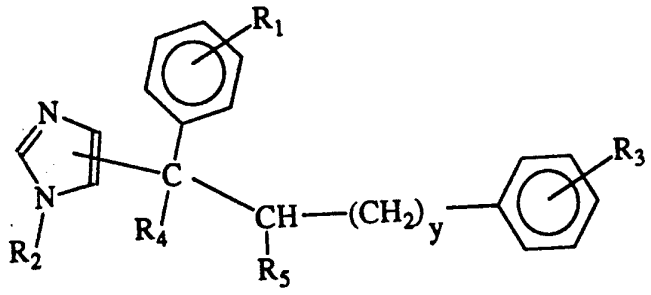
4-Oxygenated thiazoles are not included within the scope of the present invention.

In patent application EP 351 194 and in J. Med. Chem., 1991 34, 2176-2186, compounds of the general formula:



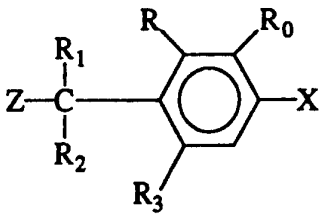
wherein Q is thiazolyl, Ar^1 is aryl of up to 10 carbon atoms, Ar^2 is 6-membered aryl, X is O, S, SO, SO_2 or NH and A is a direct link to X or is (1-6C)alkylene, (3-6C)alkenylene, (3-6C)alkynylene or cyclo(3-6C)alkylene are disclosed as 5-lipoxygenase inhibitors. The substituent Ar^1-A-X is not included within the scope of R^1 in claim 1 of the present invention.

In patent application EP 390 558, imidazoles of the following general structure:



are disclosed as aromatase inhibitors. Such compounds are deleted from the scope of the present invention by a disclaimer in claim 1.

In patent application EP 477 141, compounds of the general formula:



wherein Z is a five-membered aza-aromatic ring and X is cyano, carbamoyl or substituted carbamoyl are claimed. Said compounds are aromatase inhibitors. Specific

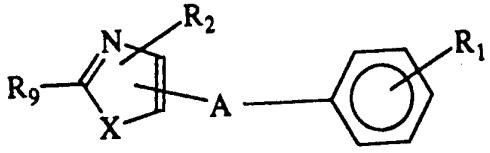
examples are 1-(4-cyanophenyl)-1-(5-thiazolyl)ethene and 1-(4-cyanophenyl)-1-(5-thiazolyl)ethanol. Such substituents X are not included within the scope of the present invention.

In Tetrahedron, 1971, 27, 1211-1219 the compound 1-(1,2-dimethyl-4-imidazolyl)-1-phenylethanol is described. This compound is deleted from the scope of the present invention by a disclaimer in claim 1 .

The present invention

A primary objective of the present invention is to provide structurally novel heterocyclic compounds which by virtue of their pharmacological profile are expected to be of value in the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct dementia; AIDS dementia; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal circulation or in connection with brain surgery, including endarterectomy of the carotid arteries; and CNS dysfunctions as a result of exposure to neurotoxins or radiation. This utility is manifested, for example, by the ability of these compounds to inhibit delayed neuronal death in the gerbil bilateral occlusion model of ischaemia.

The present invention relates to a compound having the general formula (1)



(1)

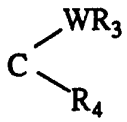
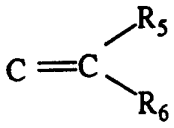
wherein:

X is O, S, Se or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

and A is  or 

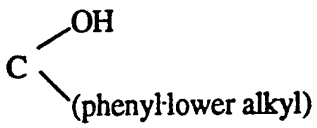
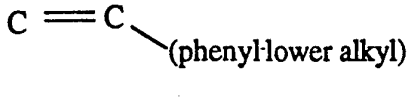
wherein W is O, S, NH or N-lower alkyl,

R_3 is H, lower alkyl or lower acyl,

R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;

R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

with the proviso that when X is N-H or N-(aryl-methyl), then A is neither

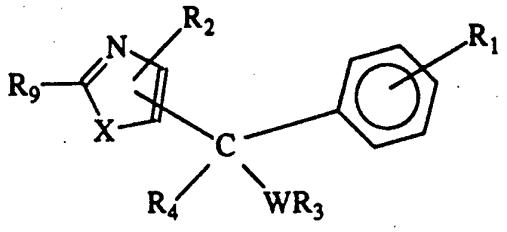
 or 

and with the proviso that the following compound is excluded:
1-(1,2-dimethyl-4-imidazolyl)-1-phenylethanol;

geometrical and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof.

The expression "pharmaceutically acceptable acid addition salts" is intended to include but is not limited to such salts as the hydrochloride, hydrobromide, hydroiodide, nitrate, hydrogen sulphate, dihydrogen phosphate, ethanedisulphonate, mesylate, fumarate, maleate and succinate.

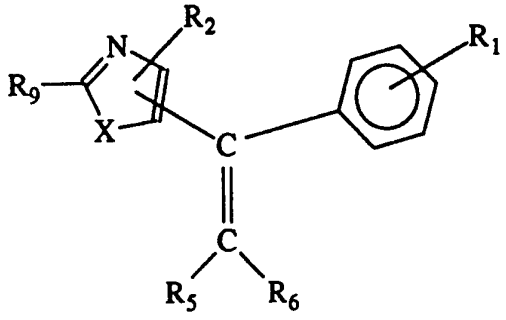
Preferred embodiments of this invention relate to compounds having the general formula (2)



(2)

wherein:
X is O or S;
W is O;
and R_1, R_2, R_3, R_4 and R_9 are as previously defined above;

and to compounds having the general formula (3)



(3)

wherein:
X is O or S;
and R_1, R_2, R_5, R_6 and R_9 are as previously defined above.

Analogous compounds wherein X is Se, for example, 1-(4-methyl-5-selenazolyl)-1-phenylethanol and 1-(4-methoxyphenyl)-1-(2,4-dimethyl-5-selenazolyl)ethene, are specifically included within the scope of the invention.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all geometrical and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof such as for instance hydrates.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "lower alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "lower perfluoroalkyl" denotes a straight or branched alkyl group having from 1 to 4 carbon atoms fully substituted by fluorine. Examples of said lower perfluoroalkyl groups include trifluoromethyl, pentafluoroethyl and heptafluoroisopropyl.

