CONVENTION

AUSTRALIA

Patents Act 1990 646926

REQUEST FOR A STANDARD PATENT

AND NOTICE OF ENTITLEMENT

The Applicant identified below requests the grant of a patent to the nominated person identified below for an invention described in the accompanying standard complete patent specification.

[70,71]Applicant and Nominated Person:

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[54]Invention Title:

ALKYLENEDIOXYPHENYL ETHER DERIVATIVES HAVING ANTI-ISCHAEMIC, MEMORY ENHANCING AND ANTI-CONVULSIVE ACTIVITY

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[31,33,32]

Details of basic application(s):-

91200618.6	EUROPE	EP	20 March 1991

Applicant states the following:

1. The nominated person is the assignee of the actual inventor(s)

2. The nominated person is
   - the applicant
   - ~~the assignee of the applicant~~
   - ~~authorised to make this application by the applicant~~

   of the basic application.

3. The basic application(~~s~~) was/~~were~~ the first made in a convention country in respect of the invention.

The nominated person is not an opponent or eligible person described in Section 33-36 of the Act.

5 March 1992

Duphar International Research B.V.
By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys
By

David B Fitzpatrick

Our Ref : 281350

5999q

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(54) Title
ALKYLENEDIOXYPHENYL ETHER DERIVATIVES HAVING ANTI-ISCHAEMIC, MEMORY ENHANCING AND ANTI-CONVULSIVE ACTIVITY

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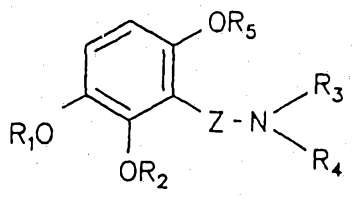
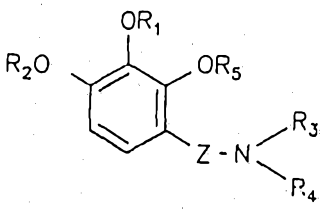
(57) Claim

1. A compound of formula 1A or 1B





(1A) (1B)

wherein:

-R_1 + R_2 together form an alkylene group having 1-3 C-atoms which may be substituted with one or more alkyl group(s) having 1-3 C-atoms;

-Z is methylene optionally substituted with one alkyl group having 1-3 C-atoms, or with one phenylalkyl group with 1-3 C-atoms in the alkyl group, which phenyl group may be substituted with a group $(R_6)_p$ wherein R_6 is halogen, hydroxy, alkyl or hydroxyalkyl having 1-5 C-atoms, alkoxy having 1-3 C-atoms, S-alkyl, S(O)-alkyl or $S(O)_2$-alkyl having 1-3 C-atoms, amino, mono- or dialkylamino having 1-3 C-atoms per alkyl group, trifluoromethyl, trifluoromethoxy, a

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sulphonylamido group SO_2NHR or a carbalkoxy group COOR wherein R is alkyl having 1-4 C-atoms, the group COOH, SO_3H, $CONH_2$, the amidino group or cyano group, and p has the value 0-3;

-R_3 and R_4 independent of each other represent hydrogen, alkyl having 1-10 C-atoms, alkenyl or alkynyl having 3-10 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl- alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C- atoms in the alkyl group, phenylalkenyl, heteroaryl- alkenyl, phenylalkynyl or heteroaryl-alkynyl group having 3-5 C-atoms in the alkenyl group or alkynyl group, which groups R_3 and R_4 may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or wherein R_3+R_4 together with the nitrogen atom form a saturated or unsaturated heterocyclic group of 5-7 ring atoms, which may contain a second hetero-atom from the group consisting of oxygen, sulphur and nitrogen, which ring may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or with phenylalkyl, heteroaryl-alkyl, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having at most 3 C-atoms in the alkyl, alkenyl or alkynyl part, which groups may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above-mentioned meanings, or which ring may be annelated with a phenylgroup;

-R_5 is alkyl having 1-12 C-atoms, alkenyl or alkynyl having 3-12 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl sub-group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having 3-5 C-atoms in the alkenyl sub-group or alkynyl sub-group, which groups may be substituted with a group $(R_6)_p$, wherein R_6 and p have the above-mentioned meanings, and which alkyl sub-groups, alkenyl sub-groups and alkynyl sub-groups may contain a group -O-, -S- or CO, or a pharmacologically acceptable salt thereof.

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5. A method of treating ischaemia, impaired memory or epilepsy, characterised in that a compound according to claim 1 is used.

