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J 1227-1

Novel (1-Phenyl-1-heterocyclyl)methanol and (1-Phenyl-1-heterocyclyl)methylamine Derivatives

5 **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
10 use of said compounds.

Background of the Invention

There exists a large group of acute and chronic neuropsychiatric disorders for which safe and clinically
15 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,
20 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.

25 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
30 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.

35 Anticonvulsant agents are widely used, particularly for the treatment of various types of epilepsy. In general, the mechanism of action of such agents is poorly

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understood and there remains a genuine need for the development of new safe and effective anticonvulsants.

5 In a paper (J. Org. Chem., 1957, 22, 559-561) on the synthesis of heterocyclic aminoethers related to the antihistamine diphenhydramine, the compounds 1-(4-methyl-5-thiazolyl)-1-phenylmethanol and 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol are described as intermediates.

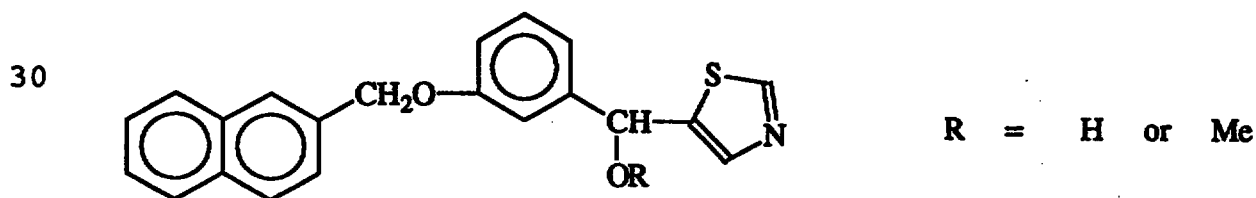
10 In J. Org. Chem., 1988, 53, 1748-1761, 1-(5-thiazolyl)-1-phenylmethanol is disclosed.

15 In J. Org. Chem., 1991, 56, 449-452, 1-(4-oxazolyl)-1-phenylmethanol is described.

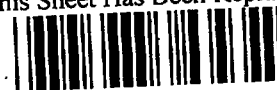
20 In J. Med. Chem., 1984, 27, 1245-1253, 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol is disclosed as an intermediate in the synthesis of certain heterocyclic analogues of chlorcyclizine with hypolipidemic activity.

25 No pharmacological activity is ascribed to any of the above compounds. These five compounds are deleted from the scope of the present invention by a disclaimer in claim 1.

In patent application EP 351 194, the compounds;



35 are disclosed. The substituent 2-naphthylmethoxy is not included within the scope of R_6 of the present invention.



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 as neuroprotective agents, as anticonvulsant agents and/or as sedative-hypnotics.

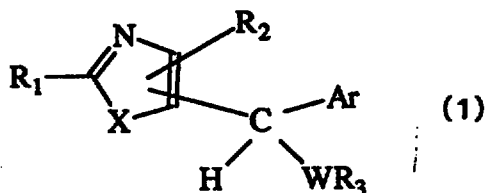
Neuroprotective agents are useful in the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal 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 amyotrophic 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.

Anticonvulsant agents are useful in the clinic for the treatment of different types of convulsive states, such as, for example, epilepsy, status epilepticus, pre-eclampsia and delirium tremens. This ability is manifested, for example, by the ability of these compounds to inhibit seizures induced by various agents such as NMDLA.

The present invention relates to a compound having the



general formula (1)



10 wherein:

X is O, S or Se;

15 R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3 ;

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

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

R_3 is H, lower alkyl or lower acyl;

25 Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6 ;

30 R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3 , OH, NO_2 or NR_4R_5 , wherein R_4 and R_5 independently are H, lower alkyl or lower acyl;

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

and with the proviso that the following five compounds



are excluded:

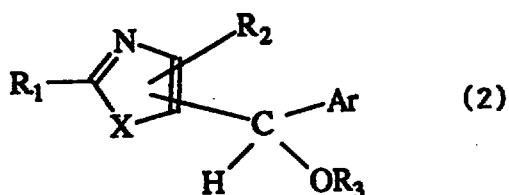
- 1-(4-methyl-5-thiazolyl)-1-phenylmethanol;
 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol;
 5 1-(5-thiazolyl)-1-phenylmethanol;
 1-(4-oxazolyl)-1-phenylmethanol;
 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol.

10 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.

15

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

20



25

wherein:

X is O or S;

and R₁, R₂, R₃ and Ar are as previously defined above.

30

Analogous compounds wherein X is Se, for example, 1-(3-furyl)-1-(4-methyl-5-selenazolyl)methanol and 1-(2-fluorophenyl)-1-(4-methyl-5-selenazolyl)methanol, are specifically included within the scope of the invention.

35

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.

5 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
10 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 acyl"
15 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"
20 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-
25 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"
30 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
35 ethoxyethyl.

Unless otherwise stated or indicated, the term "aryl-



lower alkyl" denotes a lower alkyl group as defined above substituted by a phenyl, naphthyl, furyl, thienyl, pyrrolyl or pyridyl group, itself optionally further substituted. Examples of said aryl-lower alkyl include
5 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:

10

1-(3-furyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(2-furyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(4-methyl-5-thiazolyl)-1-(2-thienyl)methanol;
1-(4-methyl-5-thiazolyl)-1-(3-thienyl)methanol;
15 1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(3-chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(4-methyl-5-oxazolyl)-1-phenylmethanol;
1-(4-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
1-(2-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
20 1-(3-aminophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(3-dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol;

25

and pharmaceutically acceptable acid addition salts or solvates thereof.

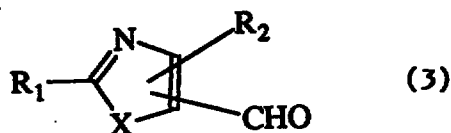
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The present invention also relates to processes for preparing the compound having formula (1). Throughout the following general description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, 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
35 for using such protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Greene, Wiley-Interscience, New York, 1981.

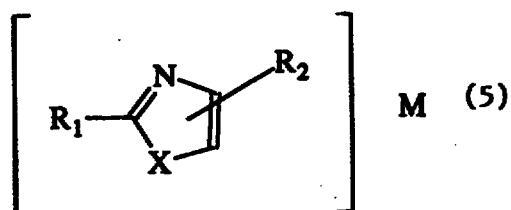


Said compound wherein W is O may be prepared by

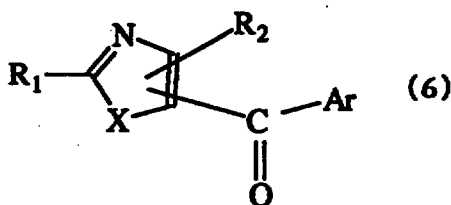
(a) reacting a compound of general formula (3) with an organometallic derivative ArM



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



or (c) by reduction of a compound of general formula (6)



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. Alternatively, the compound of formula (1) wherein W is O 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.

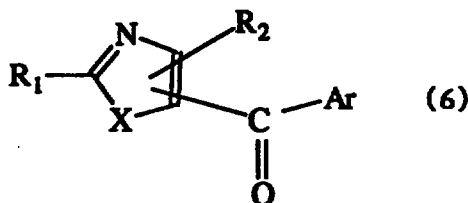


The processes (a) or (b) can be achieved for example, by reacting together an aldehyde of structure (3) or (4) with a preformed organometallic derivative ArM or (5) respectively in a suitable anhydrous solvent such as diethylether, tetrahydrofuran or hexane or mixtures thereof. Said reaction should be conducted at a suitable temperature, normally between -100°C and $+50^{\circ}\text{C}$ and preferably under an inert atmosphere, normally nitrogen or argon. In a specific variation, a solution of the aldehyde of structure (3) or (4) in anhydrous diethylether or tetrahydrofuran is added dropwise to the organometallic derivative ArM or (5) 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 WR_3 is OH may then be isolated and purified and characterised using standard techniques.

Aldehydes of general formula (3) or (4) and ketones of general formula (6) 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 formula (6), namely:

a compound of general formula (6)



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wherein R_1 , R_2 , X and Ar are as defined above with the provisos that when Ar represents phenyl, then R_1 , R_2 and R_6 are not all hydrogen; and that the following three
5 compounds are excluded:

4-bromophenyl 5-thiazolyl ketone;
4-methyl-5-thiazolyl phenyl ketone;
4-methoxyphenyl 4-methyl-5-thiazolyl ketone.

10

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

Compounds of formula (1) wherein W is NH or N-lower alkyl may be prepared, for example,

20

(a) by reductive amination of a ketone of general formula (6),

or (b) by conversion of a ketone of general formula (6)
25 to an oxime derivative followed by reduction,

or (c) by conversion of a compound of general formula (1) wherein WR_3 is OH into the corresponding azide or phthalimide using, for example, the Mitsunobu reaction,
30 and then reduction or hydrolysis respectively.

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
35 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;

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

10 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).

15 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.

Pharmacology

20 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.

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

30 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
35 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.

The anticonvulsant properties of the compounds of formula (1) are exemplified by their ability to protect mice from NMDLA induced seizures. Male TO mice (18-30g) were used.

Groups of eight mice were injected with NMDLA (300 mg/kg i.p.) and the number of mice demonstrating tonic convulsions within the following 15 min period were recorded. Drugs were administered 15 min before the NMDLA, and data are expressed as the dose required to decrease the incidence of tonic convulsions by 50% (ED₅₀).

The sedative properties of the compounds of formula (1) are exemplified by their ability to inhibit the locomotor activity of mice.

The test drug was administered to mice and starting 20 min later locomotor activity was recorded for a 10 min period. Activity was monitored using an infra-red light beam interruption system in cages measuring 40cm x 40cm. Data are expressed as the dose required to reduce locomotor activity by 50% (ED₅₀).

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; or as suppositories for rectal administration; or as 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 polyvinylpyrrolidone, 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 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 skilled 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 materials for all Examples were purchased commercially except as follows:

4-methyl-5-thiazolecarbaldehyde (J. Amer. Chem. Soc., 1982, 104, 4934-43);
2-furyllithium (J. Org. Chem., 1962, 27, 1216).

EXAMPLE 1

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methanol

4-Methylthiazole (3g) in dry diethyl ether was added dropwise to a stirred solution of n-butyllithium (1.6M in hexanes, 21ml) in diethyl ether (20ml) at -78°C under an atmosphere of dry nitrogen. After 30 minutes, trimethylsilylchloride (3.9ml) was added and the mixture was then allowed to warm to 0°C. The mixture was then cooled to -78°C and further n-butyllithium (21ml) was added. The mixture was warmed to 0°C. After 30 minutes the mixture was again cooled to -78°C and 3-furaldehyde (5g) in diethyl ether (10ml) was added. The mixture was allowed to warm to room temperature and after 30 minutes saturated aqueous sodium hydrogen carbonate was added. The reaction mixture was extracted with diethyl ether in the usual manner to give the crude product which was then purified by flash chromatography on silica gel to give the title compound. M.p. 44-46°C.

¹³C Nmr (CDCl₃) 14.8, 62.4, 108.8, 128.3, 135.7, 139.4, 143.5, 148.1 and 150.9 ppm.