Unless otherwise stated or indicated, the term "lower acyl" denotes a straight or branched acyl group having from 1 to 6 carbon atoms. Examples of said lower acyl

include formyl, acetyl, propionyl, iso-butyryl, valeryl, and pivaloyl.

Unless otherwise stated or indicated, the term "lower alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "lower alkoxy-lower alkyl" denotes a lower alkyl group as defined above substituted by a lower alkoxy group as defined above. Examples of said lower alkoxy-lower alkyl include methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl.

Unless otherwise stated or indicated, the term "aryl" denotes a phenyl, naphthyl, furyl, thienyl, pyridyl or pyrrolyl group, itself optionally substituted.

Unless otherwise stated or indicated, the term "aryl-lower alkyl" denotes a lower alkyl group as defined above substituted by an aryl group as defined above. Examples of said aryl-lower alkyl include benzyl, phenethyl, phenylpropyl, 4-fluorophenylmethyl, furfuryl, 3-furylmethyl, tolylethyl and thenyl.

Among the most preferred compounds of formula (1) according to the present invention are:

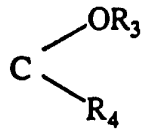
1-(4-methyl-5-oxazolyl)-1-phenylethanol;
1-(4-methyl-5-thiazolyl)-1-phenylethanol;
1-(4-methoxyphenyl)-1-(2,4-dimethyl-5-thiazolyl)ethanol;

1-(4-methyl-5-thiazolyl)-1-phenyl-2,2,2-trifluoroethanol;
1-(2,4-dimethyl-5-oxazolyl)-1-phenylethanol;
1-(4-methyl-5-thiazolyl)-1-phenylethene;

and pharmaceutically acceptable acid addition salts or solvates thereof.

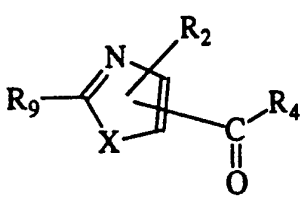
The present invention also relates to processes for preparing the compound having formula (1). Throughout the following general description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Greene, Wiley-Interscience, New York, 1981.

Said compound wherein A is

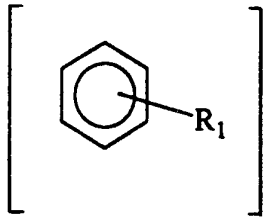


may be prepared by

(a) reacting a compound of general formula (4) with an organometallic derivative of general formula (5)

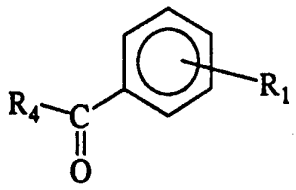


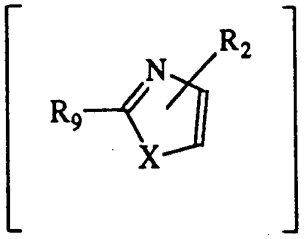
(4)



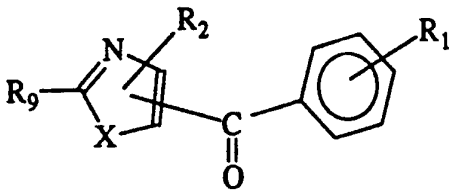
M (5)

or (b) reacting a compound of general formula (6) with an organometallic derivative of general formula (7)


(6)


(7)

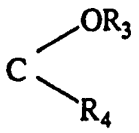
or (c) reacting a compound of general formula (8) with an organometallic derivative of general formula R_4M


(8)

and quenching the reaction mixture with a proton source (R_3 is H) or an alkylating (R_3 is lower alkyl) or acylating (R_3 is lower acyl) reagent;

or (d), particularly in cases where R_4 is perfluoroalkyl, reacting a compound of general formula (8) with a silyl derivative of general formula R_4SiMe_3.

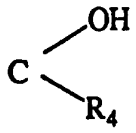
Alternatively, the compound of formula (1)

wherein A is 

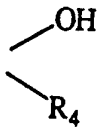
and R_3 is H may be first obtained as above and then converted into the compound wherein R_3 is lower alkyl or lower acyl.

The processes (a), (b) or (c) can be achieved for example, by reacting together a ketone of structure (4 or (6) or (8) with a preformed organometallic derivative (5) or (7) or R_4M respectively in a suitable anhydrous

solvent such as diethylether, tetrahydrofuran or hexane or mixtures thereof. Said reaction should be conducted at a suitable temperature, normally between -100°C and +50°C and preferably under an inert atmosphere, normally nitrogen or argon. In a specific variation, a solution of the ketone of structure (4) or (6) or (8) in anhydrous diethylether or tetrahydrofuran is added dropwise to the organometallic derivative (5) or (7) or R_4M respectively in anhydrous diethylether or tetrahydrofuran or hexane or mixtures thereof at a temperature of about -50°C to -78°C and under an atmosphere of nitrogen. After a suitable period of time the reaction mixture is allowed to warm to room temperature and then quenched by the addition of water or a lower alcohol. The required product (1)

wherein A is 

may then be isolated and purified and characterised using standard techniques.

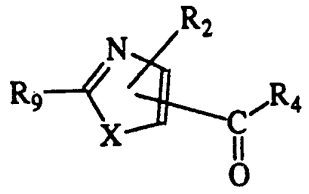
The process (d) can be achieved, for example, by treating a solution of the ketone (8) and the silyl derivative R_4SiMe_3 in a suitable anhydrous solvent such as diethylether or tetrahydrofuran with tetrabutylammonium fluoride. Said reaction should be conducted at a suitable temperature, normally between -100°C and +50°C and preferably under an inert atmosphere, normally nitrogen or argon. After a suitable period of time the reaction mixture is allowed to come to room temperature and is then treated with 6M hydrochloric acid. The required product (1) wherein A =  may then be isolated and purified and characterised using standard techniques.

Ketones of general formula (4) or (6) or (8) are either

compounds which are commercially available or have been previously described in the literature, or compounds which can be prepared by the straightforward application of known methods.

