HETEROCYCLIC DERIVATIVES IN THE TREATMENT OF ISCHAEMIA AND RELATED DISEASES

Novel substituted piperidines and piperazines or the pharmaceutically acceptable acid addition salts thereof, are calcium and/or sodium channel antagonists useful for treating mammals having a variety of disease states, such as stroke, epilepsy, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, and also for treatment of spinal injuries.
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HETEROCYCLIC DERIVATIVES IN THE TREATMENT OF ISCHAEMIA
AND RELATED DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to substituted heterocyclic derivatives of
Formula (I), the pharmaceutically acceptable salts thereof, methods of
making these compounds, and pharmaceutical compositions containing them.
The compounds of this invention are calcium and/or sodium channel
antagonists, and are efficacious for the treatment of ischaemia and other
disease states, and have protective activity against some of the
deleterious effects resultant upon cerebral ischemia.

Background Information and Related Disclosures

The compounds of this invention are various amino heterocyclic
derivatives. Compounds somewhat structurally related are described in U.S.
Patent Nos. 4,829,065, 5,043,447, 5,091,428, in GB Patent No. 1,434,854,
and in JP 49093379.

SUMMARY OF THE INVENTION

A first aspect of the present invention relates to compounds of the
Formula (I):

\[
A \quad \underset{R^1}{\text{R}} \quad (CH_2)_m \quad \underset{R^2}{N} \quad (I)
\]

wherein:
m is 0 or 1;
R' is hydrogen, hydroxy, or lower alkyl;
R^2 is hydrogen, or lower alkyl;
R^3 is

\[
-X \quad (CH_2)_n R^4 \quad R^5
\]

or R^2 and R^3 taken together with the nitrogen atom to which they are
attached represent a group of the formula:

\[
\begin{array}{c}
\text{N} \quad (CH_2)_p \quad (CH_2)_q R^4 \quad \text{or} \\
\text{R}^4 \quad R^5 \\
\text{N} \quad (CH_2)_p \quad (CH_2)_q R^4 \quad \text{or} \\
\text{R}^4 \quad R^5 \\
\end{array}
\]

wherein:
n is 0 or 1;
p is 0, 1, 2 or 3;
q is 0 or 1;
R' is hydrogen, lower alkyl, cycloalkyl, or optionally substituted phenyl;
R' is optionally substituted phenyl;
X is (CH<sub>2</sub>)<sub>n</sub>, or 4-piperidin-1-yl;
Y is CH<sub>2</sub>, CH-O-, CH-S-, or nitrogen;
Z is CH<sub>2</sub>, NH, sulfur, or oxygen; and
A is chosen from the group consisting of:

wherein:
R<sup>1</sup> is lower alkyl, or optionally substituted phenyl;
R<sup>6</sup> is hydrogen, or lower alkyl;
R<sup>11</sup> is lower alkyl or optionally substituted aryl;
R<sup>12</sup> is hydrogen, lower alkyl, lower alkoxy, halo, or trifluoromethyl; and
W is oxygen, sulfur, or NR<sup>15</sup>;

with the proviso that R<sup>8</sup>, R<sup>10</sup>, R<sup>12</sup>, and the sidechain cannot be attached to a hetero atom; or a pharmaceutically acceptable acid addition salt thereof.

A second aspect of this invention relates to pharmaceutical compositions containing at least one compound of Formula (I) and one or more pharmaceutically acceptable excipients.

A third aspect of the invention relates to use of a compound of Formula (I) for treating mammals having a disease treated by direct neuronal protection or a disease treated by calcium channel inhibition, sodium channel inhibition, or inhibition of both calcium and sodium channels, including:

diseases treated by direct neuronal protection, such as ischaemia including focal and global cerebral ischaemia, cerebral ischaemia including ischaemia-induced neurodegeneration, perinatal asphyxia, spinal injuries, peripheral nerve ischaemia, peripheral nerve damage, neuropathic pain, head trauma, primary intracerebral hemorrhage, encephalopathy, epilepsy or epileptic psychotic symptoms, and neurological diseases such as Alzheimer's, Huntington's chorea, Parkinson's and dementias; and
diseases treated by calcium channel inhibition, sodium channel inhibition, or inhibition of both calcium and sodium channels,
including:

diseases treated by inhibiting cerebrovascular vasospasm and by cerebrovascular vasodilation, such as migraine, stroke, vasospasm due to subarachnoid hemorrhage, and cerebrovascular ischaemia induced by cocaine abuse;

diseases treated by inhibiting cellular oedema, such as cerebral oedema and hyponatraemic encephalopathy;

cardiovascular diseases, such as hypertension, angina, stable and unstable angina, Prinzmetal angina, arrhythmia, thrombosis, myocardial infarction, embolism, and congestive heart failure such as chronic or acute cardiac failure;

diseases characterized by ischaemia of lower legs due to peripheral vascular disease, including intermittent claudication;

diseases characterized by spasms of smooth muscle, including reversible airways obstruction, asthma, spasms of the ureter, spasms of the bladder, uterine cramps, and irritable bowel syndrome;

prevention of vasoconstriction and/or ischaemic tissue damage during a surgical procedure, such as bypass grafts, angiography, angioplasty, organ preservation during transplant, hypertensive crisis, or post-operative hypertension;

diseases treated by diuresis; and uraemic encephalopathy,

by administering an effective amount of a compound of Formula (I), or a composition containing a compound of Formula (I), to the mammal.

A fourth aspect of the invention relates to methods for the preparation of the compounds of Formula (I).

**Definitions**

As used herein:

"Alkyl" means a monoradical branched or unbranched saturated hydrocarbon chain containing 1 to 12 carbon atoms, such as methyl, ethyl, propyl, tert-butyl, n-hexyl, n-octyl, n-decyl, and the like, unless otherwise indicated.