Found: C, 55.0; H, 4.7; N, 7.0. $C_9H_9NO_2S$
requires C, 55.4; H, 4.6; N, 7.2%

- 5 Following the general method of Example 1 and using the appropriate aldehyde, the compounds of Examples 2 to 23 were prepared.

EXAMPLE 2

- 10 1-(4-Methyl-5-thiazolyl)-1-(4-pyridyl)methanol
M.p. 131-132°C.

EXAMPLE 3

- 15 1-(4-Methyl-5-thiazolyl)-1-(3-pyridyl)methanol
The title compound was converted into the hydrochloride salt using hydrogen chloride in ethanol and diethyl ether. M.p. 180-184°C (dec.).

EXAMPLE 4

- 20 1-(4-Methyl-5-thiazolyl)-1-(2-naphthyl)methanol
The title compound was characterised as the hydrochloride salt. M.p. 176-180°C (dec.).

EXAMPLE 5

- 25 1-(2-Furyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 50-51°C.

1H Nmr ($CDCl_3$) 2.35 (3H, s), 6.08 (1H, s), 6.19 (1H, dt),
6.33 (1H, dq), 7.39 (1H, q) and 8.6 (1H, s) ppm.

30

Found: C, 55.1; H, 4.8; N, 6.8. $C_9H_9NO_2S$
requires C, 55.4; H, 4.6; N, 7.2%

EXAMPLE 6

- 35 1-(4-Methyl-5-thiazolyl)-1-(2-thienyl)methanol
M.p. 75-77°C.



¹H Nmr (CDCl₃) 2.4 (3H, s), 3.46 (1H, d), 6.34 (1H, d), 6.95 (2H, m), 7.29 (1H, m) and 8.6 (1H, s) ppm.

EXAMPLE 7

5 1-(4-Methyl-5-thiazolyl)-1-(5-nitro-2-furyl)methanol
M.p. 127-129°C.

EXAMPLE 8

10 1-(5-Methyl-2-furyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 123-125°C.

EXAMPLE 9

15 1-(1-Methyl-2-pyrrolyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 142-147°C (dec.).

EXAMPLE 10

20 1-(4-Methyl-5-thiazolyl)-1-(3-thienyl)methanol
¹H Nmr (CDCl₃) 2.43 (3H, s), 6.2 (1H, s), 7.06, 7.27 and 7.34 (each 1H, m) and 8.62 (1H, s) ppm.

EXAMPLE 11

25 1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 100-101°C.
¹H Nmr (CDCl₃) 2.45 (3H, s), 2.8 (1H, d), 6.42 (1H, d), 7.04, 7.19, 7.30 and 7.56 (each 1H, m) and 8.62 (1H, s) ppm.

30 Found: C, 58.95; H, 4.6; N, 6.0. C₁₁H₁₀FNOS requires C, 59.2; H, 4.5; N, 6.3%

EXAMPLE 12

35 1-(3-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 74-75.5°C.

Found: C, 59.2; H, 4.4; N, 6.0. C₁₁H₁₀FNOS requires C, 59.2; H, 4.5; N, 6.3%



EXAMPLE 13

1-(4-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 98.5-100°C.

5

EXAMPLE 14

1-(3-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 97-98°C.

10

^1H Nmr (CDCl_3) 2.41 (3H, s), 3.37 (1H, d), 6.07 (1H, d),
7.26 (3H, m), 7.41 (1H, m) and 8.59 (1H, s) ppm.

Found: C, 55.2; H, 4.25; N, 5.65. $\text{C}_{11}\text{H}_{10}\text{ClNOS}$ requires
C, 55.1; H, 4.2; N, 5.8%

15

EXAMPLE 15

1-(3-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 87-88°C.

20

Found: C, 60.0; H, 5.7; N, 5.75. $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$. 0.25 H_2O
requires C, 60.1; H, 5.7; N, 5.8%

25

EXAMPLE 16

1-(2-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 121-122°C.

30

EXAMPLE 17

1-(2-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 122-123°C.

35

Found: C, 55.05; H, 4.3; N, 5.8. $\text{C}_{11}\text{H}_{10}\text{ClNOS}$ requires C,
55.1; H, 4.2; N, 5.8%

EXAMPLE 18

1-(2-Methylphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 141.5-143°C.

Found: C, 65.7; H, 6.2; N, 6.25. $\text{C}_{12}\text{H}_{13}\text{NOS}$ requires C,





65.7; H, 6.0; N, 6.4%

EXAMPLE 19

1-(3-Methylphenyl)-1-(4-methyl-5-thiazolyl)methanol

5 M.p. 103-104.5°C.

Found: C, 65.8; H, 6.25; N, 6.4. $C_{12}H_{13}NOS$ requires C, 65.7; H, 6.0; N, 6.4%

10

EXAMPLE 20

1-(4-Methyl-5-thiazolyl)-1-(3-nitrophenyl)methanol

M.p. 119.5-121°C.

EXAMPLE 21

15

1-(2,6-Dimethoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 125-126°C.

EXAMPLE 22

20

1-(4-Methyl-5-thiazolyl)-1-(1-naphthyl)methanol

M.p. 115.5-116.5°C.

EXAMPLE 23

25

1-(4-Methyl-5-thiazolyl)-1-(3-trifluoro-methylphenyl)-methanol

M.p. 73.5-75°C.

Found: C, 52.6; H, 3.5; N, 5.0. $C_{12}H_{10}F_3NOS$ requires C, 52.7; H, 3.7; N, 5.1%

30

EXAMPLE 24

1-(4-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol

35

4-Methylthiazole was treated sequentially with n-butyllithium, trimethylsilylchloride, n-butyllithium and trimethylsilylchloride according to the method of J.Org.Chem., 1988, 53, 1748-61. Column chromatography on



silica gel then gave 4-methyl-5-trimethylsilylthiazole.

4-Methyl-5-trimethylsilylthiazole (3g), 4-chloro-benzaldehyde (4.9g) and caesium fluoride (2.7g) in dry tetrahydrofuran (150ml) were heated under reflux for 30 hours. The mixture was cooled, evaporated to dryness and the residue thus obtained was purified by flash chromatography to afford the title compound. M.p. 133.5-134.5°C.

Hydrochloride, m.p. 167.5-172.5°C.

Following the general method of Example 24 and using the appropriate aldehyde, the compounds of Examples 25 and 26 were prepared.

EXAMPLE 25

1-(2,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 163-164°C.

EXAMPLE 26

1-(3,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 143-144°C.

Hydrochloride, m.p. 180-188°C (dec.).
Methanesulphonate, m.p. 147-148°C.

EXAMPLE 27

1-(3,4-Dichlorophenyl)-1-(5-thiazolyl)methanol
2-Bromothiazole (5g) in dry diethyl ether (20ml) was added dropwise to a stirred solution of n-butyllithium (1.6M in hexanes, 21ml) in diethyl ether (20ml) at -70°C under an atmosphere of dry nitrogen. After 30 minutes, trimethylsilylchloride (3.9ml) was added and the mixture was allowed to warm to 0°C. The mixture was then cooled to -70°C and further n-butyllithium (21ml) was added. The mixture was warmed to 0°C and after 30 minutes was

cooled again to -70°C and 3,4-dichlorobenzaldehyde (5.8g) in diethyl ether (40ml) was added. The mixture was then allowed to warm to room temperature and after 30 minutes saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with dichloromethane and the material thus obtained was purified by chromatography on silica gel to give the title compound. The hydrochloride salt was prepared. M.p. $167-170^{\circ}\text{C}$.

EXAMPLE 28

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

4-Methyl-5-oxazolecarbaldehyde (600mg) in dry tetrahydrofuran (10ml) was added dropwise to a stirred solution of phenyllithium (2.0M solution in cyclohexane and diethyl ether, 2.8ml) in tetrahydrofuran (20ml) at -70°C under an atmosphere of dry nitrogen. After 1 hour the mixture was allowed to warm to room temperature. After a further 1 hour saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The product was purified by flash chromatography to yield the title compound. M.p. $79-81^{\circ}\text{C}$.

^1H Nmr (CDCl_3) 2.14 (3H, s), 5.94 (1H, s), 7.3-7.5 (5H, m) and 7.75 (1H, s) ppm.

EXAMPLE 29

1-(4-Fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol

4-Methyl-5-oxazolecarbaldehyde (770mg) in dry tetrahydrofuran (15ml) was added dropwise to a stirred solution of 4-fluorophenyl magnesium bromide (1M solution in tetrahydrofuran, 7.3ml) in tetrahydrofuran (30ml) at -70°C under an atmosphere of dry nitrogen. After 1 hour the mixture was allowed to warm to room temperature and was then poured into saturated aqueous sodium hydrogen carbonate. Extraction with ethyl acetate followed by flash chromatography gave the title compound.



M.p. 102.5-104°C.

¹H Nmr (CDCl₃) 2.09 (3H, s), 3.68 (1H, br), 5.88 (1H, s), 7.04 (2H, m), 7.38 (2H, m) and 7.66 (1H, s) ppm.

5

Following the general method of Example 29 and using the appropriate Grignard reagent, the compounds of Examples 30 and 31 were prepared.

10

EXAMPLE 30

1-(4-Methyl-5-oxazolyl)-1-(2-methylphenyl)methanol

M.p. 122-123°C.

EXAMPLE 31

15

1-(4-Methyl-5-oxazolyl)-1-(4-methylphenyl)methanol

M.p. 125-127°C.

EXAMPLE 32

20

1-(4-Methyl-5-oxazolyl)-1-(3-methylphenyl)methanol

25

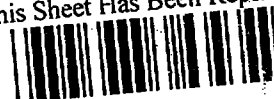
n-Butyllithium (2.5 solution in hexanes, 3.9ml) was added dropwise to a stirred solution of 3-bromotoluene (1.1ml) in dry tetrahydrofuran (20ml) at -70°C under an atmosphere of dry nitrogen. After 20 minutes, 4-methyl-5-oxazolecarbaldehyde (1.15g) in tetrahydrofuran (10ml) was added. After 1 hour the mixture was allowed to warm to room temperature and was then heated under reflux for 1 hour. The cooled solution was poured into saturated aqueous sodium hydrogen carbonate. Extraction with ethyl acetate and flash chromatography then gave the title compound. M.p. 76.5-77.5°C.

30

35

Following the general method of Example 32 and using the appropriate aryl bromide or iodide, the compounds of Examples 33 to 36 were prepared.

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EXAMPLE 33**1-(2-Fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol**

¹H Nmr (CDCl₃) 2.14 (3H, s), 3.02 (1H, br s), 6.22 (1H, s), 6.98 - 7.37 (3H, m) and 7.67 (2H, m) ppm.

5

EXAMPLE 34**1-(2,4-Difluorophenyl)-1-(4-methyl-5-oxazolyl)methanol**

M.p. 116-117.5°C.

10

EXAMPLE 35**1-(4-Methyl-5-oxazolyl)-1-(2-trifluoromethyl-phenyl)-methanol**

M.p. 105.5-107.5°C.

15

Found: C, 56.2; H, 3.7; N, 5.4. C₁₂H₁₀F₃NO₂ requires C, 56.0; H, 3.9; N, 5.45%

EXAMPLE 36

20

1-(2-Chlorophenyl)-1-(4-methyl-5-oxazolyl)methanol

M.p. 127-128°C.