Thus, the present invention also refers to some new intermediates of the general formulas (4) or (8), respectively, namely:

a compound of general formula (4)



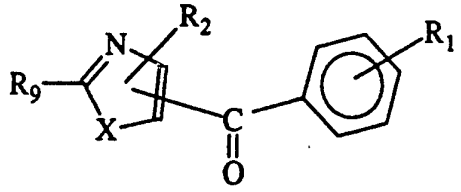
(4)

wherein X is O, S or Se;
R_4 is C_2 to C_6 alkyl;
and R_2 and R_9 are as defined in claim 1 with the

proviso that the following four compounds are excluded:

ethyl 4-thiazolyl ketone;
tert-butyl 5-thiazolyl ketone;
tert-butyl 5-oxazolyl ketone;
tert-butyl 4-tert-butyl-2-methyl-5-oxazolyl ketone;

or a compound of general formula (8)

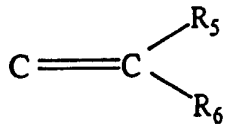


(8)

wherein X is O, S or Se;
and R_1, R_2 and R_9 are as defined in claim 1, with the provisos that when R_2 and R_9 are both H, then R_1 is not H or 4-Br; and that when R_9 is H and R_2 is CH_3, then R_1 is not H or 4-OMe.

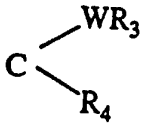
In the organometallic derivatives of general formula (5) or (7) or R_4M, M represents a metallic residue such as Li or Mg-halogen. Such compounds are either commercially available or have been previously described in the literature, or can be prepared by the straightforward application of known methods of organometallic chemistry.

Silyl derivatives of formula R_4SiMe_3 are either commercially available, for example, CF_3SiMe_3, or have been previously described in the literature or can be prepared by the straightforward application of known methods.

Compounds of formula (1) wherein A is 

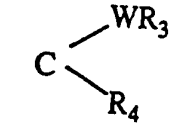
may be prepared by

(a) elimination of HWR_3 from a compound of formula (1)

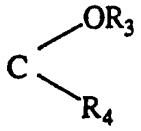
wherein A is 

or (b) by using a compound of general formula (8) as the substrate for a standard alkene forming reaction such as the Wittig reaction, the Peterson reaction or the McMurry reaction.

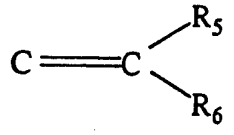
The process (a) can be achieved, for example, by treatment of a solution of a compound of formula (1)

wherein A is 

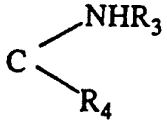
in a suitable inert solvent with an acid or a base or a reagent such as thionyl chloride or phosphorus oxychloride. Said reaction should be conducted at a suitable temperature, normally between -20°C and the reflux temperature of the solvent. In a preferred variation, a solution of a compound of formula (1)

wherein A is 

in a solvent such as dichloromethane or chloroform at 0°C to 10°C is treated with an acid such as anhydrous hydrogen chloride or p-toluenesulphonic acid, or with thionyl chloride. The reaction is then allowed to proceed at ambient temperature or above. The required product (1) wherein

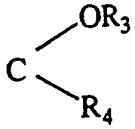
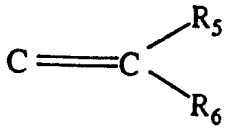
A is  may then be isolated and purified

and characterised using standard techniques.

Compounds of formula (1) wherein A is  may

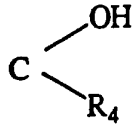
be prepared by

(a) using a compound of general formula (1) wherein A is

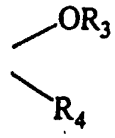
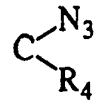
 or  as the substrate for a

Ritter reaction,

or (b) using a compound of general formula (1) wherein

A is  as the substrate for a Mitsunobu-type

reaction,

or (c) reacting a compound of general formula (1) wherein A is  with trimethylsilylazide, Me_3SiN_3, in the presence of a Lewis acid such as boron trifluoride diethyletherate to give an azide of formula (1) wherein A is  , and then reducing said azide using, for example, hydrogen in the presence of a palladium or platinum catalyst.

Some compounds of general formula (1) contain an asymmetric centre and can thus exist in enantiomeric forms. These enantiomers may be separated using methods that will be well known to one skilled in the art. Such methods include, for example,

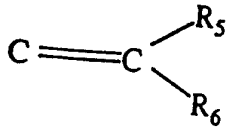
(i) direct separation by means of chiral chromatography, for example, by HPLC using a chiral column;

or (ii) recrystallisation of the diastereomeric salts formed by reacting the base (1) with an optically active acid;

or (iii) derivatization of the compound of formula (1) by reaction with an optically active reagent, separation of the resultant diastereoisomeric derivatives by, for example, crystallisation or chromatography, followed by regeneration of the compound of formula (1).

Alternatively, compounds of formula (1) may be obtained directly in an optically active form by using a chemical or enzymatic based method of asymmetric synthesis.

Some compounds of general formula (1) wherein A is



can exist as E and Z (trans and cis) isomers. Such isomers may be separated using standard techniques, for example, crystallisation or chromatography, that will be readily apparent to one skilled in the art.

Pharmacology

The neuroprotective properties of the compounds of formula (1) are exemplified by their ability to inhibit delayed neuronal death in the gerbil bilateral occlusion model of ischaemia.

Animals used were male Mongolian gerbils (60-80g). Drugs were dissolved in isotonic saline containing dimethylsulphoxide.

Ischaemia was induced in the gerbils by 5 minute occlusion of both carotid arteries following the procedure described by R. Gill, A.C. Foster and G.N. Woodruff, J. Neuroscience. 1987, 7, 3343-3349. Body temperature was maintained at 37°C throughout. Restoration of blood flow after occlusion was checked visually and the animals were allowed to survive for 4 days. The extent of neuronal degeneration in the hippocampus was then assessed. The test compounds were administered (i.p.) as a single dose 60 minutes following occlusion. No administration was made prior to the occlusion. The effectiveness of the compounds of formula (1) in decreasing damage to the CA1/CA2 hippocampal neurones in gerbils following ischaemic insult clearly illustrates the usefulness of these compounds in preventing neurodegeneration. These compounds are therefore expected to be of value in the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction.

Pharmaceutical Formulations

The administration in the novel method of treatment of this invention may conveniently be oral, rectal, topical or parenteral at a dosage level of, for example, about 0.01 to 1000 mg/kg, preferably about 1.0 to 500 mg/kg and especially about 5.0 to 200 mg/kg and may be administered on a regimen of 1 to 4 doses or treatments per day. The dose will depend on the route of administration, preferred routes being oral or intravenous administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally considered by the attending physician will influence the individual regimen and dosage most appropriate for a particular patient.