AUSTRALIA

Patents Act

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COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

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Related Art:

Name of Applicant:

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Invention Title:

ALKYLENEDIOXYPHENYL ETHER DERIVATIVES HAVING ANTI-ISCHAEMIC, MEMORY ENHANCING AND ANTI-CONVULSIVE ACTIVITY

Our Ref : 281350
POF Code: 1596/46997

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

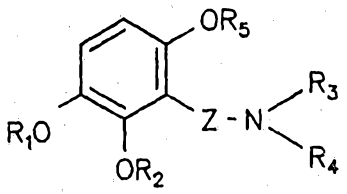
DIR 0482

Alkylenedioxyphenyl ether derivatives having anti-ischaemic, memory enhancing and anti-convulsive activity

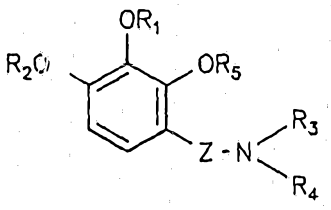
The invention relates to a group of new alkylenedioxyphenyl ether derivatives having interesting anti-ischaemic activity, memory enhancing activity and anti-convulsive activity, to a method of preparing said compounds, and to pharmaceutical compositions comprising at least one of these compounds as the active component. There is an increasing clinical interest in an effective pharmalogical symptomatic treatment for cerebral and peripheral ischaemic diseases. In patients suffering from these diseases the impaired blood supply causes an inadequate delivery of oxygen and other nutrients to the tissue as well as a diminished removal of metabolic waste products resulting in structural injury and functional deterioration.
Anti-convulsive compounds can be useful in the treatment of epilepsy.

The object of the present invention is to provide active compounds with anti-ischaemic, memory enhancing and anti-convulsive properties.

It has been found surprisingly that compounds of formulae 1A and 1B



(1A)



(1B)

wherein

-R_1 + R_2 together form an alkylene group having 1-3 C-atoms which may be substituted with one or more alkyl group(s) having 1-3 C-atoms;

-Z is methylene optionally substituted with one alkyl group having 1-3 C-atoms, or with one phenylalkyl group with 1-3 C-atoms in the alkyl group, which phenyl group may be substituted with a group $(R_6)_p$ wherein R_6 is halogen, hydroxy, alkyl or hydroxyalkyl having 1-5 C-atoms, alkoxy having 1-3 C-atoms, S-alkyl, S(O)-alkyl or $S(O)_2$-alkyl having 1-3 C-atoms, amino, mono- or dialkylamino having 1-3 C-atoms per alkyl group, trifluoromethyl, trifluoromethoxy, a sulphonylamido group SO_2NHR or a carbalkoxy group COOR wherein R is alkyl having 1-4 C-atoms, the group COOH, SO_3H, $CONH_2$,

the amidino group or cyano group, and p has the value 0-3;

-R_3 and R_4 independent of each other represent hydrogen, alkyl having 1-10 C-atoms, alkenyl or alkynyl having 3-10 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl group having 3-5 C-atoms in the alkenyl group or alkynyl group, which groups R_3 and R_4 may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or wherein $R_3 + R_4$ together with the nitrogen atom form a saturated or unsaturated heterocyclic group of 5-7 ring atoms, which may contain a second hetero-atom from the group consisting of oxygen, sulphur and nitrogen, which ring may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or with phenylalkyl, heteroaryl-alkyl, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having at most 3 C-atoms in the alkyl, alkenyl or alkynyl part, which groups may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above-mentioned meanings, or which ring may be annelated with a phenyl group;

-R_5 is alkyl having 1-12 C-atoms, alkenyl or alkynyl having 3-12 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl sub-group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having 3-5 C-atoms in the alkenyl sub-group or alkynyl sub-group, which groups may be substituted with a group $(R_6)_p$, wherein R_6 and p have the above-mentioned meanings, and which alkyl sub-groups, alkenyl sub-groups and alkynyl sub-groups may contain a group -O-, -S- or CO,

prodrugs and pharmaceutically acceptable acid addition salts thereof have interesting and valuable anti-ischaemic, memory enhancing and anti-convulsive properties.

Prodrugs are derivatives of these compounds which as such are inactive, from which, after splitting off an easily removable group, for example an ester group or an ether group, an active compound of formula 1A or 1B is obtained.

Suitable acids with which suitable addition salts can be formed are, for example, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids like citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid, etc.

One or more centres of chirality may be present in the compounds having formula

1A or 1B. The invention relates both to racemates and the individual isomers of the compounds having formulae 1A and 1B.

The anti-ischaemic and memory enhancing activity of the compounds has been determined by means of the in vivo hypobaric hypoxia test, the in vitro cardiomyocytes test and the in vivo memory test. These tests were used to characterize substances with cerebro- and/or peripheral-protective activity.

The anti-convulsive activity of the compounds has been determined by means of chemically induced tonic convulsions in vivo.

1) Hypobaric activity in vivo

Cerebro-protective activity was determined by measuring the prolongation of the survival time of conscious mice under hypobaric conditions.