EXAMPLE 37

25

Methyl 1-(4-Methyl-5-thiazolyl)-1-phenylmethyl Ether

Sodium hydride (80% dispersion in mineral oil, 80mg) was added to a stirred solution of 1-(4-methyl-5-thiazolyl)-1-phenyl-methanol (500mg) in dry N,N-dimethylformamide (10ml) at 0°C. After 10 minutes, methyl iodide (0.15ml) was added. The mixture was allowed to warm to room temperature and after a further 30 minutes the mixture was evaporated to dryness. The residue was purified by flash chromatography to give the title compound.

30

35

¹H Nmr (CDCl₃) 2.46 and 3.39 (each 3H, s), 5.52 (1H, s), 7.28 - 7.4 (5H, m) and 8.64 (1H, s) ppm.

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Following the general method of Example 37 and using the appropriate starting materials, the compounds of Example 38 to 43 were prepared.

5

EXAMPLE 38

Methyl 1-(3,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)-methyl Ether

Hydrochloride, m.p. 170-176°C (dec.).

10

EXAMPLE 39

Methyl 1-(2,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)-methyl Ether

M.p. 55-56°C.

15

EXAMPLE 40

Ethyl 1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methyl Ether

¹³C Nmr (CDCl₃) 15.1, 15.3, 64.3, 69.6, 109.0, 126.4, 133.1, 139.9, 143.6, 149.5 and 151.3 ppm.

20

EXAMPLE 41

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether

¹H Nmr (CDCl₃) 2.45 and 3.36 (each 3H, s), 5.52 (1H, s), 6.34 (1H, m), 7.38 (2H, m) and 8.68 (1H, s) ppm.

25

EXAMPLE 42

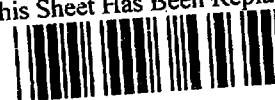
1-(2-Furyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether

30

¹H Nmr (CDCl₃) 2.44 and 3.39 (each 3H, s), 5.57 (1H, s), 6.27 and 6.32 (each 1H, m), 7.41 (1H, m) and 8.7 (1H, s) ppm.

35

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EXAMPLE 43**1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether**

5 ^1H Nmr (CDCl_3) 2.48 and 3.39 (each 3H, s), 5.86 (1H, s),
6.98 - 7.35 (3H, m), 7.52 (1H, m) and 8.65 (1H, s) ppm.

EXAMPLE 44**1-(4-Methyl-5-thiazolyl)-1-phenylmethyl Acetate**

10 Acetyl chloride (0.6ml) was added to a solution of 1-(4-methyl-5-thiazolyl)-1-phenylmethanol (800mg) and pyridine (0.5ml) in dichloromethane (30ml) at 0°C under an atmosphere of dry nitrogen. The mixture was allowed to warm room temperature and was then stirred overnight.
15 Evaporation and purification of the residue by flash chromatography gave the title compound.

^1H Nmr (CDCl_3) 2.15 and 2.51 (each 3H, s), 7.16 (1H, s),
7.35 (5H, m) and 8.66 (1H, s) ppm.

20

EXAMPLE 45**1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methyl Acetate**

Starting with 1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol and using the method of Example 44,
25 the title compound was prepared.
M.p. $53-56^\circ\text{C}$.

EXAMPLE 46**1-(3-Aminophenyl)-1-(4-methyl-5-thiazolyl)methanol**

30 1-(4-Methyl-5-thiazolyl)-1-(3-nitrophenyl)methanol (2g) and 10% palladium on charcoal (200mg) in ethanol (60ml) were shaken overnight under an atmosphere of hydrogen. The mixture was filtered and the filtrate was evaporated to dryness. The residue was converted into the
35 hydrochloride salt, recrystallised and then reconverted into the title compound.

M.p. $137-138^\circ\text{C}$.



^1H Nmr (CDCl_3) 2.38 (3H, s), 2.44 (1H, d), 3.65 (2H, br), 5.95 (1H, d), 6.56 (1H, m), 6.7 (2H, m) 7.08 (1H, m) and 8.57 (1H, s) ppm.

5 Found: C, 59.9; H, 5.55; N, 12.4. $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}$ requires C, 60.0; H, 5.5; N, 12.7%

EXAMPLE 47

10 1-(3-Dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol

The title compound was prepared from 4-methyl-5-thiazolecarbaldehyde and 3-bromo-N,N-dimethylaniline using the method of Example 32. M.p. 135-138°C.

15 ^1H Nmr (CDCl_3) 2.44 (3H, s), 2.75 (1H, s), 2.96 (6H, s), 6.04 (1H, s), 6.65-6.8 (3H, m), 7.23 (1H, t) and 8.60 (1H, s) ppm.

EXAMPLE 48

20 1-(3-Hydroxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

1-(3-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol (1g) in dry dichloromethane (10ml) was added dropwise to boron tribromide (1M solution in dichloromethane, 25ml) at 0°C. The mixture was allowed to warm to room temperature and
25 was stirred for 15 minutes. The mixture was poured onto ice (40g) and 0.88 ammonia (10ml). The precipitate was filtered off and purified by chromatography to give the title compound. M.p. 181-184°C.

30

EXAMPLE 49

1-(2-Furyl)-1-(4-methyl-5-oxazolyl)methanol

The title compound was prepared from 4-methyl-5-oxazolecarbaldehyde and 2-furyllithium using the method of Example 28. M.p. 52-54°C.

35

^1H Nmr (CDCl_3) 2.16 (3H), 2.7 (1H, br), 5.92, 6.32, 6.40, 7.44 and 7.80 (each 1H).

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Found: C, 60.0; H, 5.1; N, 7.9. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%

EXAMPLE 50

5 Resolution of 1-(4-Methyl-5-thiazolyl)-1-phenylmethanol
1-(4-Methyl-5-thiazolyl)-1-phenylmethyl acetate suspended
in pH 7.5 buffer at 37°C was treated with pig liver
esterase. The resulting product was subjected to flash
10 chromatography to give, after crystallisation, 1-(4-
methyl-5-thiazolyl)-1-phenylmethanol which was shown by
chiral HPLC to be greater than 98% one enantiomer. The 1-
(4-methyl-5-thiazolyl)-1-phenylmethyl acetate that was
also obtained from the flash chromatography was subjected
to base hydrolysis and the product recrystallised to give
15 the other enantiomer of the title compound.

EXAMPLE 51

Resolution of 1-(2-Fluorophenyl)-1-(4-methyl-5-
thiazolyl)methanol

20 The title compound was resolved by preparative HPLC on a
Chiralcel OD column using 2-propanol in hexane as
solvent. The enantiomers showed $[\alpha]_D^{20} + 61^\circ$ and -60°
respectively.

EXAMPLE 52

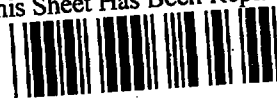
25 4-Methyl-5-oxazolecarbaldehyde

4-Methyl-5-oxazolecarbonyl chloride (Indian J. Chem.,
Sect. B, 1985, 24B, 535-8) in dry tetrahydrofuran was
treated at -78°C with lithium tri-tert-
30 butoxyaluminumhydride (1M solution in tetrahydrofuran).
Work up in the usual fashion gave the title compound.

^1H Nmr (CDCl_3) 2.55 (3H, s), 8.03 (1H, s) and 9.92 (1H,
s) ppm.

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**EXAMPLE 53****1-Azido-1-(3-furyl)-1-(4-methyl-5-thiazolyl)methane**

Borontrifluoride diethyletherate (8 mmoles) was added to a mixture of the product from Example 1 (4 mmoles) and trimethylsilylazide (8 mmoles) in dry benzene (4ml). The mixture was stirred at room temperature for 4 days and then diluted with ethyl acetate (50ml). After washing with aqueous sodium hydrogen carbonate solution and water, the organic phase was separated and dried. Evaporation gave the title compound as an oil.

^{13}C Nmr (CDCl_3) 15.1, 53.9, 108.8, 123.9, 129.9, 140.0, 143.9, 150.3 and 151.4 ppm.

EXAMPLE 54**1-Azido-1-(4-methyl-5-thiazolyl)-1-phenylmethane**

Starting with 1-(4-methyl-5-thiazolyl)-1-phenylmethanol and using the general method of Example 53, the title compound was obtained.

^{13}C Nmr (CDCl_3) 15.4, 61.4, 126.6, 128.5, 128.8, 131.0, 138.5, 150.1 and 151.6 ppm.

EXAMPLE 55**1-(4-Methyl-5-thiazolyl)-1-(N-phthalimido)-1-phenylmethane Hydrochloride**

1-(4-Methyl-5-thiazolyl)-1-phenylmethanol (30 mmoles), triphenylphosphine (40 mmoles), phthalimide (40 mmoles) and diethyl azodicarboxylate (40 mmoles) in dry tetrahydrofuran (15ml) were stirred at room temperature for 3 days. The mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel. The material thus obtained was converted into the hydrochloride salt using the standard procedure. M.p. 194-196°C.

^{13}C Nmr (CDCl_3) 12.6, 49.1, 124.1, 127.0, 129.2, 129.4,



131.2, 134.7, 135.0, 135.8, 144.8, 154.7 and 167.2 ppm.

EXAMPLE 56

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

5 The product from Example 55 (1.3 mmoles) and hydrazine hydrate (1.8 mmoles) were heated under reflux in ethanol (10ml) for 2 hours. The precipitated phthalimide was filtered off and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash
10 chromatography to yield the title compound.

^{13}C Nmr (CDCl_3) 15.4, 53.1, 126.4, 127.5, 128.6, 137.8, 143.9, 147.6 and 150.2 ppm.

15

EXAMPLE 57

N-(1-(4-Methyl-5-thiazolyl)-1-phenylmethyl)acetamide

Acetyl chloride was added to a solution of the product from Example 56 and triethylamine in dry dichloromethane. The mixture was stirred at room temperature overnight and
20 then washed with aqueous sodium hydrogen carbonate solution. The organic phase was separated, dried and evaporated and the residue was purified by flash chromatography to give the title compound.

25

^{13}C Nmr (CDCl_3) 15.3, 22.9, 50.1, 126.7, 128.0, 128.8, 133.5, 140.4, 150.0, 150.2 and 169.0 ppm.

EXAMPLE 58

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methylaniline

The product from Example 53 in ethanol was shaken with 10% palladium-on-charcoal under an atmosphere of hydrogen for 3 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. Flash chromatography
35 of the residue thus obtained gave the title compound.

^{13}C Nmr (CDCl_3) 14.7, 44.9, 108.6, 128.9, 137.0, 138.4,



142.9, 147.2 and 149.7 ppm.

PHARMACY EXAMPLES

5

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

Composition 1 - Tablets

10	Compound of Example 33	10g
	Lactose	94g
	Microcrystalline cellulose	86g
	Polyvinylpyrrolidone	8g
	Magnesium stearate	2g

15

The compound of Example 33, 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.

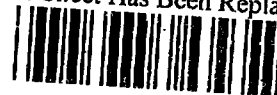
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Composition 2 - Tablets

25	Compound of Example 11	50g
	Lactose	80g
	Microcrystalline cellulose	20g
	Potato starch	40g
	Polyvinylpyrrolidone	8g
30	Magnesium stearate	2g

35

The compound of Example 11, 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 1	100g
5	Pregelatinised starch	98g
	Magnesium stearate	2g

10 The compound of Example 1 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.

15

Composition 4 - Injection Formulation

	Compound of Example 46	0.5 to 10g
	Polyethoxylated castor oil	15g
	Water for injection ad	100g

20

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
25 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
30 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.