The pharmaceutical formulations comprising the compound of this invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral solutions or suspensions for parenteral administration; suppositories for rectal administration; or suitable topical formulations. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described, for example, in "Pharmaceuticals - The Science of Dosage Form Design", M. E. Aulton, Churchill Livingstone, 1988.

To produce pharmaceutical formulations containing a compound according to the present invention in the form of dosage units for oral application the active substance may be admixed with an adjuvant/a carrier e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinyl-pyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated

tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the man skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.02% to about 20% by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to the man in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may involve the use of surface acting agents to improve solubility. They may conveniently be provided in various dosage unit ampoules.

The necessary starting material for all Preparations and Examples were purchased commercially except as follows:

4-methyl-5-oxazolecarbonyl chloride (Indian J. Chem., Sect. B., 1985, 24B, 535-8);

5-acetyl-4-methyloxazole (Chem. Ber., 1960, 93, 1998-2001);

5-acetyl-4-methylthiazole (J. Agr. Food Chem., 1974, 22, 264-9);

5-acetyl-2,4-dimethyloxazole (Chem. Ber., 1960, 93, 1998-2001).

PREPARATION 1

N-Methoxy-N-methyl-4-methyl-5-oxazolecarboxamide

4-Methyl-5-oxazolecarbonyl chloride (15g) and N,O-dimethylhydroxylamine hydrochloride (11g) in dry chloroform (100ml) were cooled to 0°C and dry pyridine (28.5g) was added. The mixture was allowed to warm to room temperature. After 30 minutes aqueous sodium hydrogen carbonate was added and the organic layer separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed, dried and evaporated. The residue was purified by flash chromatography to yield the title compound as a white

solid. M.p. 59-60°C.

^{1}H Nmr ($CDCl_3$) 2.5, 3.34 and 3.82 (each 3H, s) and 7.86 (1H, s) ppm.

Found: C, 49.0; H, 5.6; N, 16.4. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.5%

PREPARATION 2

4-Methyl-5-oxazolyl Phenyl Ketone

N-Methoxy-N-methyl-4-methyl-5-oxazolecarboxamide (3.0g) in dry tetrahydrofuran was stirred and cooled to -70°C under an atmosphere of dry nitrogen and phenyllithium (1.8M solution in cyclohexane - diethylether, 11.7ml) in dry tetrahydrofuran was added dropwise. After 30 minutes the mixture was allowed to warm to room temperature. Ethanol (5ml) was added followed by saturated aqueous sodium chloride. The mixture was extracted with dichloromethane and the material thus obtained was purified by flash chromatography to give the title compound. M.p. 84-86°C.

^{1}H Nmr ($CDCl_3$) 2.59 (3H, s), 7.5-7.68 (3H, m) and 7.96-8.06) (3H, m) ppm.

EXAMPLE 1

1-(4-Methyl-5-oxazolyl)-1-phenylethanol

5-Acetyl-4-methyloxazole (5g) in dry diethylether (25ml) at -70°C under a nitrogen atmosphere was treated dropwise with phenyllithium (1.8M solution in cyclohexane - diethylether, 27ml). After 45 minutes the mixture was allowed to warm to room temperature and water (10ml) was added. The mixture was poured into saturated aqueous sodium chloride and extracted with dichloromethane. The product thus obtained was crystallised from diethylether to give 1-(4-methyl-5-oxazolyl)-1-phenylethanol, m.p.

102-104°C.

^{1}H Nmr ($CDCl_3$) 1.94 (3H, s), 2.0 (3H, s), 7.25-7.45 (5H, m) and 7.7 (1H, s) ppm.

^{13}C Nmr ($CDCl_3$) 12.5, 29.7, 72.7, 125.1, 127.6, 128.4, 131.4, 145.2, 148.6 and 149.8 ppm.

Found: C, 70.9; H, 6.6; N, 6.5. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%

EXAMPLE 2

1-(4-Methyl-5-thiazolyl)-1-phenylethanol

4-Methylthiazole (10g) in dry tetrahydrofuran (50ml) at -70°C was stirred under a nitrogen atmosphere and n-butyllithium (2.5M solution in hexane, 44.4 ml) was added dropwise. After 30 minutes, trimethylsilylchloride (12.8 ml) was added and the reaction mixture was allowed to warm to room temperature. After 30 minutes the mixture was cooled to -70°C and n-butyllithium (44.4ml) was added dropwise. After 30 minutes, acetophenone (12.9ml) was added dropwise and the mixture stirred at -70°C for 1 hour. The reaction mixture was allowed to warm to room temperature and aqueous sodium hydrogen carbonate was added. The organic layer was separated and the aqueous layer was extracted with diethylether. The combined organic layers were then worked up to afford the title compound as a white solid, m.p. 128.5-129.5°C.

^{1}H Nmr ($CDCl_3$) 2.01 and 2.1 (each 3H, s), 3.06 (1H, br s), 7.24-7.47 (5H, m) and 8.5 (1H, s) ppm.

^{13}C Nmr ($CDCl_3$) 16.2, 31.9, 73.7, 125.5, 127.6, 128.4, 139.7, 145.9, 148.8 and 148.9 ppm.

Found: C, 65.6; H, 5.9; N, 6.3. $C_{12}H_{13}NOS$ requires C, 65.7; H, 6.0; N, 6.4%

Identical material was also obtained by the reaction of 5-acetyl-4-methylthiazole with phenyllithium according to the general method of Example 1.

EXAMPLE 3

1-(2-Methoxyphenyl)-1-(4-methyl-5-oxazolyl)ethanol

2-Bromoanisole (4.86g) in anhydrous diethylether (10ml) was added dropwise to a stirred solution of n-butyllithium (2.5M solution in hexane, 10.4ml) in diethylether (30ml) at -70°C under an atmosphere of dry nitrogen. After 45 minutes, 5-acetyl-4-methyloxazole (2.5g) in diethylether (10ml) was added dropwise. After a further 1 hour at -70°C the reaction mixture was allowed to warm to room temperature and was stirred overnight. Saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated and the aqueous layer was extracted with diethylether. The combined organic layers were further processed to give the title compound as a white solid, m.p. 74-75°C.

^{1}H Nmr ($CDCl_3$) 1.92, 2.0 and 3.78 (each 3H, s), 4.61 (1H, s), 6.92 (1H, d), 7.0 (1H, t), 7.26-7.37 (2H, m) and 7.64 (1H, s) ppm.