Groups of 3 overnight fasted male NMRI mice (15-20 g) are dosed ip (30 mg/kg), 30 minutes before being placed in a chamber at hypobaric pressure of 200 mBar. The prolongation of the survival time is expressed in percentage increase in respiration time, compared to that of the placebo treated control group.

2) Cardiomyocytes in vitro

Cyto-protective properties were determined in an in vitro model using isolated calcium tolerant cardiomyocytes according to L. Verdonck et al (Life Sciences, vol.38, (1986) 765-772).

Cardiomyocytes were isolated from male Wistar rat hearts. Rod shaped cells were incubated with the compound to be tested for 30 min. Injury was induced by e.g. veratrine (100 µg/ml) or by hypoxia upon which the cells became rounded unless protected by the compound. After 20 min. the remaining rod-shaped cells were counted and the protecting efficacy of the compound was determined.

3) Memory testing under hypoxic conditions

Cerebroprotective activity was determined by studying the prevention of hypoxia induced amnesia in gerbils.

In groups of 6-8 gerbils step through passive avoidance was measured after exposure to hypoxia (4% O_2, 96% N_2) until gasping was observed. Memory testing was performed 4 hrs after drug administration and exposure to hypoxia.

4) Chemically induced tonic convulsions in vivo

Protection against pentylene-tetrazole-induced convulsions (50 mg/kg i.v.) was demonstrated in male NMRI-mice, weighing 18-24 g.

Tonic convulsions were measured 60 minutes after oral administration of the test compound. Suppression of the tonic extensor phase was considered to be the criterion for the anti-convulsive effect. (Purpura D.P., Penry J.K., Tower D.B., Woodburry D.M., Walters R.D. (eds.), Experimental models of epilepsy, Raven Press, New York (1972)).

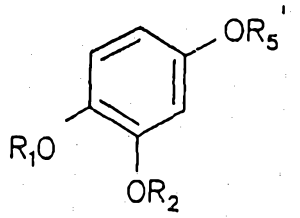
Results obtained for a representative number of compounds using tests 1 and 2 described above are shown below.

compound no	test 1 (% prolongation)	test 2 (pIC_{50}-value)
13	286	6.0
14	333	6.5
20	277	5.5
21	308	6.0
30	202	6.0
31	387	6.5
37	223	6.0

In test 1 the placebo-treated group gives a percentage of 100%. In test 2 pIC_{50}-values are measured, i.e. the negative logarithm of the concentration which gives 50% protection as compared with untreated cells.

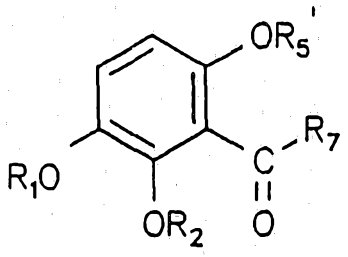
The compounds having formulae 1A and 1B, wherein the symbols have the above-mentioned meaning are new compounds which can be prepared according to methods known per se.

For example compounds having formula 1A can be obtained by first preparing a compound having formula 2



(2)

wherein R_1 and R_2 have the above mentioned meaning and wherein R'_5 is a so-called directed ortho-metallating group (see for example Acc. Chem. Res., 15, 306 (1982)), such as $-CH_2OCH_3$(MOM), $-CH(CH_3)OC_2H_5$, $-CH_2O(CH_2)_2Si(CH_3)_3$(SEM) and the like, via known procedures (see for example, "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie, Plenum Press, London (1973), Chapter 4; Synthesis, 276 (1975); Synthesis 244 (1976); J. Org. Chem., 44, 2480 (1979)), from the corresponding phenolic compounds 2 wherein R'_5 is hydrogen. The so-obtained compounds of formula 2 can be converted into the corresponding compounds of formula 3

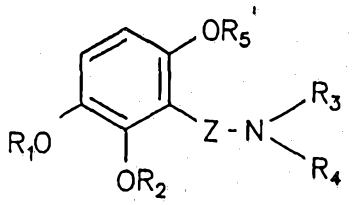


(3)

wherein R_7 is hydrogen, alkyl having 1-3 C-atoms, phenylalkyl with 1-3 C-atoms in the alkyl group, which phenyl group may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, via regioselective deprotonation with

a strong base, for example n-butyllithium and the like, followed by reaction with an electrophile R_7-CO-X, wherein X represents a leaving group, for example halogen (see for analogous ortho-directed metallations for example J.Org.Chem., 53, 3936 (1988); J.Heterocyclic Chem., 26, 1827 (1989)).