35

Composition 5 - Injection Formulation

	Compound of Example 1	0.5 to 10g
	Polyethoxylated castor oil	15g



Propylene glycol		20g
Polyoxyethylene-polyoxypropylene block copolymer (Pluronic F68)		10g
Water for injection	ad	100g

5

10 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.

15

Composition 6 - Injection Formulation

Compound of Example 5		0.5 to 10g
Hydroxypropyl- β -cyclodextrin		10g
Water for injection	ad	100g

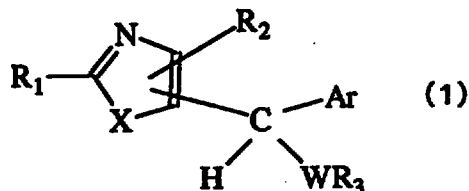
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25 Water for injection is added to a mixture of the compound of the invention and hydroxypropyl- β -cyclodextrin. The mixture is gently stirred until a clear solution is obtained. The solution is filled into bottles which are then sealed and sterilised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



CLAIMS

1. A compound having the general formula (1)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

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

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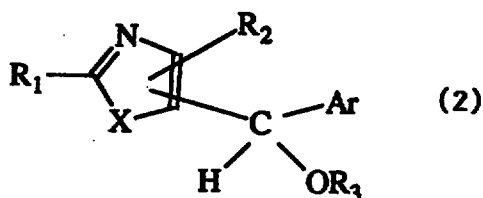




and with the proviso that the following five compounds are excluded:

- 1-(4-methyl-5-thiazolyl)-1-phenylmethanol;
- 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol;
- 1-(5-thiazolyl)-1-phenylmethanol;
- 1-(4-oxazolyl)-1-phenylmethanol;
- 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol.

2. A compound having the general formula (2)



wherein:

X is O or S;

and R₁, R₂, R₃ and Ar are as previously defined in claim 1.

3. A compound according to claim 1 being :

- 1-(3-furyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(2-furyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(4-methyl-5-thiazolyl)-1-(2-thienyl)methanol;
- 1-(4-methyl-5-thiazolyl)-1-(3-thienyl)methanol;
- 1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(3-chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(4-methyl-5-oxazolyl)-1-phenylmethanol;
- 1-(4-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
- 1-(2-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
- 1-(3-aminophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(3-dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol;

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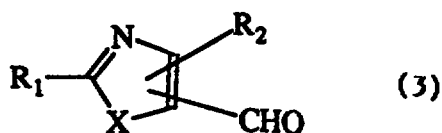


or pharmaceutically acceptable acid addition salts or solvates thereof.

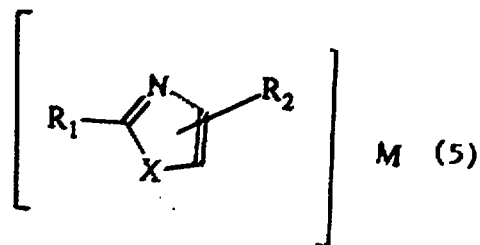
4. A process for preparing a compound according to claim 1 by

(I) in the case where W is O
by

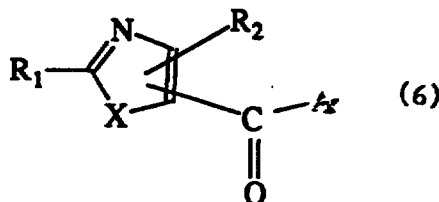
(a) reacting a compound of general formula (3) with an organometallic derivative ArM



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



or (c) by reduction of a compound of general formula (6)



and quenching the reaction mixture with a proton which (R₃ is H) or an alkylating (R₃ is lower alkyl), an acylating (R₃ is lower acyl) reagent;





(II) in the case where R_3 is lower alkyl or lower acyl the compound of formula (1) wherein W is O 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;

5

(III) in the case where W is NH or N-lower alkyl by, for example,

(a) reductive amination of a ketone of general formula (6),

10

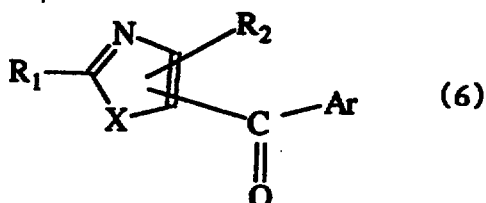
or (b) by conversion of a ketone of general formula (6) to an oxime derivative followed by reduction,

or (c) by conversion of a compound of general formula (1) wherein WR_3 is OH into the corresponding azide or phthalimide using, for example, the Mitsunobu reaction, and then reduction or hydrolysis respectively.

15

5. A compound of general formula (6)

20



25

wherein R_1 , R_2 , X and Ar are as defined in claim 1 with the provisos that when Ar represents phenyl, then R_1 , R_2 and R_6 are not all hydrogen; and that the following three compounds are excluded:

30

4-bromophenyl 5-thiazolyl ketone;

4-methyl-5-thiazolyl phenyl ketone;

35

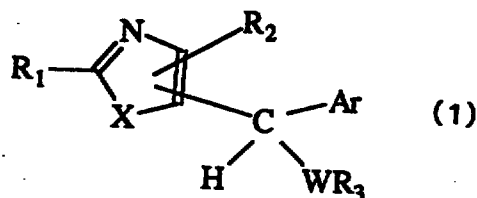
4-methoxyphenyl 4-methyl-5-thiazolyl ketone.

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



10 wherein:

X is O, S or Se;

15 R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

25 Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

30 R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

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

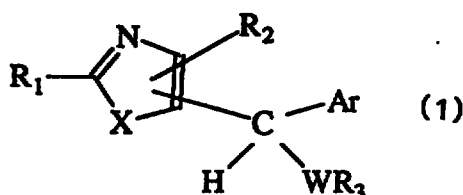
as active ingredient and a pharmaceutically acceptable carrier.

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7. A compound having the general formula (1)



wherein:

X is O, S or Se;

10 R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3 ;

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

15

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

R_3 is H, lower alkyl or lower acyl;

20 Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6 ;

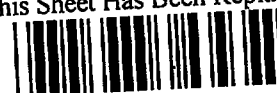
25 R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3 , OH, NO_2 or NR_4R_5 , wherein R_4 and R_5 independently are H, lower alkyl or lower acyl;

30 geometrical 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.

35 8. A compound as defined in claim 7 for use as a neuroprotective agent and/or an anticonvulsant agent and/or a sedative-hypnotic agent.

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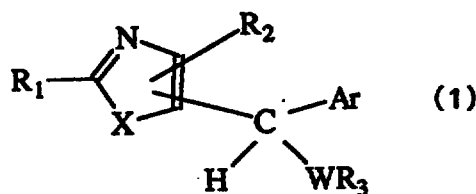


9. A compound as defined in claim 8 for the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction and for the treatment of different types of convulsive states.

10. A compound as defined in claim 9 for the treatment of acute and chronic neuropsychiatric disorders, such as 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.

11. A compound as defined in claim 9 for the treatment of different types of convulsive states, such as epilepsy, status epilepticus, pre-eclampsia and delirium tremens.

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



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

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R_3 is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6 ;

R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3 , OH, NO_2 or NR_4R_5 , wherein R_4 and R_5 independently are H, lower alkyl or lower acyl;

geometrical 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 neurodegenerative disorders and/or convulsive states and/or agitation and sleep disorders.

13. The use according to claim 12 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 and for the treatment of different types of convulsive states.

14. The use according to claim 13 for the manufacture of a medicament for the treatment of acute and chronic neuropsychiatric disorders, such as 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.

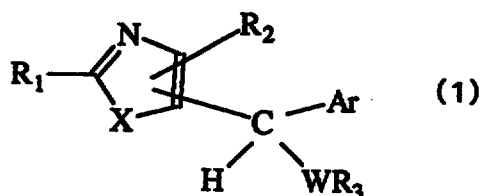
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15. The use according to claim 13 for the manufacture of a medicament for the treatment of different types of convulsive states, such as epilepsy, status epilepticus, pre-eclampsia and delirium tremens.

16. A method for the treatment of neurodegenerative disorders and/or convulsive states and/or agitation and sleep disorders by administering to a host in need of such treatment a sufficient amount of a compound having the general formula (1)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

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

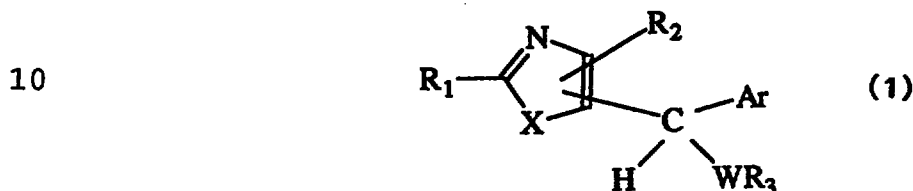
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ABSTRACT

5 The present invention relates to novel heterocyclic compounds having the general formula (1)



15 wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

20 R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

25 R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

30 R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

35 geometrical 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
40 formulations containing said compounds and the medicinal use of said compounds.

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☐	Drawing(s) : paged to paged	
☒	Abstract : paged ...43. to paged ...55.	
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Novel (1-Phenyl-1-heterocyclyl)methanol and (1-Phenyl-1-heterocyclyl)methylamine Derivatives

8-80-03030

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Novel (1-Phenyl-1-heterocyclyl)methanol and (1-Phenyl-1-heterocyclyl)methylamine Derivatives

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.

Anticonvulsant agents are widely used, particularly for the treatment of various types of epilepsy. In general, the mechanism of action of such agents is poorly

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understood and there remains a genuine need for the development of new safe and effective anticonvulsants.

In a paper (J. Org. Chem., 1957, 22, 559-561) on the synthesis of heterocyclic aminoethers related to the antihistamine diphenhydramine, the compounds 1-(4-methyl-5-thiazolyl)-1-phenylmethanol and 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol are described as intermediates.

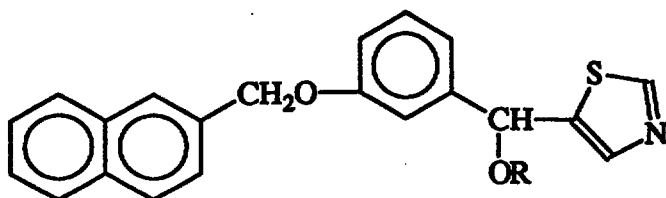
In J. Org. Chem., 1988, 53, 1748-1761, 1-(5-thiazolyl)-1-phenylmethanol is disclosed.

In J. Org. Chem., 1991, 56, 449-452, 1-(4-oxazolyl)-1-phenylmethanol is described.

In J. Med. Chem., 1984, 27, 1245-1253, 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol is disclosed as an intermediate in the synthesis of certain heterocyclic analogues of chlorcyclizine with hypolipidemic activity.

No pharmacological activity is ascribed to any of the above compounds. These five compounds are deleted from the scope of the present invention by a disclaimer in claim 1.

In patent application EP 351 194, the compounds;



R = H or Me

are disclosed. The substituent 2-naphthylmethoxy is not included within the scope of R₆ of the present invention.