^{13}C Nmr ($CDCl_3$) 12.1, 27.0, 55.6, 72.3, 111.5, 121.1, 126.6, 129.3, 130.2, 132.4, 148.0, 149.8 and 156.9 ppm.

Found: C, 66.8; H, 6.7; N, 6.05. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%

EXAMPLE 4

1-(4-Methoxyphenyl)-1-(4-methyl-5-oxazolyl)ethanol

Following the general method of Example 3 but starting with 4-bromoanisole, the title compound was prepared. M.p. 115-116°C.

^{1}H Nmr ($CDCl_3$) 1.9, 1.98 and 3.8 (each 3H, s), 3.07 (1H,

s), 6.87 (1H, d), 7.33 (1H, d) and 7.65 (1H, s) ppm.

^{13}C Nmr ($CDCl_3$) 12.4, 29.7, 55.2, 72.3, 113.7, 126.4, 131.1, 137.5, 148.5, 150.0 and 159.0 ppm.

Found: C, 67.1; H, 6.5; N, 6.1. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%

EXAMPLE 5

1-(4-Methyl-5-oxazolyl)-1-(2-trifluoromethylphenyl)-ethanol

Following the general method of Example 3 but starting with 2-trifluoromethylbromobenzene, the title compound was prepared. M.p. 108-109°C.

^{1}H Nmr ($CDCl_3$) 1.95 and 2.02 (each 3H, s), 2.59 (1H, s), 7.43 and 7.56 (each 1H, t), 7.7 (1H, s) and 7.73-7.78 (2H, m) ppm.

Found: C, 57.3; H, 4.3; N, 5.1. $C_{13}H_{12}F_3NO_2$ requires C, 57.6; H, 4.5; N, 5.2%

Treatment of the above product with anhydrous hydrogen chloride in diethylether gave 1-(4-methyl-5-oxazolyl)-1-(2-trifluoromethylphenyl)ethanol hydrochloride as a white solid, m.p. 104-105°C.

Found: C, 50.6; H, 4.1; N, 4.5. $C_{13}H_{12}F_3NO_2$.HCl requires C, 50.7; H, 4.3; N, 4.55%

EXAMPLE 6

1-(4-Methyl-5-thiazolyl)-1-phenylethene

1-(4-Methyl-5-thiazolyl)-1-phenylethanol (2.5g) in chloroform (25ml) was treated with thionyl chloride (4.5ml). The mixture was heated under reflux overnight and then evaporated to dryness. Aqueous sodium hydrogen carbonate was added and the mixture was extracted with

dichloromethane. The material thus obtained was purified by flash chromatography to give the title compound as an oil. Treatment with anhydrous hydrogen chloride in diethylether gave 1-(4-methyl-5-thiazolyl)-1-phenylethene hydrochloride, m.p. 131-133.5°C.

^{1}H Nmr (d_6-DMSO) 1.85 (3H, s), 5.15 and 5.52 (each 1H, s), 6.96-7.07 (5H, m) and 8.82 (1H, s) ppm.

^{13}C Nmr (d_6-DMSO) 15.4, 119.2, 126.6, 128.3, 128.5, 131.2, 138.8, 139.4, 148.7 and 152.4 ppm.

Found: C, 60.6; H, 5.0; N, 5.7. $C_{12}H_{11}NS.HCl$ requires C, 60.6; H, 5.1; N, 5.9%

EXAMPLE 7

1-(4-Methyl)-5-oxazolyl)-1-(4-trifluoromethylphenyl)-ethanol

Following the general method of Example 3 but starting with 4-trifluoromethylbromobenzene, the title compound was prepared. M.p. 89-91°C.

^{1}H Nmr ($CDCl_3$) 1.93 and 2.01 (each 3H, s), 3.18 (1H, s), 7.54 and 7.62 (each 2H, d) amd 7.7 (1H, s) ppm.

The corresponding hydrochloride salt was prepared, m.p. 110-111°C.

EXAMPLE 8

1-(4-Methoxyphenyl)-1-(2,4-dimethyl-5-thiazolyl)ethanol

Following the general method of Example 3 but starting with 4-bromoanisole and 5-acetyl-2,4-dimethylthiazole, the title compound was prepared. M.p. 114-115.5°C.

^{13}C Nmr ($CDCl_3$) 16.2, 18.8, 31.9, 55.2, 73.5, 113.6, 126.8, 138.5, 139.2, 147.6, 159.2 and 162.3 ppm.

EXAMPLE 9

1-(4-Methyl-5-thiazolyl)-1-phenyl-2,2,2-trifluoroethanol

Following the general method of Example 2 but starting with 2,2,2-trifluoroacetophenone, the title compound was prepared. M.p. 180-181.5°C.

^{1}H Nmr (d_6-DMSO) 1.6 (3H, s), 7.1 (5H, m) and 8.66 (1H, s) ppm.

EXAMPLE 10

1-(4-Methoxyphenyl)-1-(2,4-dimethyl-5-thiazolyl)ethene

1-(4-Methoxyphenyl)-1-(2,4-dimethyl-5-thiazolyl)ethanol (3.69g) in chloroform (50ml) was treated with hydrogen chloride in dry diethyl ether (1M, 14.5ml). After 2 hours at room temperature, aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform. The material thus obtained was purified by flash chromatography to yield the title compound.

^{1}H Nmr ($CDCl_3$) 2.2, 2.65 and 3.83 (each 3H, s), 5.27 and 5.60 (each 1H, s), and 6.86 and 7.28 (each 2H, d) ppm.

Hydrochloride, m.p. 139-140°C.

^{13}C Nmr (d_6-DMSO) 15.1, 17.9, 55.1, 113.9, 117.1, 128.0, 131.0, 131.7, 138.0, 146.5, 159.4 and 164.3 ppm.

EXAMPLE 11

1-(2,4-Dimethyl-5-thiazolyl)-1-phenylethanol

The title compound was prepared following the general method of Example 1 but starting with 5-acetyl-2,4-dimethylthiazole. M.p. 131-132°C.

^{13}C Nmr ($CDCl_3$) 16.2, 18.7, 32.3, 73.6, 125.4, 127.4, 128.3, 138.8, 146.4, 147.6 and 161.8 ppm.

EXAMPLE 12

1-(2,4-Dimethyl-5-oxazolyl)-1-phenylethanol

The title compound was prepared following the general method of Example 1 but starting with 5-acetyl-2,4-dimethyloxazole. M.p. 94.5-96°C.