"Lower alkyl" means a monoradical branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, tert-butyl, butyl, n-hexyl, and the like, unless otherwise indicated.

"Cycloalkyl" means a saturated monovalent monocyclic hydrocarbon radical containing 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, optionally substituted by lower alkyl as defined above.

"Lower alkoxy" means the group -O-R wherein R is lower alkyl as defined above.

The term "halo" means fluoro, bromo, chloro or iodo, unless otherwise indicated.

The terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ("CHCl_3"), methylene chloride (or dichloromethane or "CH_2Cl_2"), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The compounds of Formula (I) form acid addition salts by virtue of the presence of basic nitrogen atoms. "Pharmacologically acceptable salt" means those salts which retain the biological effectiveness and properties of the compounds of Formula (I), and which are not biologically or otherwise undesirable. Acid addition salts may be formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

The compounds of this invention may have one or more asymmetric centers (for example where R^1 is not hydrogen, or where q is 0 and R^4 is lower alkyl), and can be produced as racemic mixtures or as individual stereoisomers. The individual stereoisomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of a compound of Formula (I). It is understood that the individual stereoisomers as well as racemic and non-racemic mixtures of stereoisomers are encompassed within the scope of the present invention.

The term "aryl" means a monocyclic aromatic ring, and includes carbocycles and heterocycles. Examples of aryl groups are phenyl, thiophene, furan, imidazole, pyridine, pyrimidine, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted phenyl" or "optionally substituted aryl" means that phenyl or aryl may or may not be
substituted with a substituent selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, nitro, trifluoromethyl and halo, and encompasses all possible isomeric phenyl radicals that are mono, di or trisubstituted.

The term "Y" is defined as CH, CH-O-, CH-S-, or nitrogen. This definition is intended to indicate that Y forms part of a ring having the structures:

The term "mammal" includes humans and all domestic and wild mammals, including, without limitation, cattle, horses, swine, sheep, goats, dogs, cats, rabbits, and the like.

The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes:

(i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease, i.e. arresting its development; or

(iii) relieving the disease, i.e. causing regression of the disease.

The term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

The naming and numbering of the compounds of the present invention is illustrated below.

A compound of Formula (I) where A is a furan, thiophene, or pyrrole derivative is illustrated below as a compound of Formula (IB), and is numbered as follows:

A compound of Formula (IB) wherein \( R^0 \) is 5-(4-trifluoromethylphenyl); \( R^0 \) is 3-methyl; \( W \) is oxygen; and the sidechain is in the 2-position, in which \( m = 0 \); \( R^1 \) is hydrogen; and \(-NR^2R^3\) represents a group of the formula:
where \( p \) and \( q \) are 0; \( R' \) and \( R'' \) are both phenyl; and \( Y \) is carbon; is named: 4-diphenylmethyl-1-\{(5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl)methyl\}piperidine.

A compound of Formula (I) where \( A \) is:

is illustrated below as a compound of Formula (IDA), and is numbered as follows:

However, when \( R^{11} \) is optionally substituted phenyl, the compounds are biphenyl derivatives, and are numbered accordingly:

Thus, a compound of Formula (IDA) wherein \( R^{11} \) is 4-methoxyphenyl; \( R^{12} \) is 4-methyl; and the sidechain is in the 3-position; in which \( m \) is 0; \( R' \) is hydrogen; and \(-NR'R''\) represents a group of the formula:

where \( p \) and \( q \) are 0; \( R' \) is hydrogen; \( R'' \) is 2,3,4-trimethoxyphenyl; and \( Y \) is nitrogen; is named:

1-(2,3,4-trimethoxyphenyl)methyl-4-[4-methyl-4'-methoxybiphenyl-3-ylmethyl]piperazine.

**Preferred Embodiments**

Among the family of compounds of the present invention, one preferred category includes the compounds of Formula (I) where \( A \) is:
Within this category one preferred group includes the compounds where $R^2$ and $R^1$ taken together with the nitrogen atom to which they are attached represent a group of the formula:

\[
\begin{array}{c}
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\end{array}
\]

\[
Y - \left( \text{CH}_2 \right)_p - \left( \text{CH}_2 \right)_q R^d
\]

especially where $m$ is 0, $q$ is 0, and $R^1$ is hydrogen or lower alkyl, $R^2$ is optionally substituted phenyl and $R^3$ is lower alkyl. Within this group one preferred subgroup includes the compounds where $p$ is 0, $R^1$ is hydrogen, and $R^2$ and $R^3$ are both phenyl, more especially where $Y$ is nitrogen.

Another preferred group within this category includes the compounds where $R^2$ and $R^1$ taken together with the nitrogen atom to which they are attached represent a group of the formula:

\[
\begin{array}{c}
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\end{array}
\]

\[
Z
\]

especially where $Z$ is oxygen, and $R^1$ and $R^2$ are both phenyl.

Another preferred category includes the compounds of Formula (I) where $A$ is:

\[
\begin{array}{c}
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\text{\textbullet} \\
\end{array}
\]

Within this category one preferred group includes the compounds where $R^2$ and $R^1$ taken together with the nitrogen atom to which they are attached represent a group illustrated as (II) above, especially where $m$ is 0, $q$ is 0, and $R^1$ is hydrogen or lower alkyl, $R^2$ is optionally substituted phenyl and $R^3$ is lower alkyl.

**Preparation of Compounds of Formula (IB)**

Compounds of Formula (I) where $A$ is a furan, thiophene, or pyrrole derivative, illustrated as compounds of Formula (IB), may be prepared from
compounds of Formulae (9) or (10), as shown below in Reaction Schemes IIIA
and IIIB.