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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 as neuroprotective agents, as anticonvulsant agents and/or as sedative-hypnotics.

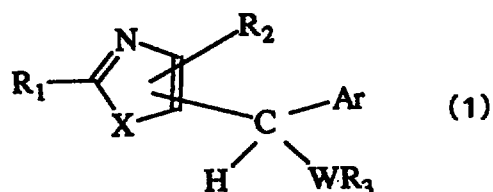
Neuroprotective agents are useful in the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal 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 amyotrophic 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.

Anticonvulsant agents are useful in the clinic for the treatment of different types of convulsive states, such as, for example, epilepsy, status epilepticus, pre-eclampsia and delirium tremens. This ability is manifested, for example, by the ability of these compounds to inhibit seizures induced by various agents such as NMDLA.

The present invention relates to a compound having the

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general formula (1)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

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

and with the proviso that the following five compounds

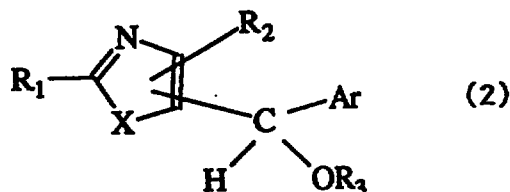
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are excluded:

1-(4-methyl-5-thiazolyl)-1-phenylmethanol;
 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol;
 1-(5-thiazolyl)-1-phenylmethanol;
 1-(4-oxazolyl)-1-phenylmethanol;
 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol.

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)



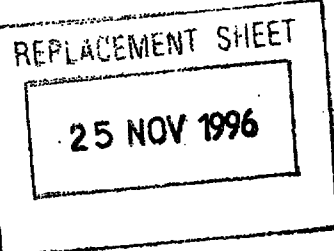
wherein:

X is O or S;

and R₁, R₂, R₃ and Ar are as previously defined above.

Analogous compounds wherein X is Se, for example, 1-(3-furyl)-1-(4-methyl-5-selenazolyl)methanol and 1-(2-fluorophenyl)-1-(4-methyl-5-selenazolyl)methanol, 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, isobutyl, t-butyl and straight- and branched-chain pentyl and hexyl.

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-

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lower alkyl" denotes a lower alkyl group as defined above substituted by a phenyl, naphthyl, furyl, thienyl, pyrrolyl or pyridyl group, itself optionally further substituted. 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:

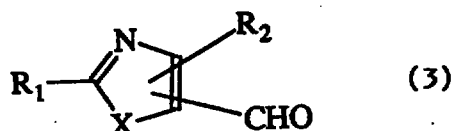
1-(3-furyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(2-furyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(4-methyl-5-thiazolyl)-1-(2-thienyl)methanol;
1-(4-methyl-5-thiazolyl)-1-(3-thienyl)methanol;
1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(3-chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(4-methyl-5-oxazolyl)-1-phenylmethanol;
1-(4-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
1-(2-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
1-(3-aminophenyl)-1-(4-methyl-5-thiazolyl)methanol;
1-(3-dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol;

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 W is O may be prepared by

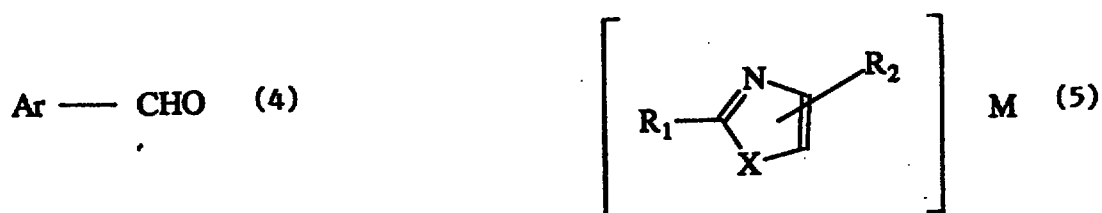
(a) reacting a compound of general formula (3) with an organometallic derivative ArM



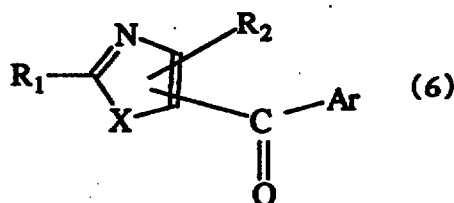
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or (b) reacting a compound of general formula (4) with an organometallic derivative of general formula (5)



or (c) by reduction of a compound of general formula (6)



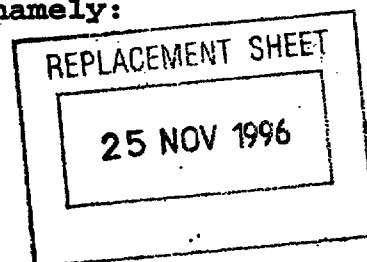
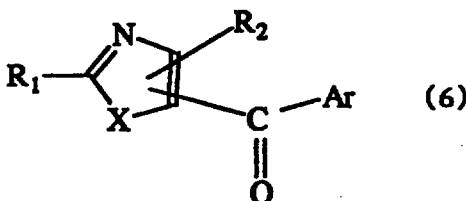
and quenching the reaction mixture with a proton source (R_3 is H) or an alkylating (R_3 is lower alkyl) or acylating (R_3 is lower acyl) reagent. Alternatively, the compound of formula (1) wherein W is O and R_3 is H may be first obtained as above and then converted into the compound wherein R_3 is lower alkyl or lower acyl.

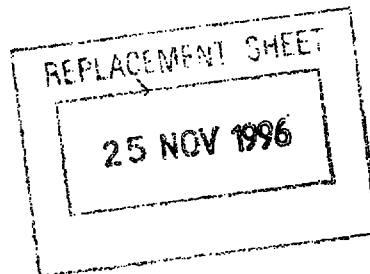
The processes (a) or (b) can be achieved for example, by reacting together an aldehyde of structure (3) or (4) with a preformed organometallic derivative ArM or (5) respectively in a suitable anhydrous solvent such as diethylether, tetrahydrofuran or hexane or mixtures thereof. Said reaction should be conducted at a suitable temperature, normally between -100°C and $+50^{\circ}\text{C}$ and preferably under an inert atmosphere, normally nitrogen or argon. In a specific variation, a solution of the aldehyde of structure (3) or (4) in anhydrous diethylether or tetrahydrofuran is added dropwise to the organometallic derivative ArM or (5) 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 WR_3 is OH may then be isolated and purified and characterised using standard techniques.

Aldehydes of general formula (3) or (4) and ketones of general formula (6) 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 formula (6), namely:

a compound of general formula (6)





wherein R_1 , R_2 , X and Ar are as defined above with the provisos that when Ar represents phenyl, then R_1 , R_2 and R_6 are not all hydrogen; and that the following three compounds are excluded:

4-bromophenyl 5-thiazolyl ketone;
4-methyl-5-thiazolyl phenyl ketone;
4-methoxyphenyl 4-methyl-5-thiazolyl ketone.

In the organometallic derivatives of general formula ArM or (5), 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.

Compounds of formula (1) wherein W is NH or N-lower alkyl may be prepared, for example,

(a) by reductive amination of a ketone of general formula (6),

or (b) by conversion of a ketone of general formula (6) to an oxime derivative followed by reduction,

or (c) by conversion of a compound of general formula (1) wherein WR_3 is OH into the corresponding azide or phthalimide using, for example, the Mitsunobu reaction, and then reduction or hydrolysis respectively.

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,

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(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.

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

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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.

The anticonvulsant properties of the compounds of formula (1) are exemplified by their ability to protect mice from NMDLA induced seizures. Male TO mice (18-30g) were used.

Groups of eight mice were injected with NMDLA (300 mg/kg i.p.) and the number of mice demonstrating tonic convulsions within the following 15 min period were recorded. Drugs were administered 15 min before the NMDLA, and data are expressed as the dose required to decrease the incidence of tonic convulsions by 50% (ED₅₀).

The sedative properties of the compounds of formula (1) are exemplified by their ability to inhibit the locomotor activity of mice.

The test drug was administered to mice and starting 20 min later locomotor activity was recorded for a 10 min period. Activity was monitored using an infra-red light beam interruption system in cages measuring 40cm x 40cm. Data are expressed as the dose required to reduce locomotor activity by 50% (ED₅₀).

Pharmaceutical Formulations

The administration in the novel method of treatment of this invention may conveniently be oral, rectal, topical

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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; or as suppositories for rectal administration; or as 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 polyvinylpyrrolidone, 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,

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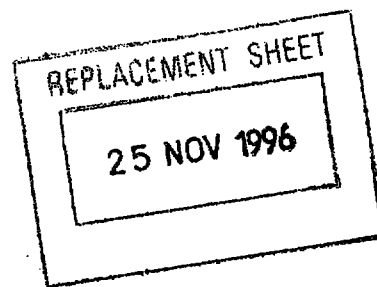
titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the man skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing 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 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 skilled 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 materials for all Examples were purchased commercially except as follows:

4-methyl-5-thiazolecarbaldehyde (J. Amer. Chem. Soc., 1982, 104, 4934-43);

2-furyllithium (J. Org. Chem., 1962, 27, 1216).

EXAMPLE 1

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methanol

4-Methylthiazole (3g) in dry diethyl ether was added dropwise to a stirred solution of n-butyllithium (1.6M in hexanes, 21ml) in diethyl ether (20ml) at -78°C under an atmosphere of dry nitrogen. After 30 minutes, trimethylsilylchloride (3.9ml) was added and the mixture was then allowed to warm to 0°C . The mixture was then cooled to -78°C and further n-butyllithium (21ml) was added. The mixture was warmed to 0°C . After 30 minutes the mixture was again cooled to -78°C and 3-furaldehyde (5g) in diethyl ether (10ml) was added. The mixture was allowed to warm to room temperature and after 30 minutes saturated aqueous sodium hydrogen carbonate was added. The reaction mixture was extracted with diethyl ether in the usual manner to give the crude product which was then purified by flash chromatography on silica gel to give the title compound. M.p. $44-46^{\circ}\text{C}$.

^{13}C Nmr (CDCl_3) 14.8, 62.4, 108.8, 128.3, 135.7, 139.4, 143.5, 148.1 and 150.9 ppm.

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Found: C, 55.0; H, 4.7; N, 7.0. $C_9H_9NO_2S$
requires C, 55.4; H, 4.6; N, 7.2%

Following the general method of Example 1 and using the appropriate aldehyde, the compounds of Examples 2 to 23 were prepared.

EXAMPLE 2

1-(4-Methyl-5-thiazolyl)-1-(4-pyridyl)methanol
M.p. 131-132°C.

EXAMPLE 3

1-(4-Methyl-5-thiazolyl)-1-(3-pyridyl)methanol
The title compound was converted into the hydrochloride salt using hydrogen chloride in ethanol and diethyl ether. M.p. 180-184°C (dec.).

EXAMPLE 4

1-(4-Methyl-5-thiazolyl)-1-(2-naphthyl)methanol
The title compound was characterised as the hydrochloride salt. M.p. 176-180°C (dec.).

EXAMPLE 5

1-(2-Furyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 50-51°C.

1H Nmr ($CDCl_3$) 2.35 (3H, s), 6.08 (1H, s), 6.19 (1H, dt), 6.33 (1H, dq), 7.39 (1H, q) and 8.6 (1H, s) ppm.