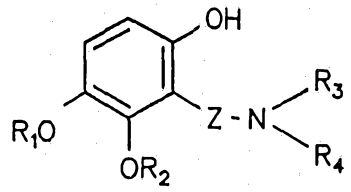
The so-obtained compounds of formula 3 can be converted into the corresponding compounds of formula 4



(4)

by a reductive amination reaction with an amine of the formula R_3R_4NH, in which formulae R_1-R_4 and Z have the meanings given in formula 1A, and R'_5 and R_7 have the meanings given above. This reductive amination reaction can be carried out with a suitable reducing agent such as $NaCNBH_3$ in an inert solvent, for example acetonitrile, or by other reductive amination methods (see for example Russ.Chem.Rev., 49, 14 (1980), or Synthesis, 135 (1975)). In some cases the addition of an acid catalyst may be desirable to enhance the reaction rate.

The so-obtained compounds of formula 4 can be converted into the corresponding compounds of formula 5



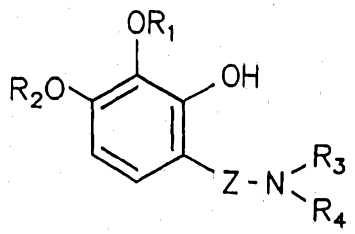
(5)

in which formula R_1-R_4 and Z have the meanings given in formula 1A, by means of an acid-catalyzed removal of R'_5.

The so-obtained compounds of formula 5 can be converted into the corresponding compounds of formula 1A wherein R_5 has the above mentioned meanings by means of a reaction with a compound of the formula R_5-X, wherein X is a so-called leaving group. This reaction is preferably carried out in an inert solvent such as dimethylsulphoxide (DMSO), N,N-dimethylformamide (DMF) and the like, in the presence of a suitable base such as sodium hydride or potassium tert-butoxide and the like. Sometimes the addition of sodium iodide is desirable. The reaction may be

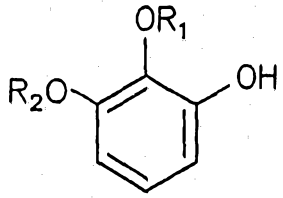
carried out at somewhat elevated temperatures.

Compounds having general formula 1B can be obtained for example by first preparing a compound having formula 6



(6)

wherein R_1-R_4 and Z have the above mentioned meanings, by reacting a compound of the formula 7



(7)

with a compound of the formula R_3R_4NH and an aldehyde of the formula R_7CHO, in which formulae R_1-R_4 and R_7 have the above mentioned meaning. This so-called Mannich-reaction is preferably carried out in an inert organic solvent, such as ethanol or acetonitrile.

The starting compounds of formula 7 are known or can be obtained analogously to known compounds (see for example W. Baker and R.I. Savage, J.Chem.Soc., 1602 (1938)).

The so-obtained compounds of formula 6 can be converted into the corresponding compounds of formula 1B wherein R_5 has the above mentioned meanings in the same manner as described above for the preparation of compounds having formula 1A from compounds having formula 5.

Example I

a) 5-(1-ethoxyethoxy)-1,3-benzodioxole

A stirred solution of 3,4-methylenedioxyphenol (6.0 g, 43.5 mmol), ethyl vinyl ether (3.75 g, 52.0 mmol) and a catalytic amount of trichloroacetic acid (50 mg, 0.3 mmol) in chloroform (50 ml) was stirred for two hours at room temperature. Aqueous NaOH (2N, 50 ml) was added and the resulting mixture was extracted with

diethyl ether (3 times). The combined ether extracts were washed with aqueous NaOH (2N) and water, respectively, dried over Na_2SO_4, filtered and evaporated in vacuo to yield 5-(1-ethoxyethoxy)-1,3-benzodioxole (8.96 g, 98% yield; compound no. 1) as an oil.

b) 5-(1-ethoxyethoxy)-4-formyl-1,3-benzodioxole

n-Butyllithium (18.6 ml of a 2.5 M solution in hexane, 46.5 mmol) and N,N,N',N'-tetramethylethylenediamine (5.38 g, 46.3 mmol), respectively, were added (using a syringe) to a stirred solution of 5-(1-ethoxyethoxy)-1,3-benzodioxole (8.9 g, 42.4 mmol) in dry THF (100 ml) in a nitrogen atmosphere at -78°C. The resulting solution was allowed to attain room temperature and then cooled to -78°C. A solution of N,N-dimethylformamide (3.70 g, 50.6 mmol) in dry THF (20 ml) was added using a syringe, and the reaction mixture was allowed to attain room temperature. The resulting mixture was quenched with water and extracted with diethyl ether (3 times). The combined ether layers were washed with water (2 times), dried over Na_2SO_4, filtered and evaporated in vacuo to yield 5-(1-ethoxyethoxy)-4-formyl-1,3-benzodioxole (9.7 g, 96% yield; compound no. 2) as a pale yellow solid, m.p. 48-50°C.