A. Preparation of Compounds of Formula (IB) where m is 0 and R₁ is Hydrogen

REACTION SCHEME IIIA

\[ \text{Step 1} \quad \text{Step 2} \]

where m is 0, R₁ is hydrogen, and R², R³, R⁴, R⁵, and W are as defined in the
Summary of the Invention.

Starting Materials
The compounds of Formula (9) are commercially available, or can be
made by the methods disclosed in Utimoto et al., Tet. Lett., Vol. 22, pp
Khimi, Vol. 43, p2749 (1973), Mukaiyama et al., Chem. Lett., pp 527,

Step 1 - Preparation of Compounds of Formula (9a)
To prepare compounds of Formula (9a), first about 1 molar equivalent
of phosphorus oxychloride is reacted with about 1 molar equivalent of N,N-
dimethylformamide, preferably in the absence of solvent, at a temperature
of about -10 to 10°C, preferably at about 0°C, for about 10 minutes to 2
hours, preferably about 30 minutes. About 1 molar equivalent of a compound
of Formula (9) dissolved in an inert solvent (such as dichloromethane,
chloroform, dichloroethane, preferably dichloroethane) is then added. The
reaction is carried out at a temperature of about 0 to 40°C, preferably at
about 25°C, for about 30 minutes to 5 hours, preferably about 1½ hours.
When the reaction is substantially complete, the formyl compound of Formula
(9a) is isolated and purified by conventional means, preferably flash
chromatography.

Step 2 - Preparation of Compounds of Formula (IB) where m is 0 and R₁ is Hydrogen
To prepare compounds of Formula (IB) where m is 0 and R₁ is hydrogen,
an amine of formula HNR₁R₃ is reacted with about 1 to 3 molar equivalents,
preferably about 1.2 molar equivalents of a compound of Formula (9a) in the
presence of a titanium(IV) catalyst (for example titanium tetrachloride,
titanium(IV) ethoxide, titanium(IV) isopropoxide, preferably titanium(IV)
isopropoxide). The reaction is carried out in a protic solvent (for
example methanol, ethanol, propanol, preferably ethanol), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 10 minutes to 4 hours, preferably about 1 hour. To the reaction mixture is then added a reducing agent (for example sodium borohydride, sodium cyanoborohydride, preferably sodium cyanoborohydride), and the reaction continued for about 10 minutes to 4 hours, preferably about 1 hour. When the reaction is substantially complete, the product of Formula (IB) is isolated and purified by conventional means, preferably flash chromatography followed by conversion to an acid salt, preferably a hydrochloride salt. Such a reaction is also described in Mattson, J.O.C., Vol. 55, p2552 (1990).

Alternative Step 2 - Preparation of Compounds of Formula (IB) where \( m = 0 \) and \( R' \) is Lower Alkyl

To prepare compounds of Formula (IB) where \( m = 0 \) and \( R' \) is lower alkyl, a compound of Formula (9a) is first reacted with an amine of formula \( \text{HNR}_2R' \) in the presence of a titanium(IV) catalyst, as shown above in Reaction Scheme IIIA, but the intermediate imine is then reacted with a Grignard reagent of formula \( R'\text{MgBr} \) (in place of the reducing agent), by means well known in the art. When the reaction is substantially complete, the product of Formula (IB) where \( m = 0 \) and \( R' \) is lower alkyl is isolated and purified by conventional means, preferably flash chromatography followed by conversion to an acid salt, preferably a hydrochloride salt.

B. Preparation of Compounds of Formula (IB) where \( m = 1 \) and \( R' \) is Hydroxy

**REACTION SCHEME IIIB**

![Reaction Scheme IIIB](image)

where \( m = 1 \), \( R' \) is hydroxy, and \( R^2, R^3, R^4, R^6, \) and \( W \) are as defined in the
Summary of the Invention.

Starting Materials

The compounds of Formula (10) are commercially available, or can be made by the methods disclosed in J.A.C.S. Vol. 75, 5056 (1953), Tetrahedron, Vol. 44, 3343 (1988), and Ber., 616 (1964).

Preparation of Compounds of Formula (IB) where m is 1 and R' is Hydroxy

To prepare compounds of Formula (IB) where m is 1 and R' is hydroxy, a compound of Formula (10) is first reacted with a halogenating agent (for example, bromine, pyrrolidine hydrotribromide, preferably pyrrolidine hydrotribromide). The reaction is carried out in an ethereal solvent (for example ether, dimethoxymethane, tetrahydrofuran, preferably tetrahydrofuran), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 16 hours. When the reaction is substantially complete, the product (an acyl bromide) is isolated and reacted with about 1 to 3 molar equivalents, preferably about 1.1 molar equivalents, of an amine of formula HRNR'R in the presence of excess base, preferably potassium carbonate. The reaction is carried out in a protic solvent (for example methanol, ethanol, propanol, preferably propanol), at a temperature of about 40 to 100°C, preferably at about reflux temperature, for about 30 minutes to 4 hours, preferably about 2 hours. When the reaction is substantially complete, the product of Formula (11) is isolated and purified by conventional means, preferably flash chromatography.

The compound of Formula (11) is then reduced conventionally, preferably with sodium borohydride in methanol, to give the compound of Formula (IB) where m is 1 and R' is hydroxy.

Preparation of Compounds of Formula (ID)

Preparation of Compounds of Formula (IDA)

Compounds of Formula (I) where A is:

\[
\begin{array}{c}
R^1 \text{ or } R^2 \\
R^3 \\
\end{array}
\]

are illustrated as compounds of Formula (IDA). They may be prepared from compounds of Formula (19), the preparation of which is shown below in Reaction Scheme V.
where R is lower alkyl, and R', R", R', and R", are as defined in the Summary of the Invention.