Found: C, 55.1; H, 4.8; N, 6.8. $C_9H_9NO_2S$
requires C, 55.4; H, 4.6; N, 7.2%

EXAMPLE 6

1-(4-Methyl-5-thiazolyl)-1-(2-thienyl)methanol
M.p. 75-77°C.

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^1H Nmr (CDCl_3) 2.4 (3H, s), 3.46 (1H, d), 6.34 (1H, d), 6.95 (2H, m), 7.29 (1H, m) and 8.6 (1H, s) ppm.

EXAMPLE 7

1-(4-Methyl-5-thiazolyl)-1-(5-nitro-2-furyl)methanol

M.p. 127-129°C.

EXAMPLE 8

1-(5-Methyl-2-furyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 123-125°C.

EXAMPLE 9

1-(1-Methyl-2-pyrrolyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 142-147°C (dec.).

EXAMPLE 10

1-(4-Methyl-5-thiazolyl)-1-(3-thienyl)methanol

^1H Nmr (CDCl_3) 2.43 (3H, s), 6.2 (1H, s), 7.06, 7.27 and 7.34 (each 1H, m) and 8.62 (1H, s) ppm.

EXAMPLE 11

1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 100-101°C.

^1H Nmr (CDCl_3) 2.45 (3H, s), 2.8 (1H, d), 6.42 (1H, d), 7.04, 7.19, 7.30 and 7.56 (each 1H, m) and 8.62 (1H, s) ppm.

Found: C, 58.95; H, 4.6; N, 6.0. $\text{C}_{11}\text{H}_{10}\text{FNOS}$ requires C, 59.2; H, 4.5; N, 6.3%

EXAMPLE 12

1-(3-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 74-75.5°C.

Found: C, 59.2; H, 4.4; N, 6.0. $\text{C}_{11}\text{H}_{10}\text{FNOS}$ requires C, 59.2; H, 4.5; N, 6.3%

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EXAMPLE 13

1-(4-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 98.5-100°C.

EXAMPLE 14

1-(3-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 97-98°C.

^1H Nmr (CDCl_3) 2.41 (3H, s), 3.37 (1H, d), 6.07 (1H, d), 7.26 (3H, m), 7.41 (1H, m) and 8.59 (1H, s) ppm.

Found: C, 55.2; H, 4.25; N, 5.65. $\text{C}_{11}\text{H}_{10}\text{ClNOS}$ requires C, 55.1; H, 4.2; N, 5.8%

EXAMPLE 15

1-(3-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 87-88°C.

Found: C, 60.0; H, 5.7; N, 5.75. $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S} \cdot 0.25 \text{H}_2\text{O}$ requires C, 60.1; H, 5.7; N, 5.8%

EXAMPLE 16

1-(2-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 121-122°C.

EXAMPLE 17

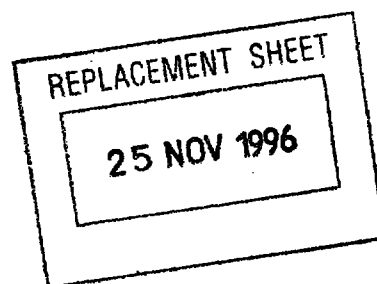
1-(2-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 122-123°C.

Found: C, 55.05; H, 4.3; N, 5.8. $\text{C}_{11}\text{H}_{10}\text{ClNOS}$ requires C, 55.1; H, 4.2; N, 5.8%

EXAMPLE 18

1-(2-Methylphenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 141.5-143°C.

Found: C, 65.7; H, 6.2; N, 6.25. $\text{C}_{12}\text{H}_{13}\text{NOS}$ requires C,



65.7; H, 6.0; N, 6.4%

EXAMPLE 19

1-(3-Methylphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 103-104.5°C.

Found: C, 65.8; H, 6.25; N, 6.4. $C_{12}H_{13}NOS$ requires C, 65.7; H, 6.0; N, 6.4%

EXAMPLE 20

1-(4-Methyl-5-thiazolyl)-1-(3-nitrophenyl)methanol

M.p. 119.5-121°C.

EXAMPLE 21

1-(2,6-Dimethoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

M.p. 125-126°C.

EXAMPLE 22

1-(4-Methyl-5-thiazolyl)-1-(1-naphthyl)methanol

M.p. 115.5-116.5°C.

EXAMPLE 23

1-(4-Methyl-5-thiazolyl)-1-(3-trifluoro-methylphenyl)-methanol

M.p. 73.5-75°C.

Found: C, 52.6; H, 3.5; N, 5.0. $C_{12}H_{10}F_3NOS$ requires C, 52.7; H, 3.7; N, 5.1%

EXAMPLE 24

1-(4-Chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol

4-Methylthiazole was treated sequentially with n-butyllithium, trimethylsilylchloride, n-butyllithium and trimethylsilylchloride according to the method of J.Org.Chem., 1988, 53, 1748-61. Column chromatography on

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silica gel then gave 4-methyl-5-trimethylsilylthiazole.

4-Methyl-5-trimethylsilylthiazole (3g), 4-chlorobenzaldehyde (4.9g) and caesium fluoride (2.7g) in dry tetrahydrofuran (150ml) were heated under reflux for 30 hours. The mixture was cooled, evaporated to dryness and the residue thus obtained was purified by flash chromatography to afford the title compound. M.p. 133.5-134.5°C.

Hydrochloride, m.p. 167.5-172.5°C.

Following the general method of Example 24 and using the appropriate aldehyde, the compounds of Examples 25 and 26 were prepared.

EXAMPLE 25

1-(2,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 163-164°C.

EXAMPLE 26

1-(3,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)methanol
M.p. 143-144°C.

Hydrochloride, m.p. 180-188°C (dec.).

Methanesulphonate, m.p. 147-148°C.

EXAMPLE 27

1-(3,4-Dichlorophenyl)-1-(5-thiazolyl)methanol
2-Bromothiazole (5g) in dry diethyl ether (20ml) was added dropwise to a stirred solution of n-butyllithium (1.6M in hexanes, 21ml) in diethyl ether (20ml) at -70°C under an atmosphere of dry nitrogen. After 30 minutes, trimethylsilylchloride (3.9ml) was added and the mixture was allowed to warm to 0°C. The mixture was then cooled to -70°C and further n-butyllithium (21ml) was added. The mixture was warmed to 0°C and after 30 minutes was

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cooled again to -70°C and 3,4-dichlorobenzaldehyde (5.8g) in diethyl ether (40ml) was added. The mixture was then allowed to warm to room temperature and after 30 minutes saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with dichloromethane and the material thus obtained was purified by chromatography on silica gel to give the title compound. The hydrochloride salt was prepared. M.p. $167-170^{\circ}\text{C}$.

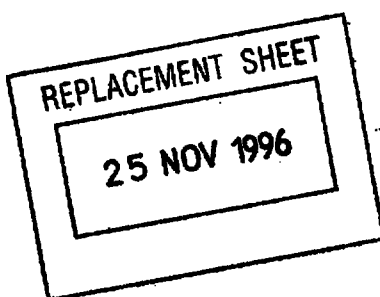
EXAMPLE 28**1-(4-Methyl-5-oxazolyl)-1-phenylmethanol**

4-Methyl-5-oxazolecarbaldehyde (600mg) in dry tetrahydrofuran (10ml) was added dropwise to a stirred solution of phenyllithium (2.0M solution in cyclohexane and diethyl ether, 2.8ml) in tetrahydrofuran (20ml) at -70°C under an atmosphere of dry nitrogen. After 1 hour the mixture was allowed to warm to room temperature. After a further 1 hour saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The product was purified by flash chromatography to yield the title compound. M.p. $79-81^{\circ}\text{C}$.

^1H Nmr (CDCl_3) 2.14 (3H, s), 5.94 (1H, s), 7.3-7.5 (5H, m) and 7.75 (1H, s) ppm.

EXAMPLE 29**1-(4-Fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol**

4-Methyl-5-oxazolecarbaldehyde (770mg) in dry tetrahydrofuran (15ml) was added dropwise to a stirred solution of 4-fluorophenyl magnesium bromide (1M solution in tetrahydrofuran, 7.3ml) in tetrahydrofuran (30ml) at -70°C under an atmosphere of dry nitrogen. After 1 hour the mixture was allowed to warm to room temperature and was then poured into saturated aqueous sodium hydrogen carbonate. Extraction with ethyl acetate followed by flash chromatography gave the title compound.



M.p. 102.5-104°C.

¹H Nmr (CDCl₃) 2.09 (3H, s), 3.68 (1H, br), 5.88 (1H, s), 7.04 (2H, m), 7.38 (2H, m) and 7.66 (1H, s) ppm.

Following the general method of Example 29 and using the appropriate Grignard reagent, the compounds of Examples 30 and 31 were prepared.

EXAMPLE 30

1-(4-Methyl-5-oxazolyl)-1-(2-methylphenyl)methanol

M.p. 122-123°C.

EXAMPLE 31

1-(4-Methyl-5-oxazolyl)-1-(4-methylphenyl)methanol

M.p. 125-127°C.

EXAMPLE 32

1-(4-Methyl-5-oxazolyl)-1-(3-methylphenyl)methanol

n-Butyllithium (2.5 solution in hexanes, 3.9ml) was added dropwise to a stirred solution of 3-bromotoluene (1.1ml) in dry tetrahydrofuran (20ml) at -70°C under an atmosphere of dry nitrogen. After 20 minutes, 4-methyl-5-oxazolecarbaldehyde (1.15g) in tetrahydrofuran (10ml) was added. After 1 hour the mixture was allowed to warm to room temperature and was then heated under reflux for 1 hour. The cooled solution was poured into saturated aqueous sodium hydrogen carbonate. Extraction with ethyl acetate and flash chromatography then gave the title compound. M.p. 76.5-77.5°C.

Following the general method of Example 32 and using the appropriate aryl bromide or iodide, the compounds of Examples 33 to 36 were prepared.

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EXAMPLE 331-(2-Fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol

¹H Nmr (CDCl₃) 2.14 (3H, s), 3.02 (1H, br s), 6.22 (1H, s), 6.98 - 7.37 (3H, m) and 7.67 (2H, m) ppm.

EXAMPLE 341-(2,4-Difluorophenyl)-1-(4-methyl-5-oxazolyl)methanol

M.p. 116-117.5°C.

EXAMPLE 351-(4-Methyl-5-oxazolyl)-1-(2-trifluoromethyl-phenyl)-methanol

M.p. 105.5-107.5°C.

Found: C, 56.2; H, 3.7; N, 5.4. C₁₂H₁₀F₃NO₂ requires C, 56.0; H, 3.9; N, 5.45%

EXAMPLE 361-(2-Chlorophenyl)-1-(4-methyl-5-oxazolyl)methanol

M.p. 127-128°C.

EXAMPLE 37Methyl 1-(4-Methyl-5-thiazolyl)-1-phenylmethyl Ether

Sodium hydride (80% dispersion in mineral oil, 80mg) was added to a stirred solution of 1-(4-methyl-5-thiazolyl)-1-phenyl-methanol (500mg) in dry N,N-dimethylformamide (10ml) at 0°C. After 10 minutes, methyl iodide (0.15ml) was added. The mixture was allowed to warm to room temperature and after a further 30 minutes the mixture was evaporated to dryness. The residue was purified by flash chromatography to give the title compound.