^{13}C Nmr ($CDCl_3$) 12.3, 13.6, 29.8, 72.5, 125.1, 127.4, 128.2, 131.4, 145.6, 149.2 and 158.9 ppm.

EXAMPLE 13

1-Phenyl-1-(5-thiazolyl)ethanol

n-Butyllithium (2.5M solution in hexane, 7ml) in diethyl ether (30ml) was stirred at -70°C under a nitrogen atmosphere and 2-trimethylsilylthiazole (2.5g) in diethyl ether (10ml) was added dropwise. After 30 minutes, acetophenone (2.3g) in diethyl ether (10ml) was added dropwise. After a further 45 minutes the mixture was allowed to warm to room temperature and was then left overnight. Water was added and the mixture was extracted with diethyl ether. The material thus obtained was purified by flash chromatography to give the title compound. M.p. 86-87°C.

^{13}C Nmr ($CDCl_3$) 32.2, 73.3, 125.1, 127.5, 128.3, 139.4, 146.5, 148.6 and 153.1 ppm.

EXAMPLE 14

1-(4-Methoxyphenyl)-1-(4-methyl-5-oxazolyl)ethylamine

Boron trifluoride diethyletherate (1.5 mmoles) was added at room temperature to a suspension of the product from Example 4 (1.3 mmoles) and trimethylsilylazide (1.5 mmoles) in benzene under dry nitrogen. After 40 hours the mixture was diluted with ethyl acetate, washed with water, then aqueous sodium hydrogen carbonate, then saturated aqueous sodium chloride, and dried and evaporated. Flash chromatography then gave 1-azido-1-(4-methoxyphenyl)-1-(4-methyl-5-oxazolyl)ethane. This azide

in ethanol was shaken with 10% palladium-on-charcoal under an atmosphere of hydrogen for 4 hours. Filtration, evaporation and chromatography then gave 1-(4-methoxyphenyl)-1-(4-methyl-5-oxazolyl)ethylamine.
M.p. 47-48°C.

^{13}C Nmr ($CDCl_3$) 12.7, 30.5, 54.7, 55.1, 113.6, 126.5, 129.6, 138.4, 148.0, 151.8 and 158.6 ppm.

PHARMACY EXAMPLES

The following examples illustrate suitable pharmaceutical compositions to be used in the method of the invention.

Composition 1 - Tablets

Compound of Example 2	10g
Lactose	94g
Microcrystalline cellulose	86g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 2, lactose, cellulose and polyvinylpyrrolidone are sieved and blended. The magnesium stearate is sieved and then blended into the above mixture. Compression using suitable punches then yields 1000 tablets each containing 10mg of the active ingredient. If desired, the obtained tablets can then be film coated.

Composition 2 - Tablets

Compound of Example 9	50g
Lactose	80g
Microcrystalline cellulose	20g
Potato starch	40g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 9, lactose, cellulose and part of the starch are mixed and granulated with 10% starch paste. The resulting mixture is dried and blended with the remaining starch, the polyvinylpyrrolidone and the sieved magnesium stearate. The resulting blend is then compressed to give 1000 tablets each containing 50mg of the active ingredient.

Composition 3 - Capsules

Compound of Example 12	100g
Pregelatinised starch	98g
Magnesium stearate	2g

The compound of Example 12 and the starch are sieved, blended together and then lubricated with the sieved magnesium stearate. The blend is used to fill 1000 hard gelatine capsules of a suitable size. Each capsule contains 100mg of the active ingredient.

Composition 4 - Injection Formulation

Compound of Example 2	0.5 to 10g
Polyethoxylated castor oil	15g
Water for injection ad	100g

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included.

The solution is prepared, clarified and filled into appropriate size bottles and sealed. The formulation is sterilised by heating in an autoclave. Alternatively, the solution may be sterilised by filtration and filled into sterile bottles under aseptic conditions. The solution may be packed under a nitrogen blanket.

Composition 5 - Injection Formulation

Compound of Example 6		0.5 to 10g
Polyethoxylated castor oil		15g
Propylene glycol		20g
Polyoxyethylene-polyoxypropylene block copolymer (Pluronic F68)		10g
Water for injection	ad	100g

The compound of the invention is added to a mixture of polyethoxylated castor oil, propylene glycol and Pluronic F68. The mixture is gently heated until a clear solution is obtained. This solution is sterilised by heating in an autoclave or alternatively, by the process of filtration. A concentrated sterile solution is thus obtained, which is suitable for dilution with sterile water in order to form a composition suitable for parenteral administration.

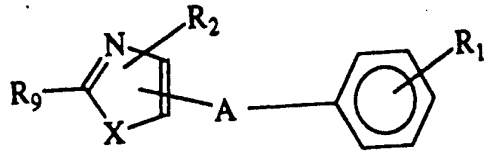
Composition 6 - Injection Formulation

Compound of Example 12		0.5 to 10g
Hydroxypropyl-ß-cyclodextrin		10g
Water for injection	ad	100g

Water for injection is added to a mixture of the compound of the invention and hydroxypropyl-ß-cyclodextrin. The mixture is gently stirred until a clear solution is obtained. The solution is filled into bottles which are then sealed and sterilised by heating in an autoclave or alternatively, by the process of filtration.

CLAIMS

1. A compound having the general formula (1)



(1)

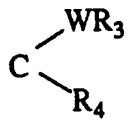
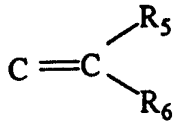
wherein:

X is O, S, Se, or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

and A is  or 

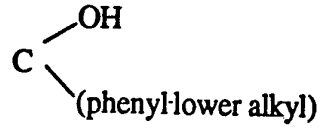
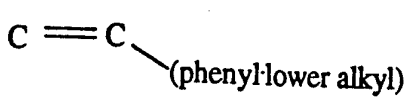
wherein W is O, S, NH or N-lower alkyl;

R_3 is H, lower alkyl or lower acyl;

R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;

R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

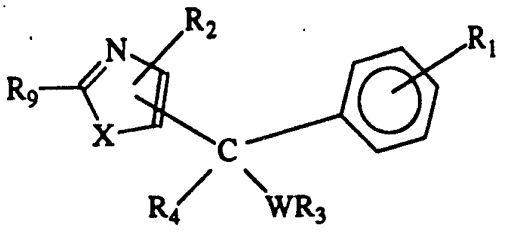
with the proviso that when X is N-H or N-(aryl-methyl), then A is neither

 or 

and with the proviso that the following compound is excluded:
1-(1,2-dimethyl-4-imidazolyl)-1-phenylethanol;

geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof.