**Starting Materials**

The compounds of Formulae (15) and (16) are commercially available from Aldrich, for example, or can be made by the methods disclosed in *Tet. Lett.*, Vol. 29 (11), pp 1293-1294 (1988) and *J. Med. Chem.*, Vol. 32, pp 105 118 (1989), or can be made for example as shown in Reaction Scheme VA below.

**REACTION SCHEME VA**

The nitro ester is reduced to the amino ester by means well known in the art, for example hydrogenation using palladium on carbon as a catalyst. The amine is then converted to the iodo compound by means well known in the art, for example diazotisation of the amine with sodium nitrite, followed by treatment with potassium iodide.

**Step 1 - Preparation of Compounds of Formula (17)**

To prepare compounds of Formula (17), a compound of Formula (16) is reacted with about 1 to 3 molar equivalents, preferably about 1.5 molar equivalents, of a compound of Formula (15) in the presence of a Grignard reaction catalyst (for example about 0.05 molar equivalents of nickel(II) chloride, [1,3-bis(diphenylphosphino)propane]nickel(II) chloride, or
reduced palladium prepared in situ from [1,3-bis(triphenylphosphino)-palladium(II) chloride and diisobutylaluminum hydride, preferably nickel(II) chloride). The reaction is carried out in an ethereal solvent (for example ether, dimethoxymethane, tetrahydrofuran, preferably tetrahydrofuran), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 16 hours. When the reaction is substantially complete, the ester of Formula (17) is isolated and purified by conventional means, preferably flash chromatography.

Step 2 - Preparation of Compounds of Formula (18)

To prepare compounds of Formula (18), a compound of Formula (17) is hydrolysed conventionally, for example by heating with a strong base in a protic solvent, for example sodium hydroxide in aqueous ethanol, and isolating and purifying the acid of Formula (18) by conventional means.

Step 3 - Preparation of Compounds of Formula (19)

To prepare compounds of Formula (19), a compound of Formula (18) is first reacted with about 1 to 1.5 molar equivalents, preferably about 1.2 molar equivalents, of a halogenating agent (for example, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, preferably thionyl chloride). The reaction is carried out in a mixture of an inert solvent (for example chloroform, ethyl acetate, methylene chloride, preferably methylene chloride) and dimethylformamide, at a temperature of about 40 to 80°C, preferably at about reflux temperature, until the reaction is complete. This mixture is then reacted with about 1 to 3 molar equivalents, preferably about 1.5 molar equivalents, of an amine of formula HNR₃. The reaction is carried out at a temperature of about 0 to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 16 hours. When the reaction is substantially complete, the amide of Formula (19) is isolated and purified by conventional means, preferably flash chromatography.

Preparation of Compounds of Formula (IDA)

Compounds of Formula (IDA) are prepared from the derivatives of Formula (19), as shown in Reaction Scheme VI.

**REACTION SCHEME VI**

[Diagram of Reaction Scheme VI]

where \( R^7, R^3, R^{11} \) and \( R^{12} \) are as defined in the Summary of the Invention.
Step 4 - Preparation of Compounds of Formula (IDA) where m is 0 and R₁ is Hydrogen

To prepare compounds of Formula (IDA) where m is 0 and R₁ is hydrogen, a compound of Formula (19) is reacted with about 1 to 3 molar equivalents, preferably about 1.5 molar equivalents, of a suitable reducing agent (for example borane, triethylloxonium fluoroborate followed by sodium borohydride, or preferably lithium aluminum hydride). The reaction is carried out in an ethereal solvent (for example ether, dimethoxymethane, tetrahydrofuran, preferably a mixture of ether and tetrahydrofuran), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 30 minutes to 8 hours, preferably about 1½ hours. When the reaction is substantially complete, the amine of Formula (IDA) is isolated and purified by conventional means, preferably flash chromatography followed by conversion to an acid salt, preferably a hydrochloride salt.

Alternative Preparation of Compounds of Formula (ID)

Alternatively, compounds of Formula (IDA) where m is 0 and R₁ is hydrogen may be prepared from the compounds of Formula (17), as shown in Reaction Scheme VII.

REACTION SCHEME VII

where R², R³, R¹₁ and R¹₂ are as defined in the Summary of the Invention.

Step 1 - Preparation of Compounds of Formula (20)

Compounds of Formula (20) are prepared from compounds of Formula (17). A compound of Formula (17) is reacted with about 1 to 3 molar equivalents, preferably about 1.5 molar equivalents, of a suitable reducing agent (for example borane, triethylloxonium fluoroborate followed by sodium borohydride, sodium borohydride in the presence of a carboxylic acid, or preferably lithium aluminum hydride). The reaction is carried out in an ethereal solvent (for example ether, dimethoxymethane, tetrahydrofuran, preferably a mixture of ether and tetrahydrofuran), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 30 minutes to 8 hours, preferably about 1½ hours. When the reaction is substantially complete, the alcohol of Formula (20) is isolated and purified by conventional means, preferably flash chromatography.
Step 2 - Preparation of Compounds of Formula (IDA) where m is 0 and R' is Hydrogen