¹H Nmr (CDCl₃) 2.46 and 3.39 (each 3H, s), 5.52 (1H, s), 7.28 - 7.4 (5H, m) and 8.64 (1H, s) ppm.

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Following the general method of Example 37 and using the appropriate starting materials, the compounds of Example 38 to 43 were prepared.

EXAMPLE 38

Methyl 1-(3,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)-methyl Ether

Hydrochloride, m.p. 170-176°C (dec.).

EXAMPLE 39

Methyl 1-(2,4-Dichlorophenyl)-1-(4-methyl-5-thiazolyl)-methyl Ether

M.p. 55-56°C.

EXAMPLE 40

Ethyl 1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methyl Ether

¹³C Nmr (CDCl₃) 15.1, 15.3, 64.3, 69.6, 109.0, 126.4, 133.1, 139.9, 143.6, 149.5 and 151.3 ppm.

EXAMPLE 41

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether

¹H Nmr (CDCl₃) 2.45 and 3.36 (each 3H, s), 5.52 (1H, s), 6.34 (1H, m), 7.38 (2H, m) and 8.68 (1H, s) ppm.

EXAMPLE 42

1-(2-Furyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether

¹H Nmr (CDCl₃) 2.44 and 3.39 (each 3H, s), 5.57 (1H, s), 6.27 and 6.32 (each 1H, m), 7.41 (1H, m) and 8.7 (1H, s) ppm.

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EXAMPLE 43**1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methyl Methyl Ether**

¹H Nmr (CDCl₃) 2.48 and 3.39 (each 3H, s), 5.86 (1H, s), 6.98 - 7.35 (3H, m), 7.52 (1H, m) and 8.65 (1H, s) ppm.

EXAMPLE 44**1-(4-Methyl-5-thiazolyl)-1-phenylmethyl Acetate**

Acetyl chloride (0.6ml) was added to a solution of 1-(4-methyl-5-thiazolyl)-1-phenylmethanol (800mg) and pyridine (0.5ml) in dichloromethane (30ml) at 0°C under an atmosphere of dry nitrogen. The mixture was allowed to warm room temperature and was then stirred overnight. Evaporation and purification of the residue by flash chromatography gave the title compound.

¹H Nmr (CDCl₃) 2.15 and 2.51 (each 3H, s), 7.16 (1H, s), 7.35 (5H, m) and 8.66 (1H, s) ppm.

EXAMPLE 45**1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methyl Acetate**

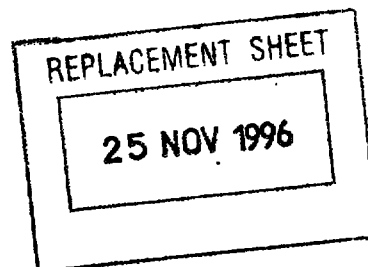
Starting with 1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol and using the method of Example 44, the title compound was prepared.

M.p. 53-56°C.

EXAMPLE 46**1-(3-Aminophenyl)-1-(4-methyl-5-thiazolyl)methanol**

1-(4-Methyl-5-thiazolyl)-1-(3-nitrophenyl)methanol (2g) and 10% palladium on charcoal (200mg) in ethanol (60ml) were shaken overnight under an atmosphere of hydrogen. The mixture was filtered and the filtrate was evaporated to dryness. The residue was converted into the hydrochloride salt, recrystallised and then reconverted into the title compound.

M.p. 137-138°C.



^1H Nmr (CDCl_3) 2.38 (3H, s), 2.44 (1H, d), 3.65 (2H, br), 5.95 (1H, d), 6.56 (1H, m), 6.7 (2H, m) 7.08 (1H, m) and 8.57 (1H, s) ppm.

Found: C, 59.9; H, 5.55; N, 12.4. $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}$ requires C, 60.0; H, 5.5; N, 12.7%

EXAMPLE 47

1-(3-Dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol

The title compound was prepared from 4-methyl-5-thiazolecarbaldehyde and 3-bromo-N,N-dimethylaniline using the method of Example 32. M.p. 135-138°C.

^1H Nmr (CDCl_3) 2.44 (3H, s), 2.75 (1H, s), 2.96 (6H, s), 6.04 (1H, s), 6.65-6.8 (3H, m), 7.23 (1H, t) and 8.60 (1H, s) ppm.

EXAMPLE 48

1-(3-Hydroxyphenyl)-1-(4-methyl-5-thiazolyl)methanol

1-(3-Methoxyphenyl)-1-(4-methyl-5-thiazolyl)methanol (1g) in dry dichloromethane (10ml) was added dropwise to boron tribromide (1M solution in dichloromethane, 25ml) at 0°C. The mixture was allowed to warm to room temperature and was stirred for 15 minutes. The mixture was poured onto ice (40g) and 0.88 ammonia (10ml). The precipitate was filtered off and purified by chromatography to give the title compound. M.p. 181-184°C.

EXAMPLE 49

1-(2-Furyl)-1-(4-methyl-5-oxazolyl)methanol

The title compound was prepared from 4-methyl-5-oxazolecarbaldehyde and 2-furyllithium using the method of Example 28. M.p. 52-54°C.

^1H Nmr (CDCl_3) 2.16 (3H), 2.7 (1H, br), 5.92, 6.32, 6.40, 7.44 and 7.80 (each 1H).

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Found: C, 60.0; H, 5.1; N, 7.9. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%

EXAMPLE 50

Resolution of 1-(4-Methyl-5-thiazolyl)-1-phenylmethanol
1-(4-Methyl-5-thiazolyl)-1-phenylmethyl acetate suspended in pH 7.5 buffer at 37°C was treated with pig liver esterase. The resulting product was subjected to flash chromatography to give, after crystallisation, 1-(4-methyl-5-thiazolyl)-1-phenylmethanol which was shown by chiral HPLC to be greater than 98% one enantiomer. The 1-(4-methyl-5-thiazolyl)-1-phenylmethyl acetate that was also obtained from the flash chromatography was subjected to base hydrolysis and the product recrystallised to give the other enantiomer of the title compound.

EXAMPLE 51

Resolution of 1-(2-Fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol

The title compound was resolved by preparative HPLC on a Chiralcel OD column using 2-propanol in hexane as solvent. The enantiomers showed $[\alpha]_D^{20} + 61^\circ$ and -60° respectively.

EXAMPLE 52

4-Methyl-5-oxazolecarbaldehyde

4-Methyl-5-oxazolecarbonyl chloride (Indian J. Chem., Sect. B, 1985, 24B, 535-8) in dry tetrahydrofuran was treated at $-78^\circ C$ with lithium tri-tert-butoxyaluminumhydride (1M solution in tetrahydrofuran). Work up in the usual fashion gave the title compound.

1H Nmr ($CDCl_3$) 2.55 (3H, s), 8.03 (1H, s) and 9.92 (1H, s) ppm.

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EXAMPLE 53**1-Azido-1-(3-furyl)-1-(4-methyl-5-thiazolyl)methane**

Borontrifluoride diethyletherate (8 mmoles) was added to a mixture of the product from Example 1 (4 mmoles) and trimethylsilylazide (8 mmoles) in dry benzene (4ml). The mixture was stirred at room temperature for 4 days and then diluted with ethyl acetate (50ml). After washing with aqueous sodium hydrogen carbonate solution and water, the organic phase was separated and dried. Evaporation gave the title compound as an oil.

^{13}C Nmr (CDCl_3) 15.1, 53.9, 108.8, 123.9, 129.9, 140.0, 143.9, 150.3 and 151.4 ppm.

EXAMPLE 54**1-Azido-1-(4-methyl-5-thiazolyl)-1-phenylmethane**

Starting with 1-(4-methyl-5-thiazolyl)-1-phenylmethanol and using the general method of Example 53, the title compound was obtained.

^{13}C Nmr (CDCl_3) 15.4, 61.4, 126.6, 128.5, 128.8, 131.0, 138.5, 150.1 and 151.6 ppm.

EXAMPLE 55**1-(4-Methyl-5-thiazolyl)-1-(N-phthalimido)-1-phenylmethane Hydrochloride**

1-(4-Methyl-5-thiazolyl)-1-phenylmethanol (30 mmoles), triphenylphosphine (40 mmoles), phthalimide (40 mmoles) and diethyl azodicarboxylate (40 mmoles) in dry tetrahydrofuran (15ml) were stirred at room temperature for 3 days. The mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel. The material thus obtained was converted into the hydrochloride salt using the standard procedure. M.p. 194-196°C.

^{13}C Nmr (CDCl_3) 12.6, 49.1, 124.1, 127.0, 129.2, 129.4,

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131.2, 134.7, 135.0, 135.8, 144.8, 154.7 and 167.2 ppm.

EXAMPLE 56

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

The product from Example 55 (1.3 mmoles) and hydrazine hydrate (1.8 mmoles) were heated under reflux in ethanol (10ml) for 2 hours. The precipitated phthalimide was filtered off and the filtrate was evaporated to dryness. The residue thus obtained was purified by flash chromatography to yield the title compound.

^{13}C Nmr (CDCl_3) 15.4, 53.1, 126.4, 127.5, 128.6, 137.8, 143.9, 147.6 and 150.2 ppm.

EXAMPLE 57

N-(1-(4-Methyl-5-thiazolyl)-1-phenylmethyl)acetamide

Acetyl chloride was added to a solution of the product from Example 56 and triethylamine in dry dichloromethane. The mixture was stirred at room temperature overnight and then washed with aqueous sodium hydrogen carbonate solution. The organic phase was separated, dried and evaporated and the residue was purified by flash chromatography to give the title compound.

^{13}C Nmr (CDCl_3) 15.3, 22.9, 50.1, 126.7, 128.0, 128.8, 133.5, 140.4, 150.0, 150.2 and 169.0 ppm.

EXAMPLE 58

1-(3-Furyl)-1-(4-methyl-5-thiazolyl)methylaniline

The product from Example 53 in ethanol was shaken with 10% palladium-on-charcoal under an atmosphere of hydrogen for 3 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. Flash chromatography of the residue thus obtained gave the title compound.

^{13}C Nmr (CDCl_3) 14.7, 44.9, 108.6, 128.9, 137.0, 138.4,

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142.9, 147.2 and 149.7 ppm.