In a similar manner 5-methoxymethoxy-1,3-benzodioxole was converted into 4-formyl-5-methoxymethoxy-1,3-benzodioxole (compound no. 3), melting point 84-86°C.

c) 5-(1-ethoxyethoxy)-4-(4-methylpiperazinylmethyl)-1,3-benzodioxole

$NaCNBH_3$ (6.4 g, 101.8 mmol) was added to a stirred solution of 5-(1-ethoxyethoxy)-4-formyl-1,3-benzodioxole (16.0 g, 67.2 mmol) and 1-methylpiperazine (20.2 g, 201.7 mmol) in CH_3CN (150 ml). Acetic acid (10 ml) was added dropwise to the solution in one hour at room temperature, to keep the pH neutral (pH = 7). After 3 hours of additional stirring, most of the CH_3CN was evaporated in vacuo. Aqueous NaOH (2N, 300 ml) was added and the resulting mixture was extracted with diethyl ether (3 times). The combined ether extracts were washed with an aqueous solution of Na_2CO_3, dried over Na_2SO_4, filtered and evaporated to yield 26 g of a crude oil. This oil was purified by flash chromatography (eluent gradient; dichloromethane/methanol/25% aqueous ammonia = 95/4.5/0.5 to 85/14/1 (v/v)) to give 5-(1-ethoxyethoxy)-4-(4-methyl-piperazinylmethyl)-1,3-benzodioxole (16.0 g, 74% yield, compound no. 4) as a colorless oil.

In a similar manner the compounds of formula 4, wherein R_1-R'_5 and Z have the meanings indicated in Table A were prepared.

TABLE A

Comp. no.	R_1+R_2	R_3 (+) R_4	R'_5	Z	m.p. (°C)
5	$-CH_2-$	$-(CH_2)_5-$	$-CH(CH_3)OC_2H_5$	$-CH_2-$	oil
6	$-CH_2-$	$-(CH_2)_2N((CH_2)_2CH_3)(CH_2)_2-$	$-CH(CH_3)OC_2H_5$	$-CH_2-$	oil
7	$-CH_2-$	C_2H_5 C_2H_5	$-CH_2OCH_3$	$-CH_2-$	oil

d) 5-hydroxy-4-(4-methylpiperazinylmethyl)-1,3-benzodioxole

Aqueous HCl (300 ml, 0.5 N) was added to a stirred solution of 5-(1-ethoxyethoxy)-4-(4-methylpiperazinylmethyl)-1,3-benzodioxole (16.0 g, 49.7 mmol) in 2-propanol (300 ml) at room temperature, and stirring was continued for 15 minutes. The solution was extracted with diethyl ether, the aqueous layer was neutralised (pH = 7) by adding aqueous NaOH(2N), and the water layer was evaporated in vacuo. The residue was extracted with diethyl ether (3 times). The combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo to yield a crude oil (9.6 g). This oil was purified by flash chromatography (eluent: acetone/ethyl acetate = 1/1 (v/v)) to yield 5-hydroxy-4-(4 methylpiperazinyl-methyl) -1,3-benzodioxole (7.6 g, 61% yield, compound no. 8) as a solid, m.p. 85-87°C.

In a similar manner the compounds of formula 5 wherein R_1-R_4 and Z have the meanings indicated in Table B were prepared.

TABLE B

Comp. no.	R_1+R_2	R_3 (+) R_4	Z	m.p. (°C)
9	$-CH_2-$	C_2H_5 C_2H_5	$-CH_2-$	oil
10	$-CH_2-$	$-(CH_2)_5-$	$-CH_2-$	oil
11	$-CH_2-$	$-(CH_2)_2N((CH_2)_2CH_3)(CH_2)_2-$	$-CH_2-$	190

e) 4-(4-methylpiperazinylmethyl)-5-phenylpropoxy-1,3-benzodioxole .2HCl)

3-Phenylpropyl bromide (1.81 g, 9.1 mmol) was added to a mixture of 5-hydroxy-4-(4-methylpiperazinylmethyl)-1,3-benzodioxole (1.9 g, 7.6 mmol), sodium iodide (0.1 g, 0.7 mmol) and potassium tert-butoxide (1.12 g, 9.9 mmol) in DMSO (30 ml). The stirred mixture was heated at 80°C for two hours. Thereafter, the mixture was allowed to attain room temperature, water was added and the resulting solution was extracted with diethyl ether (3 times), the combined ether extracts were washed with 2N aqueous NaOH and water respectively, and dried over Na_2SO_4. Gaseous HCl was added and the formed precipitate was filtered. This precipitate was recrystallised from 2-propanol/methanol = 9/1 (v/v) to yield 4-(4-methylpiperazinylmethyl)-5-phenylpropoxy-1,3-benzodioxole. 2HCl (2.9 g, 87% yield; compound no. 12) as a white solid, m.p. 223-225°C.