To prepare compounds of Formula (IDA) where m is 0 and R' is hydrogen, the hydroxy group of the -CH₂OH moiety of a compound of Formula (20) is first converted into a leaving group, for example by conversion to a halo group by means well known in the art, or preferably by reacting with about 1 to 1.5 molar equivalents, preferably about 1.2 molar equivalents, of a sulfonylating agent (for example, p-toluenesulfonyl chloride, or preferably methanesulfonyl chloride) in an inert organic solvent (such as benzene, toluene, ethyl acetate, acetonitrile, tetrahydrofuran, diethyl ether, chloroform, or dichloromethane, preferably dichloromethane) containing from 1 to 10 molar equivalents, preferably about 1.3 molar equivalents, of an inorganic base (such as sodium carbonate, potassium bicarbonate or the like), or preferably a tertiary organic base (such as pyridine, N-methylpiperidine and the like, preferably triethylamine), at a temperature of about 0 to 40°C, preferably at about 25°C, for about 2 to 24 hours, preferably about 16 hours. The product is isolated and purified by conventional means, and then reacted with about 1 to 3 molar equivalents, preferably about 1.2 molar equivalents, of an amine of formula HNR²R'. The reaction is carried out in an inert solvent as defined above, preferably acetonitrile, in the presence of about 1 to 3 molar equivalents, preferably about 1.2 molar equivalents, of an organic base or inorganic base as defined above, preferably potassium bicarbonate, at a temperature of about 20 to 100°C, preferably at about 60°C, for about 1 to 8 hours, preferably about 3 hours. When the reaction is substantially complete, the compound of Formula (IDA) is isolated and purified by conventional means, preferably flash chromatography followed by conversion to an acid salt, preferably a hydrochloride salt.

Isolation and Purification of the Compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Examples hereinafter. However, other equivalent separation or isolation procedures could, of course, also be used.

Salts of Compounds of Formula (I)

The compounds of Formula (I) may be converted to a corresponding acid addition salt by virtue of the presence of basic nitrogen atoms. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid,
sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, menthane sulfonic acid, ethanesulfonic acid, p-toluene sulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained at 0° to 50°C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

In summary, the compounds of the present invention are made by the procedures outlined below:

A process for the preparation of a compound represented by the Formula:

\[
\text{A} \quad \text{(I)}
\]

wherein:

- \( m \) is 0 or 1;
- \( R^1 \) is hydrogen, hydroxy, or lower alkyl;
- \( R^2 \) is hydrogen, or lower alkyl;
- \( R^3 \) is

\[
-X-(\text{CH}_2)_n \quad R^4
\]

or \( R^2 \) and \( R^3 \) taken together with the nitrogen atom to which they are attached represent a group of the formula:

\[
\text{or}
\]

wherein:

- \( n \) is 0 or 1;
- \( p \) is 0, 1, 2 or 3;
- \( q \) is 0 or 1;
- \( R^4 \) is hydrogen, lower alkyl, cycloalkyl, or optionally substituted phenyl;
R is optionally substituted phenyl;
X is (CH)_n, or 4-piperidin-1-yl;
Y is CH, CH-O-, CH-S-, or nitrogen;
Z is CH, NH, sulfur, or oxygen; and

A is chosen from the group consisting of:

wherein:
R' is lower alkyl, or optionally substituted phenyl;
R' is hydrogen, or lower alkyl;
R' is lower alkyl or optionally substituted aryl;
R' is hydrogen, lower alkyl, lower alkoxy, halo, or
trifluoromethyl; and
W is oxygen, sulfur, or NR';

wherein R' is hydrogen or lower alkyl;

with the proviso that R', R', R', and the sidechain cannot be attached to a
hetero atom; or a pharmaceutically acceptable acid addition salt thereof,
which comprises

a) reacting a compound of the formula

wherein R' and R' are as defined above, with an amine of the formula HNR'R',
wherein R' and R' are as defined above, in the presence of a titanium (IV)
catalyst, followed by the addition of a reducing agent (if R' is hydrogen)
or a Grignard reagent (if R' is lower alkyl) to form a compound of Formula

b) reacting a compound of the formula

wherein R', R', R', and R' are as defined above, with a reducing agent to
form a compound of Formula I wherein R' is hydroxy; or

c) reacting a compound of the formula
wherein $R^{11}$, $R^{12}$, $R^{2}$, and $R^{3}$ are as defined above, with a reducing agent to form a compound of Formula I; or

d) reacting a compound of the formula

wherein $R^{11}$ and $R^{12}$ are as defined above, and $L$ is a leaving group with an amine of the formula $HNR^{2}R^{3}$ wherein $R^{2}$ and $R^{3}$ are as defined above to form a compound of Formula I; or

e) reacting the free base of a compound of Formula I with an acid to give a pharmaceutically acceptable acid addition salt; or

f) reacting an acid addition salt of a compound of Formula I with a base to give the corresponding free base; or

g) converting an acid addition salt of a compound of Formula I to another pharmaceutically acceptable acid addition salt.

Utility and Methods of Administration

General Utility

The compounds of this invention are useful for treating mammals having a variety of vascular disease states, and have protective activity against some of the deleterious effects resultant upon cerebral ischemia. The compounds are useful for treating mammals having a disease treated by direct neuronal protection or a disease treated by calcium channel inhibition, sodium channel inhibition, or inhibition of both calcium and sodium channels, including:

diseases treated by direct neuronal protection, such as

ischaemia including focal and global cerebral ischaemia, cerebral ischaemia including ischaemia-induced neurodegeneration, perinatal asphyxia, spinal injuries, peripheral nerve ischaemia, peripheral nerve damage, neuropathic pain, head trauma, primary intracerebral hemorrhage, encephalopathy, epilepsy or epileptic psychotic symptoms, and neurological diseases such as Alzheimer's, Huntington's chorea, Parkinson's and dementias; and

diseases treated by calcium channel inhibition, sodium channel inhibition, or inhibition of both calcium and sodium channels, including:
diseases treated by inhibiting cerebrovascular vasospasm and by cerebrovascular vasodilation, such as migraine, stroke, vasospasm due to subarachnoid hemorrhage, and cerebrovascular ischaemia induced by cocaine abuse;

diseases treated by inhibiting cellular oedema, such as cerebral oedema and hyponatraemic encephalopathy;

cardiocvascular diseases, such as hypertension, angina, stable and unstable angina, Prinzmetal angina, arrhythmia, thrombosis, myocardial infarction, embolism, and congestive heart failure such as chronic or acute cardiac failure;

diseases characterized by ischaemia of lower legs due to peripheral vascular disease, including intermittent claudication;

diseases characterized by spasms of smooth muscle, including reversible airways obstruction, asthma, spasms of the ureter, spasms of the bladder, uterine cramps, and irritable bowel syndrome;

prevention of vasoconstriction and/or ischemic tissue damage during a surgical procedure, such as bypass grafts, angiography, angioplasty, organ preservation during transplant, hypertensive crisis, or post-operative hypertension;

diseases treated by diuresis; and uraemic encephalopathy.