PHARMACY EXAMPLES

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

Composition 1 - Tablets

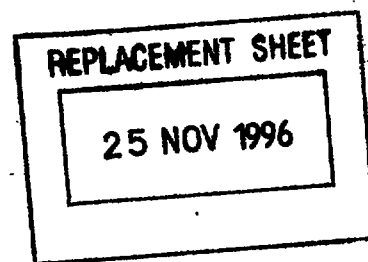
Compound of Example 33	10g
Lactose	94g
Microcrystalline cellulose	86g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 33, 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 11	50g
Lactose	80g
Microcrystalline cellulose	20g
Potato starch	40g
Polyvinylpyrrolidone	8g
Magnesium stearate	2g

The compound of Example 11, 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 1	100g
Pregelatinised starch	98g
Magnesium stearate	2g

The compound of Example 1 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 46	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 1	0.5 to 10g
Polyethoxylated castor oil	15g

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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

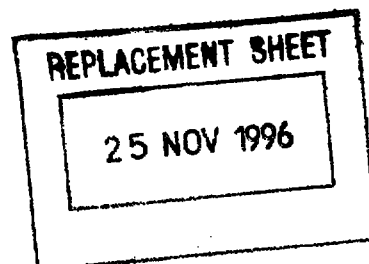
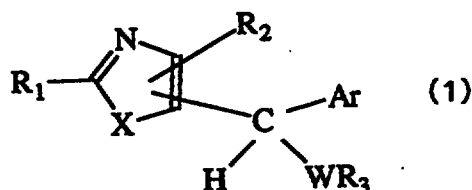
Compound of Example 5		0.5 to 10g
Hydroxypropyl- β -cyclodextrin		10g
Water for injection	ad	100g

Water for injection is added to a mixture of the compound of the invention and hydroxypropyl- β -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)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

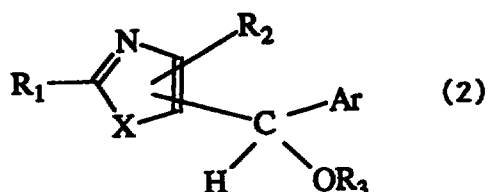
geometrical and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof;



and with the proviso that the following five compounds are excluded:

- 1-(4-methyl-5-thiazolyl)-1-phenylmethanol;
- 1-(2,4-dimethyl-5-oxazolyl)-1-phenylmethanol;
- 1-(5-thiazolyl)-1-phenylmethanol;
- 1-(4-oxazolyl)-1-phenylmethanol;
- 1-(2,4-dimethyl-5-thiazolyl)-1-(2-chlorophenyl)methanol.

2. A compound having the general formula (2)



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wherein:

X is O or S;

and R₁, R₂, R₃ and Ar are as previously defined in claim 1.

3. A compound according to claim 1 being :

- 1-(3-furyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(2-furyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(4-methyl-5-thiazolyl)-1-(2-thienyl)methanol;
- 1-(4-methyl-5-thiazolyl)-1-(3-thienyl)methanol;
- 1-(2-fluorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(3-chlorophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(4-methyl-5-oxazolyl)-1-phenylmethanol;
- 1-(4-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
- 1-(2-fluorophenyl)-1-(4-methyl-5-oxazolyl)methanol;
- 1-(3-aminophenyl)-1-(4-methyl-5-thiazolyl)methanol;
- 1-(3-dimethylaminophenyl)-1-(4-methyl-5-thiazolyl)-methanol;

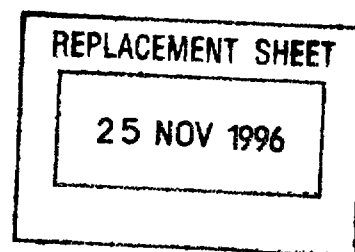
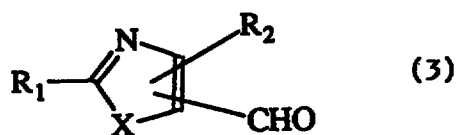


or pharmaceutically acceptable acid addition salts or solvates thereof.

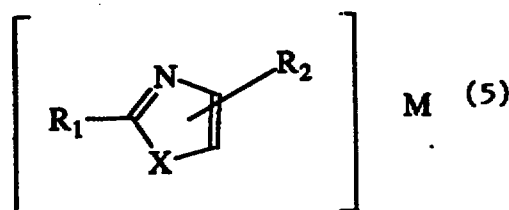
4. A process for preparing a compound according to claim 1 by

(I) in the case where W is O
by

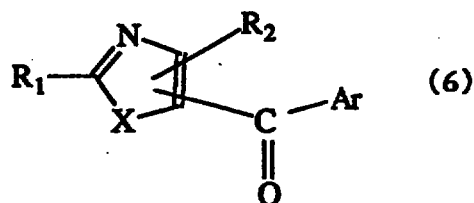
(a) reacting a compound of general formula (3) with an organometallic derivative ArM



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



or (c) by reduction of a compound of general formula (6)



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;



(II) in the case where R_3 is lower alkyl or lower acyl the compound of formula (1) wherein W is O 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;

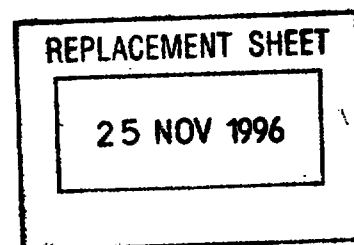
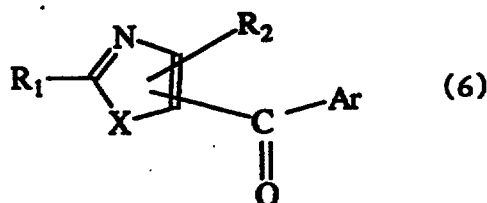
(III) in the case where W is NH or N-lower alkyl by, for example,

(a) reductive amination of a ketone of general formula (6),

or (b) by conversion of a ketone of general formula (6) to an oxime derivative followed by reduction,

or (c) by conversion of a compound of general formula (1) wherein WR_3 is OH into the corresponding azide or phthalimide using, for example, the Mitsunobu reaction, and then reduction or hydrolysis respectively.

5. A compound of general formula (6)

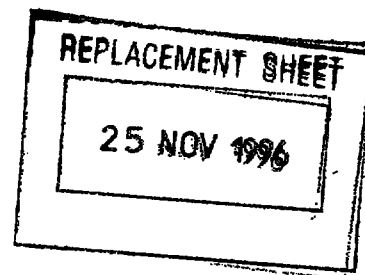
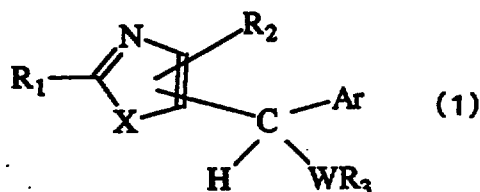


wherein R_1 , R_2 , X and Ar are as defined in claim 1 with the provisos that when Ar represents phenyl, then R_1 , R_2 and R_6 are not all hydrogen; and that the following three compounds are excluded:

- 4-bromophenyl 5-thiazolyl ketone;
- 4-methyl-5-thiazolyl phenyl ketone;
- 4-methoxyphenyl 4-methyl-5-thiazolyl ketone.



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



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

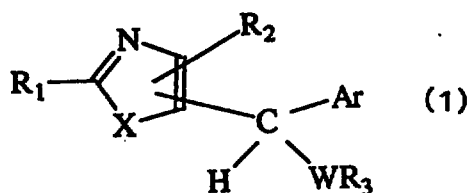
R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

geometrical 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.



7. A compound having the general formula (1)



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wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

geometrical 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.

8. A compound as defined in claim 7 for use as a neuroprotective agent and/or an anticonvulsant agent and/or a sedative-hypnotic agent.

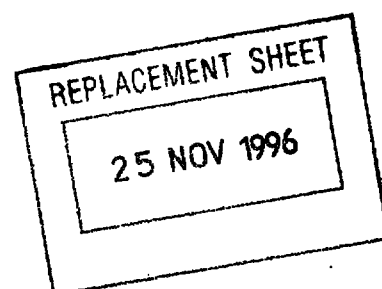
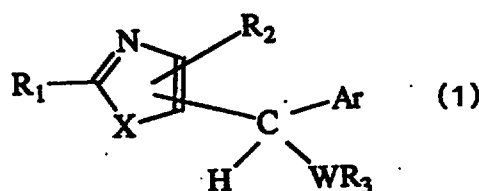


9. A compound as defined in claim 8 for the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction and for the treatment of different types of convulsive states.

10. A compound as defined in claim 9 for the treatment of acute and chronic neuropsychiatric disorders, such as 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.

11. A compound as defined in claim 9 for the treatment of different types of convulsive states, such as epilepsy, status epilepticus, pre-eclampsia and delirium tremens.

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



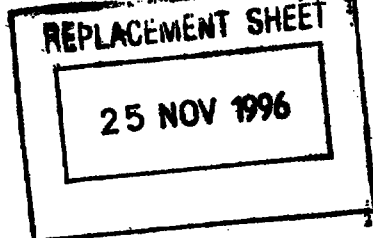
wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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



R_3 is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6 ;

R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3 , OH, NO_2 or NR_4R_5 , wherein R_4 and R_5 independently are H, lower alkyl or lower acyl;

geometrical 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 neurodegenerative disorders and/or convulsive states and/or agitation and sleep disorders.

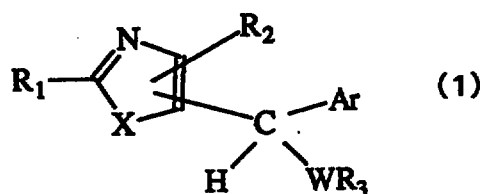
13. The use according to claim 12 for the manufacture of a medicament for the treatment of acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to neuronal cell death and dysfunction and for the treatment of different types of convulsive states.

14. The use according to claim 13 for the manufacture of a medicament for the treatment of acute and chronic neuropsychiatric disorders, such as 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.



15. The use according to claim 13 for the manufacture of a medicament for the treatment of different types of convulsive states, such as epilepsy, status epilepticus, pre-eclampsia and delirium tremens.

16. A method for the treatment of neurodegenerative disorders and/or convulsive states and/or agitation and sleep disorders by administering to a host in need of such treatment a sufficient amount of a compound having the general formula (1)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

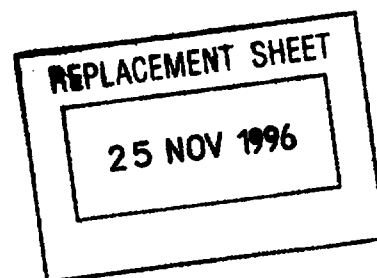
R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

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

R₃ is H, lower alkyl or lower acyl;

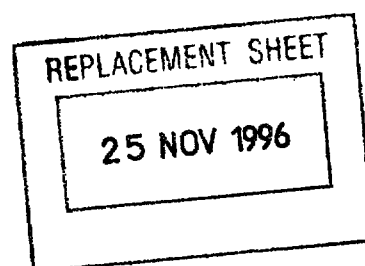
Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;





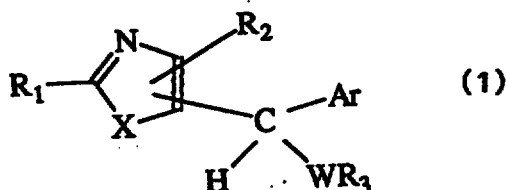
geometrical and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof.



NOVEL (1-PHENYL-1-HETEROCYCLYL)METHANOL AND (1-PHENYL-1-HETEROCYCLYL)METHYLAMINE DERIVATIVES

ABSTRACT

The present invention relates to novel heterocyclic compounds having the general formula (1)



wherein:

X is O, S or Se;

R₁ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

R₂ is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF₃;

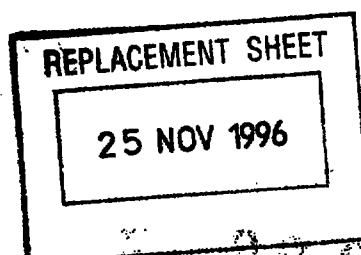
W is O, S, NH or N-lower alkyl;

R₃ is H, lower alkyl or lower acyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R₆;

R₆ is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF₃, OH, NO₂ or NR₄R₅, wherein R₄ and R₅ independently are H, lower alkyl or lower acyl;

geometrical 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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