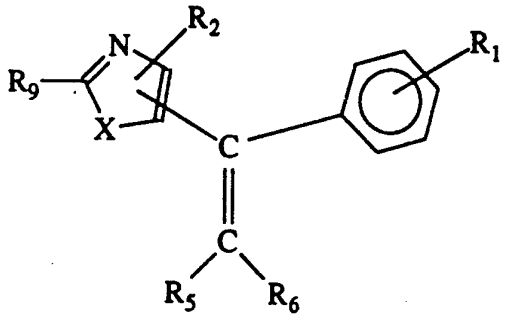
2. A compound according to claim 1 having the general formula (2)



(2)

wherein:
X is O or S;
W is O;
and R_1, R_2, R_3, R_4 and R_9 are as defined in claim 1.

3. A compound according to claim 1 having the general formula (3)



(3)

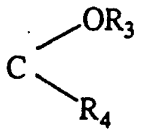
wherein:
X is O or S;
and R_1, R_2, R_5, R_6 and R_9 are as defined in claim 1.

4. A compound according to claim 1 being:

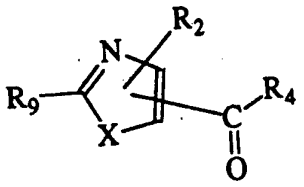
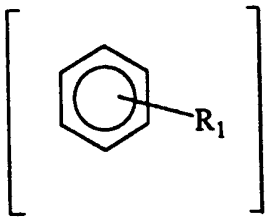
1-(4-methyl-5-oxazolyl)-1-phenylethanol;
1-(4-methyl-5-thiazolyl)-1-phenylethanol;
1-(4-methoxyphenyl)-1-(2,4-dimethyl-5-thiazolyl)ethanol;
1-(4-methyl-5-thiazolyl)-1-phenyl-2,2,2-trifluoroethanol;
1-(2,4-dimethyl-5-oxazolyl)-1-phenylethanol;
1-(4-methyl-5-thiazolyl)-1-phenylethene;

or pharmaceutically acceptable acid addition salts or solvates thereof.

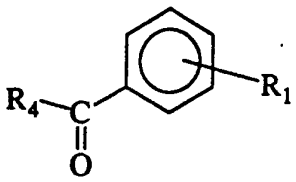
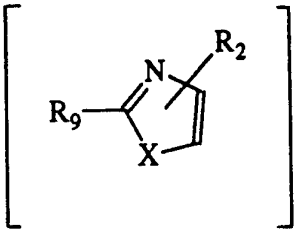
5. A process for preparing a compound according to claim 1 by

(I) in the case where A is 

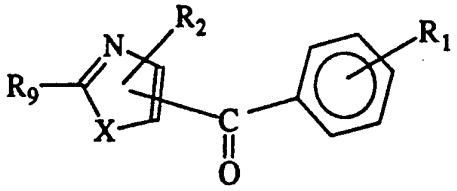
(a) reacting a compound of general formula (4) with an organometallic derivative of general formula (5)

 (4)  M (5)

or (b) reacting a compound of general formula (6) with an organometallic derivative of general formula (7)

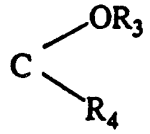
 (6)  M (7)

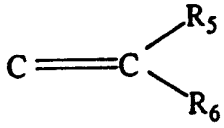
or (c) reacting a compound of general formula (8) with an organometallic derivative of general formula R_4M

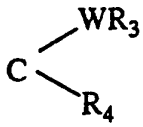
 (8)

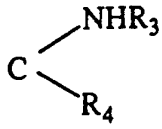
and quenching the reaction mixture with a proton source (R_3 is H) or an alkylating (R_3 is lower alkyl) or acylating (R_3 is lower acyl) reagent;

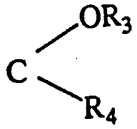
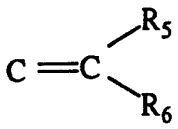
or (d) reacting a compound of general formula (8) with a silyl derivative of general formula R_4SiMe_3.

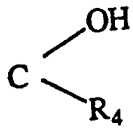
(II) in the case where R_3 is lower alkyl or lower acyl the compound wherein A is  and R_3 is H may be first obtained as above and then converted into the compound wherein R_3 is lower alkyl or lower acyl;

(III) in the case where A is  by

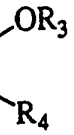
(a) elimination of HWR_3 from a compound of formula (1) wherein A is  or (b) by using a compound of general formula (8) as the substrate for a standard alkene forming reaction; or

(IV) in the case where A is  by

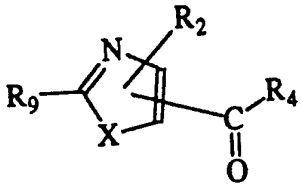
(a) using a compound of general formula (1) wherein A is  or  as the substrate for a Ritter reaction,

or (b) using a compound of general formula (1) wherein A is  as the substrate for a Mitsunobu-type

reaction,

or (c) reacting a compound of general formula (1) wherein A is  with trimethylsilylazide and a Lewis acid, and then reducing the resultant azide.

6. A compound of general formula (4)



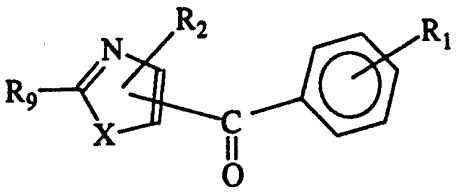
(4)

wherein X is O, S or Se;
R_4 is C_2 to C_6 alkyl;
R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;
R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8, where R_7 and R_8 independently are H, lower alkyl or lower acyl;

with the proviso that the following four compounds are excluded:

ethyl 4-thiazolyl ketone;
tert-butyl 5-thiazolyl ketone;
tert-butyl 5-oxazolyl ketone;
tert-butyl 4-tert-butyl-2-methyl-5-oxazolyl ketone.