Generally, vascular disease states are found in mammals, including: domestic commercial animals such as horses, cattle, sheep and pigs; domestic house animals such as dogs, cats, and the like; and particularly humans.

Activity Testing
Affinity for sodium channels and interaction with sodium and calcium currents can be determined in vitro, and activity for treating cerebrovascular disease states can be determined in vivo by ascertaining the neuroprotective effect. Sodium channel affinity is determined in vitro by measuring the displacement of [3H]-batrachotoxin from its binding sites on the sodium channel, as shown in Example 13.

Sodium and calcium channel activities are determined in vitro by whole cell voltage-clamp recordings of sodium and channel currents, as shown in Example 14.

In vivo activity can be determined according to the mouse model of focal ischaemia (the mouse middle cerebral artery occlusion, or "MCA" model) Gotti, B. et al., Brain Res, 1990, 522, 290-307. The MCA model entails an indirect measure of neuronal cell death following an ischemic
event (i.e., occlusion of the left middle cerebral artery), as described in Example 16 below.

General Administration

The compounds of this invention are administered at a therapeutically effective dosage, i.e., a dosage sufficient to provide treatment for the disease states previously described. Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for agents that serve similar utilities.

Generally, a daily dose of from 0.02 to 50 mg/kg of body weight per day of the active compound of Formula I. Most conditions respond to treatment comprising a dosage level on the order of 0.1 to 4 mg/kilogram of body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 1.4 to 3500 mg per day, preferably about 7.0 to 280 mg per day.

Depending on the specific disease state, administration can be via any accepted systemic route, for example, via parenteral, oral, intravenous, or nasal routes, in the form of solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, aerosols, emulsions or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula (I) and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The compounds of this invention are generally administered as a pharmaceutical composition which comprises a pharmaceutical excipient in combination with a compound of Formula (I). The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about 0.01 percent by weight (%wt) to about 99.99%wt of the drug based on the total formulation and about 0.01%wt to 99.99%wt excipient. Preferably, the formulation will be about 3.5 to 60%wt of the pharmaceutically active compound, with the rest being suitable pharmaceutical excipients.

Oral Administration

The preferred manner of administration, for the conditions detailed above, is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such oral administration, a pharmaceutically acceptable, non-toxic composition is
formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talc, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between 0.01%wt and 99.99%wt of the compound of Formula (I), but preferably such compositions will contain between 25%wt and about 80%wt.

Preferably the compositions will take the form of a pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, polyvinylpyrrolidone, gum acacia, gelatin, cellulose and derivatives thereof, and the like.

**Suppositories**

For systemic administration via suppository, traditional binders and carriers include, for example, polyalkaline glycol or triglycerides [e.g., PEG 1000 (96%) and PEG 4000 (4%)]. Such suppositories may be formed from mixtures containing active ingredients in the range of from about 0.5%wt to about 10%wt; preferably from about 1%wt to about 2%wt.

**Liquides**

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1980. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings of this invention.

**EXAMPLES**

The following preparations and examples are given to enable those skilled in the art to more clearly understand and practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative of the preferred embodiments of the present invention.

Unless specified to the contrary, these preparations and examples are carried out under an inert atmosphere, for example nitrogen or argon.
PREPARATION 1
Preparation of Compounds of Formula (9a)

A. Preparation of (9a) where R^8 is 5-(4-Methylphenyl), R^9 is 3-Methyl, W is Oxygen, and -CHO is in the 2-Position

Phosphorus oxychloride (12 ml) was added slowly to dimethylformamide (9.85 ml) with stirring at 0°C, and the mixture stirred at 0°C for 30 minutes. A solution of 3-methyl-5-(4-methylphenyl)furan (22 g) in 50 ml of dichloroethane was added dropwise over a period of 15 minutes, maintaining the temperature at 0°C. The mixture was then stirred at room temperature for 1½ hours. Ice water was then added, and the pH of the aqueous layer adjusted to about 8 with dilute sodium hydroxide. The organic layer was separated, the aqueous layer extracted with dichloromethane, the organic portions combined and solvent removed under reduced pressure. The solvent was removed from the filtrate under reduced pressure, and the residue flash chromatographed on silica gel, eluting with 10% ethyl acetate in heptane, to yield 19.2 g of 2-formyl-3-methyl-5-(4-methylphenyl)furan.