In a similar manner the compounds of formula 1A, wherein R_1-R_5 and Z have the meanings indicated in Table C were prepared.

TABLE C

Comp. no.	R_1+R_2	R_3 (+) R_4	R_5	Z	salt	m.p. (°C)
13	$-CH_2-$	C_2H_5 C_2H_5	$n-C_5H_{11}$	$-CH_2-$	HBr	130-2
14	$-CH_2-$	C_2H_5 C_2H_5	$(CH_2)_3C_6H_5$	$-CH_2-$	HBr	145-7
15	$-CH_2-$	$-(CH_2)_5-$	$n-C_3H_7$	$-CH_2-$	HCl	134-6
16	$-CH_2-$	$-(CH_2)_5-$	$n-C_5H_{11}$	$-CH_2-$	HCl	142-4
17	$-CH_2-$	$-(CH_2)_5-$	$CH_2C_6H_5$	$-CH_2-$	free base	100-2
18	$-CH_2-$	$-(CH_2)_5-$	$(CH_2)_3C_6H_5$	$-CH_2-$	HBr	129-33
19	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$n-C_4H_9$	$-CH_2-$	2HCl	208 dec
20	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$CH_2C_6H_5$	$-CH_2-$	2HCl	100-5 dec
21	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	CH_2-2-Cl-C_6H_4	$-CH_2-$	2HCl	172-5
22	$-CH_2-$	$-(CH_2)_2N((CH_2)_2CH_3)(CH_2)_2-$	$n-C_4H_9$	$-CH_2-$	2HCl	210-12
23	$-CH_2-$	$-(CH_2)_2N((CH_2)_2CH_3)(CH_2)_2-$	$CH_2C_6H_5$	$-CH_2-$	2HCl	219-21
24	$-(CH_2)_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$(CH_2)_3C_{10}H_5$	$-CH_2-$	2HCl	198-201

Example II

a) 4-hydroxy-5-(4-propylpiperazinylmethyl)-1,3-benzodioxole

Aqueous formaldehyde (37%; 3.67 g, 45.3 mmol) was added dropwise to a stirred solution of 4-hydroxy-1,3-benzodioxole (5.2 g, 37.8 mmol) and N-propylpiperazine (5.8 g, 45.3 mmol) in acetonitrile (25 ml). The reaction mixture was stirred at room temperature for one hour and evaporated in vacuo. The remaining oil (13.0 g) was purified chromatographically (with ethylacetate/methanol = 9/1 (v/v) as an eluent to give 4-hydroxy-5-(4-propylpiperazinylmethyl)-1,3-benzodioxole (5.9 g, 56% yield; compound no. 25), m.p. 115-117°C.

In a similar manner the compounds of formula 6 wherein Z and R_1-R_4 have the meanings indicated in Table D were prepared.

TABLE D

Comp. no.	$R_1 + R_2$	R_3 (+) R_4	Z	m.p. (°C)
26	$-CH_2-$	C_2H_5 C_2H_5	$-CH_2-$	oil
27	$-CH_2-$	$-(CH_2)_5-$	$-CH_2-$	156-8
28	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$-CH_2-$	118-20

b) 4-butoxy-5-(4-propylpiperazinylmethyl)-1,3-benzodioxole .2HCl

Butyl bromide (1.71 g, 12.5 mmol) was added to a mixture of 5-(4-propylpiperazinylmethyl)-4-hydroxy-1,3-benzodioxole (2.9 g, 10.4 mmol), sodium iodide (0.1 g, 0.7 mmol) and potassium tert-butoxide (1.53 g, 13.5 mmol) in DMSO (30 ml). The stirred mixture was heated at 80°C for 2 hours. Thereafter, the mixture was allowed to attain room temperature, water was added and the resulting solution was extracted with diethyl ether (3 times). The combined ether extracts were washed with 2N aqueous NaOH and water, respectively. The combined ether extracts were extracted twice with HCl (10 ml of a 10% aqueous solution). The combined aqueous layers were extracted with diethyl ether and made alkaline (pH = 13) by addition of NaOH (25 ml of a 50% aqueous solution).

The resulting solution was extracted twice with diethyl ether. The combined ether extracts were dried over Na_2SO_4 and filtered. The filtrate was saturated with gaseous hydrogen chloride and evaporated in vacuo to yield 4-butoxy-5-(4-propylpiperazinyl-methyl)-1,3-benzodioxole.2HCl (2.04 g, 48% yield; compound no. 29) as a pure white solid, m.p. 245°C (decomposition).