7. A compound of general formula (8)



(8)

wherein X is O, S or Se;

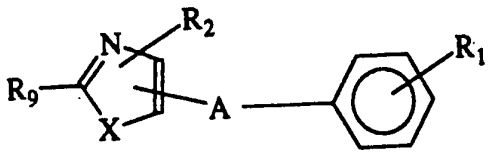
R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8, where R_7 and R_8 independently are H, lower alkyl or lower acyl;

with the provisos that when R_2 and R_9 are both H, then R_1 is not H or 4-Br; and that when R_9 is H and R_2 is CH_3, then R_1 is not H or 4-OMe.

8. A pharmaceutical formulation containing a compound having the general formula (1)



(1)

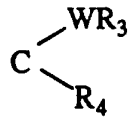
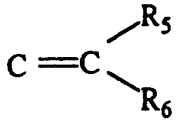
wherein:

X is O, S, Se, or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

and A is  or 

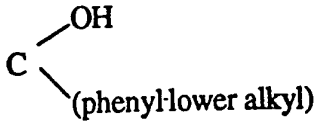
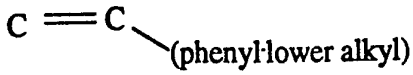
wherein W is O, S, NH or N-lower alkyl;

R_3 is H, lower alkyl or lower acyl;

R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;

R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

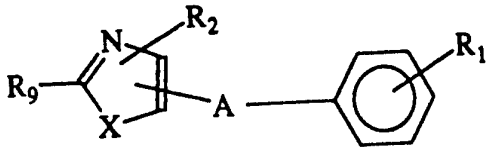
with the proviso that when X is N-H or N-(aryl-methyl), then A is neither

 or 

geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof,

as active ingredient and a pharmaceutically acceptable carrier.

9. A compound having the general formula (1)

 (1)

wherein:

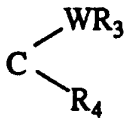
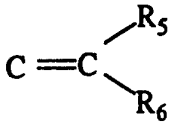
X is O, S, Se, or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower

acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

and A is  or 

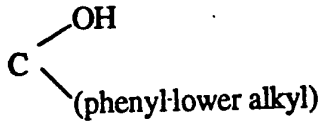
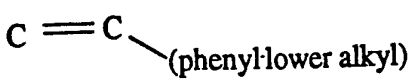
wherein W is O, S, NH or N-lower alkyl;

R_3 is H, lower alkyl or lower acyl;

R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;

R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

with the proviso that when X is N-H or N-(aryl-methyl), then A is neither

 or 

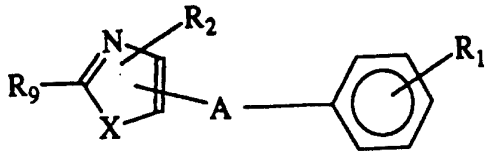
geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof

for use in therapy.

10. A compound as defined in claim 9 for use as an agent in the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction.

11. A compound as defined in claim 10 for the treatment of stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia; multi-infarct dementia; AIDS dementia; neurodegenerative diseases; brain dysfunction in connection with surgery; and CNS dysfunctions as a result of exposure to neurotoxins or radiation.

12. The use of a compound having the general formula (1)



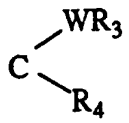
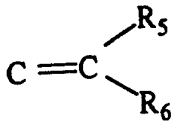
(1)

wherein:
X is O, S, Se, or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

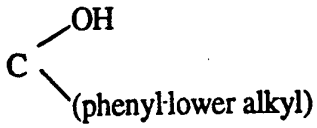
R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

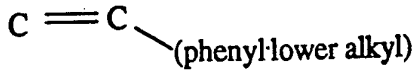
and A is  or 

wherein W is O, S, NH or N-lower alkyl;
R_3 is H, lower alkyl or lower acyl;
R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;
R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

with the proviso that when X is N-H or N-(aryl-methyl), then A is neither



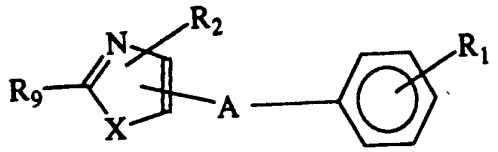
or



geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof for the manufacture of a medicament for the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction.

13. The use according to claim 12 for the manufacture of a medicament for the treatment of stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia; multi-infarct dementia; AIDS dementia; neurodegenerative diseases; brain dysfunction in connection with surgery; and CNS dysfunctions as a result of exposure to neurotoxins or radiation.

14. A method for the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction by administering to a host in need of such treatment a sufficient amount of a compound having the general formula (1)



(1)

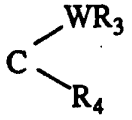
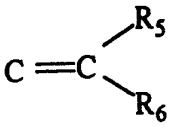
wherein:

X is O, S, Se, or NR_2;

R_1 is one or more groups selected from H, lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8 where R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_2 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_9 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, CF_3 or NR_7R_8;

and A is  or 

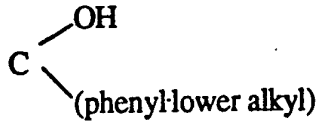
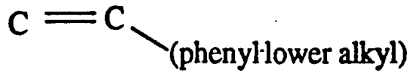
wherein W is O, S, NH or N-lower alkyl;

R_3 is H, lower alkyl or lower acyl;

R_4 is lower alkyl, aryl-lower alkyl or lower perfluoroalkyl;

R_5 and R_6 independently are H, lower alkyl, or aryl-lower alkyl;

with the proviso that when X is N-H or N-(aryl-methyl), then A is neither

 or 

geometric and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00664

A. CLASSIFICATION OF SUBJECT MATTER

IPC : C07D 263/30, C07D 277/20, C07D 233/54
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 : C07D

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

SE,DK,FI,NO classes as above

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

CA, REG, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0477141 (CIBA-GEIGY AG), 25 March 1992 (25.03.92) --	1-13
A	J. Org. Chem., Volume 53, 1988, Alessandro Dondoni et al, "Synthesis of (Trimethylsilyl) thiazoles and Reactions with Carbonyl Compounds. Selectivity Aspects and Synthetic Utility1", page 1748 - page 1761, see table 1, page 1753 -- --------	7

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"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

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 1994	17 -10- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gomez Lagerlöf Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/08/94

International application No.
PCT/SE 94/00664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0477141	25/03/92	AU-A- 8388791	26/03/92
		CA-A- 2051479	19/03/92
		JP-A- 4247075	03/09/92
		NZ-A- 239809	25/03/94
		US-A- 5246952	21/09/93