B. Preparation of (9a) varying R^8, R^9, W, and the Position of the Formyl Group

Similarly, following the procedures of Preparation 1A above, but replacing 3-methyl-5-(4-methylphenyl)furan with other compounds of Formula (9), the following intermediates of Formula (9a) were prepared:

- 2-formyl-3-methyl-5-(n-butyl)furan, as an oil;
- 2-formyl-3-methyl-5-(t-butyl)furan, as an oil;
- 2-formyl-3-methyl-5-phenylfuran, m.p. 55°C;
- 2-formyl-3-methyl-5-(4-trifluoromethylphenyl)furan, m.p. 80°C;
- 2-formyl-3-methyl-5-cyclohexylfuran, as an oil;
- 2-formyl-3-methyl-5-phenylpyrrole, m.p. 152-153°C;
- 3-formyl-2-methyl-5-phenylpyrrole, m.p. 150°C;
- 3-formyl-1,2-dimethyl-5-phenylpyrrole, m.p. 97°C;
- 2-formyl-1,3-dimethyl-5-phenylpyrrole, m.p. oil;
- 2-formyl-3-methyl-5-phenylthiophene, m.p. 110°C; and
- 3-formyl-2-methyl-5-phenylthiophene, m.p. 82-83°C.

PREPARATION 2
Preparation of Compounds of Formula (17)

A. Preparation of (17) where R'^11 is 4-Methylphenyl, R'^12 is Hydrogen, and R is Ethyl

Magnesium (1.6 g) and p-bromotoluene (10.26 g) in 60 ml of tetrahydrofuran were stirred and warmed until the reaction commenced. When the exothermic reaction had finished, the mixture was refluxed overnight. In a separate flask, 4 ml of DIBAL (1M in toluene) was added to a
suspension of bis(triphenyolphosphine)palladium(II) chloride (1.4 g) in 100 ml of tetrahydrofuran, followed by ethyl 3-iodobenzoate (11.04 g). To this mixture, the magnesium reagent prepared above was added dropwise, causing an exothermic reaction. The reaction mixture was stirred overnight at room temperature, and then quenched by addition of dilute hydrochloric acid. The mixture was extracted with ether, and the organic layer washed with water, and then saturated brine. The organic layer was separated, dried over sodium sulfate, the solvent evaporated under reduced pressure, and the residue chromatographed on silica gel, eluting with 5% ethyl acetate in heptane, to yield 5.69 g of ethyl 4'-methylbiphenyl-3-carboxylate, a compound of Formula (17), as a pale yellow oil.

B. Preparation of (17) where R is Ethyl, varying R^11 and R^12

Similarly, following the procedures of Preparation 2A above, but optionally replacing p-bromotoluene with other arylhalo precursors to Formula (15), and optionally replacing ethyl 3-iodobenzoate with other compounds of Formula (16), the following intermediates of Formula (17) were prepared:

- ethyl 4,4'-dimethylbiphenyl-3-carboxylate;
- ethyl 4-methyl-4'-fluorobiphenyl-3-carboxylate;
- ethyl 4-methyl-4'-trifluoromethylbiphenyl-3-carboxylate;
- ethyl 4-methyl-4'-methoxybiphenyl-3-carboxylate;
- ethyl 4'-methoxybiphenyl-3-carboxylate;
- ethyl 4'-dimethylaminobiphenyl-3-carboxylate; and
- ethyl 4-methyl-3'-methoxybiphenyl-3-carboxylate.

Preparation of Compounds of Formula (18)

A. Preparation of (18) where R^11 is 4-Methylphenyl, and R^12 is Hydrogen

To a solution of ethyl 4'-methylbiphenyl-3-carboxylate (4.0 g) in ethanol (50 ml) was added a solution of 10 ml of 10% aqueous sodium hydroxide, and the mixture refluxed for 2 hours. Solvent was removed under reduced pressure, water added to the residue, and the solution filtered. The filtrate was acidified with dilute hydrochloric acid, and the white solid filtered off and dried under vacuum, yielding 2.4 g of 4'-methylbiphenyl-3-carboxylic acid m.p. 192°C.

B. Preparation of (18), varying R^11 and R^12

Similarly, following the procedures of Preparation 3A above, but replacing ethyl 3-(4-methylphenyl)benzoate with other compounds of Formula (17), the following intermediates of Formula (18) are prepared:

- 4,4'-dimethylbiphenyl-3-carboxylic acid;
- 4-methyl-4'-fluorobiphenyl-3-carboxylic acid;
4'-methyl-4''-trifluoromethylbiphenyl-3-carboxylic acid;
4'-methyl-4''-methoxybiphenyl-3-carboxylic acid;
4''-methoxybiphenyl-3-carboxylic acid;
4''-dimethylaminobiphenyl-3-carboxylic acid; and
4'-methyl-3''-methoxybiphenyl-3-carboxylic acid.

**PREPARATION 4**

**Preparation of Compounds of Formula (19)**

A. Preparation of (19) where -NR'R'' represents Diphenylmethylpiperazine, R'' is 4-Methylphenyl, and R'' is Hydrogen

To a suspension of 4'-methylbiphenyl-3-carboxylic acid (2.2 g) in a mixture of methylene chloride (20 ml) and dimethylformamide (0.5 ml) was added thionyl chloride (1.48 g). The mixture was refluxed until the suspension dissolved, after which the temperature was allowed to cool to room temperature. To this solution was added 1-(diphenylmethyl)piperazine (3.94 g) in methylene chloride dropwise, and the reaction mixture allowed to stand overnight. Sodium hydroxide (30 ml of 1N) and 50 ml of methylene chloride was added, the organic layer separated, washed with brine, dried over sodium sulfate, and solvent removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 25% ethyl acetate in heptane, to yield 3.8 g of 1-diphenylmethyl-4-(4'-methylbiphenyl-3-carbonyl)piperazine. The dihydrochloride salt was prepared and recrystallized from ethanol, m.p. 226°C.