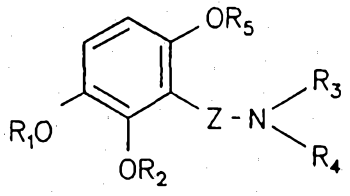
In a similar manner the compounds of formula 1B wherein R_1-R_5 and Z have the meanings indicated in Table E were prepared.

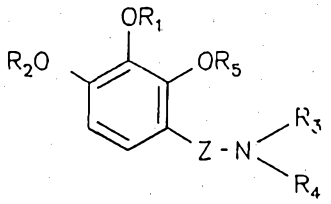
TABLE E

Comp. no.	R_1+R_2	R_3 (+) R_4	R_5	Z	salt	m.p. (°C)
30	$-CH_2-$	C_2H_5 C_2H_5	$n\text{-}C_5H_{11}$	$-CH_2-$	HCl	103-5
31	$-CH_2-$	C_2H_5 C_2H_5	$(CH_2)_3C_6H_5$	$-CH_2-$	HCl	116-8
32	$-CH_2-$	$-(CH_2)_5-$	$n\text{-}C_5H_{11}$	$-CH_2-$	HCl	168-70
33	$-CH_2-$	$-(CH_2)_5-$	$CH_2C_6H_5$	$-CH_2-$	HCl	205-8
34	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$n\text{-}C_4H_9$	$-CH_2-$	2H	198-201
35	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$CH_2C_6H_5$	$-CH_2-$	2HCl	262 dec.
36	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$CH_2\text{-}2\text{-}Cl\text{-}C_6H_4$	$-CH_2-$	2HCl	257 dec.
37	$-CH_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	$(CH_2)_3C_6H_5$	$-CH_2-$	2HCl	247 dec.
38	$-CH_2-$	$-(CH_2)_2N((CH_2)_2CH_3)(CH_2)_2-$	$CH_2C_6H_5$	$-CH_2-$	2HCl	242 dec.

The claims defining the invention are as follows:

1. A compound of formula 1A or 1B





(1A) (1B)

wherein:

-R_1 + R_2 together form an alkylene group having 1-3 C-atoms which may be substituted with one or more alkyl group(s) having 1-3 C-atoms;

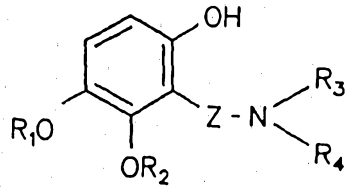
-Z is methylene optionally substituted with one alkyl group having 1-3 C-atoms, or with one phenylalkyl group with 1-3 C-atoms in the alkyl group, which phenyl group may be substituted with a group $(R_6)_p$ wherein R_6 is halogen, hydroxy, alkyl or hydroxyalkyl having 1-5 C-atoms, alkoxy having 1-3 C-atoms, S-alkyl, S(O)-alkyl or $S(O)_2$-alkyl having 1-3 C-atoms, amino, mono- or dialkylamino having 1-3 C-atoms per alkyl group, trifluoromethyl, trifluoromethoxy, a sulphonylamido group SO_2NHR or a carbalkoxy group COOR wherein R is alkyl having 1-4 C-atoms, the group COOH, SO_3H, $CONH_2$, the amidino group or cyano group, and p has the value 0-3;

-R_3 and R_4 independent of each other represent hydrogen, alkyl having 1-10 C-atoms, alkenyl or alkynyl having 3-10 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl- alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C- atoms in the alkyl group, phenylalkenyl, heteroaryl- alkenyl, phenylalkynyl or heteroaryl-alkynyl group having 3-5 C-atoms in the alkenyl group or alkynyl group, which groups R_3 and R_4 may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or wherein R_3+R_4 together with the nitrogen atom form a saturated or unsaturated

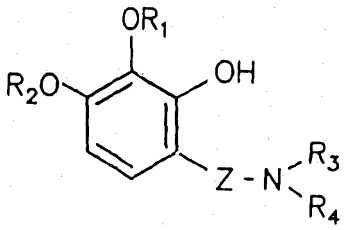
heterocyclic group of 5-7 ring atoms, which may contain a second hetero-atom from the group consisting of oxygen, sulphur and nitrogen, which ring may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or with phenylalkyl, heteroaryl-alkyl, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having at most 3 C-atoms in the alkyl, alkenyl or alkynyl part, which groups may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above-mentioned meanings, or which ring may be annelated with a phenylgroup;

$-R_5$ is alkyl having 1-12 C-atoms, alkenyl or alkynyl having 3-12 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl sub-group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having 3-5 C-atoms in the alkenyl sub-group or alkynyl sub-group, which groups may be substituted with a group $(R_6)_p$, wherein R_6 and p have the above-mentioned meanings, and which alkyl sub-groups, alkenyl sub-groups and alkynyl sub-groups may contain a group -O-, -S- or CO, or a pharmacologically acceptable salt thereof.

2. A method of preparing an alkylenedioxyphenyl ether derivative, characterized in that a compound having formula 1A or 1B, wherein Z and R_1-R_5 have the meanings given in claim 1 is prepared by reacting a compound having formula 5 or 6



(5)



(6)

with a compound of the formula R_5-X wherein R_5 has the meaning given in claim 1 and X is a leaving group.

3. A composition having anti-ischaemic, memory enhancing and anti-convulsive activity which includes at least one compound as claimed in claim 1 together with a pharmaceutically acceptable carrier.

4. A method of preparing a composition as claimed in claim 3, characterized in that a compound of formula 1A or 1B wherein the symbols have the meaning mentioned in claim 1, or a salt thereof, is brought into a form suitable for administration.

5. A method of treating ischaemia, impaired memory or epilepsy, characterised in that a compound according to claim 1 is used.

6. A compound as claimed in claim 1 substantially as hereinbefore described with reference to any one of the examples.

7. A composition as claimed in claim 3 substantially as hereinbefore described with reference to any one of the examples.

8. A method as claimed in claim 2 or claim 4 substantially as hereinbefore described with reference to any one of the examples.

9. A method as claimed in claim 5 substantially as hereinbefore described with reference to any one of the examples.

DATED: 10 January 1994
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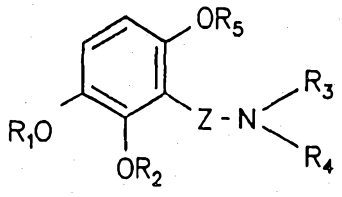
David B Fitzpatrick

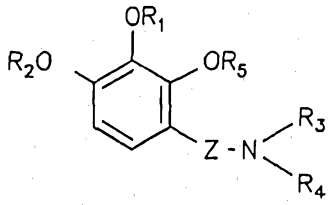
WDN

Abstract

The invention relates to compounds having anti-ischaemic activity, memory enhancing activity and anti-convulsive activity of the formulae 1A and 1B



(1A)



(1B)

wherein

-R_1 + R_2 together form an alkylene group having 1-3 C-atoms which may be substituted with one or more alkyl group(s) having 1-3 C-atoms;

-Z is methylene optionally substituted with one alkyl group having 1-3 C-atoms, or with one phenylalkyl group with 1-3 C-atoms in the alkyl group, which phenyl group may be substituted with a group $(R_6)_p$ wherein R_6 is halogen, hydroxy, alkyl or hydroxyalkyl having 1-5 C-atoms, alkoxy having 1-3 C-atoms, S-alkyl, S(O)-alkyl or $S(O)_2$-alkyl having 1-3 C-atoms, amino, mono- or dialkylamino having 1-3 C-atoms per alkyl group, trifluoromethyl, trifluoromethoxy, a sulphonylamido group SO_2NHR or a carbalkoxy group COOR wherein R is alkyl having 1-4 C-atoms, the group COOH, SO_3H,$CONH_2$, the amidino group or cyano group, and p has the value 0-3;

-R_3 and R_4 independent of each other represent hydrogen, alkyl having 1-10 C-atoms, alkenyl or alkynyl having 3-10 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl group having 3-5 C-atoms in the alkenyl group or alkynyl group, which groups R_3 and R_4 may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or wherein $R_3 + R_4$ together with

the nitrogen atom form a saturated or unsaturated heterocyclic group of 5-7 ring atoms, which may contain a second hetero-atom from the group consisting of oxygen, sulphur and nitrogen, which ring may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above mentioned meanings, or with phenylalkyl, heteroarylalkyl, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having at most 3 C-atoms in the alkyl, alkenyl or alkynyl part, which groups may be substituted with a group $(R_6)_p$ wherein R_6 and p have the above-mentioned meanings, or which ring may be annelated with a phenyl group;

$-R_5$ is alkyl having 1-12 C-atoms, alkenyl or alkynyl having 3-12 C-atoms, cycloalkyl having 3-8 C-atoms, cycloalkyl-alkyl having 3-8 ring atoms and 1-5 C-atoms in the alkyl group, phenylalkyl or heteroaryl-alkyl having 1-5 C-atoms in the alkyl sub-group, phenylalkenyl, heteroaryl-alkenyl, phenylalkynyl or heteroaryl-alkynyl having 3-5 C-atoms in the alkenyl sub-group or alkynyl sub-group, which groups may be substituted with a group $(R_6)_p$, wherein R_6 and p have the above-mentioned meanings, and which alkyl sub-groups, alkenyl sub-groups and alkynyl sub-groups may contain a group -O-, -S- or CO, or a pharmacologically acceptable salt thereof.