B. Preparation of (19), varying -NR'R'', R'' and R''

Similarly, following the procedures of Preparation 4A above, but replacing 4'-methylbiphenyl-3-carboxylic acid with other compounds of Formula (18), the following intermediates of Formula (19) are prepared:

1-diphenylmethyl-4-(4''-dimethylbiphenyl-3-carbonyl)piperazine;
1-diphenylmethyl-4-(4'-fluorobiphenyl-3-carbonyl)piperazine;
1-diphenylmethyl-4-(4'-trifluoromethylbiphenyl-3-carbonyl)piperazine;
1-diphenylmethyl-4-(4'-methoxybiphenyl-3-carbonyl)piperazine;
1-diphenylmethyl-4-(4'-methoxybiphenyl-3-carbonyl)piperazine;
1-diphenylmethyl-4-(4'-dimethylaminobiphenyl-3-carbonyl)piperazine;
and
1-diphenylmethyl-4-(4'-methoxybiphenyl-3-carbonyl)piperazine.
PREPARATION 5
Preparation of Compounds of Formula (20)

A. Preparation of (20) where \( R^2 \) is 4-Methylphenyl, and \( R^{12} \) is 4-Methyl

To a suspension of lithium aluminum hydride (0.2 g) in 50 ml of ether at 0°C was added dropwise a solution of ethyl 4,4'-dimethylbiphenyl-3-carboxylate (2 g) in ether. After the addition was complete, the mixture was allowed to slowly rise to room temperature, and stirred for 2 hours. Excess reagent was hydrolysed with wet sodium sulfate. The mixture was filtered, the solvent evaporated from the filtrate under reduced pressure, and the residue flash-chromatographed on silica gel, eluting with 25% ethyl acetate in heptane, to yield 3-hydroxymethyl-4,4'-dimethylbiphenyl as an oil.

B. Preparation of (20), varying \( R^2 \) and \( R^{12} \)

Similarly, following the procedures of Preparation 5A above, but replacing ethyl 4,4'-dimethylbiphenyl-3-carboxylate with other compounds of Formula (17), the following intermediates of Formula (20) were prepared:

- 3-hydroxymethyl-4-methyl-4'-fluorobiphenyl, as an oil;
- 3-hydroxymethyl-4-methyl-4'-trifluoromethylbiphenyl, m.p. 92°C;
- 3-hydroxymethyl-4'-methoxybiphenyl, m.p. 91°C;
- 3-hydroxymethyl-4-methylbiphenyl, as an oil;
- 3-hydroxymethyl-4'-methoxybiphenyl, as an oil;
- 3-hydroxymethyl-4'-dimethylyaminobiphenyl, m.p. 94°C;
- 3-hydroxymethyl-4-methyl-3'-methoxybiphenyl, as an oil;
- 3-hydroxymethyl-4-methyl-4'-methoxybiphenyl, m.p. 85°C;
- 4-hydroxymethyl-4'-methylbiphenyl, m.p. 130°C; and
- 4-hydroxymethyl-4,4'-dimethylbiphenyl, oil.

EXAMPLE 1
Preparation of Compounds of Formula (IB)

A. Preparation of (IB) where \( m \) is 0, \( R^1 \) is Hydrogen, \(-NR^2R^3\) represents 1-diphenylmethyl piperidine, \( R^2 \) is 4-trifluoromethylphenyl, and \( R^3 \) is 3-methyl

A solution of 2-formyl-3-methyl-5(4-trifluoromethylphenyl)furan (0.5 g), 1-diphenylpiperidine (0.54 g), and titanium(IV) isopropoxide (0.73 g) was allowed to stand for 1 hour at room temperature. Ethanol (10 ml) was added, and the resultant solution was stirred for 1 hour. Sodium cyanoborohydride (90 mg) was then added, and the mixture stirred overnight. Sodium hydroxide was then added until the pH was just over 7, the solvent removed under reduced pressure, and the residue partitioned between methylene chloride/water. The mixture was filtered, the organic layer separated, dried over anhydrous magnesium sulfate, filtered and evaporated.
The residue was flash-chromatographed on silica gel, eluting with ethyl acetate/methanol/ammonia (97/3/0.5), to yield 4-diphenylmethyl-1-[(5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl)methyl] piperidine. Treatment with anhydrous hydrochloric acid in ethanol converted the base to its hydrochloride salt, m.p. 240°C.

B. Preparation of (IB), where m is 0 and R¹ is Hydrogen, varying -NR²R³, P⁰ and R⁰

Similarly, following the procedures of Example 1A above, but replacing 2-formyl-3-methyl-5(4-trifluoromethylphenyl)furan with compounds of Formula (9a), and optionally replacing 1-diphenylmethyl piperidine with amines of formula HNR²R³, the following compounds of Formula (IB) were prepared:

1-diphenylmethyl-4-[(5-phenyl-3-methylfuran-2-yl)methyl]piperazine dihydrochloride, m.p. 170°C;

1-diphenylmethyl-4-[(5-n-butyl-3-methylfuran-2-yl)methyl]piperazine dihydrochloride, m.p. 145°C;

1-diphenylmethyl-4-[(5-t-butyl-3-methylfuran-2-yl)methyl]piperazine dihydrochloride, m.p. 160°C;

1-diphenylmethyl-4-[(5-cyclohexyl-3-methylfuran-2-yl)methyl]piperazine, m.p. 120°C; m.p. dihydrochloride 184°C;

1-diphenylmethyl-4-[(5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl)methyl]piperazine, m.p. 150°C; m.p. dihydrochloride 180°C;

1-diphenylmethyl-4-[(5-(4-methylphenyl)-3-methylfuran-2-yl)methyl]piperazine dihydrochloride, m.p. 225°C;

1-diphenylmethyl-4-[(5-(4-methoxyphenyl)-3-methylfuran-2-yl)methyl]piperazine fumarate, m.p. 216-218°C;

4-diphenylmethyl-1-[(5-phenyl-3-methylfuran-2-yl)methyl]piperidine dihydrochloride, m.p. 250°C;

1-(2,3,4-trimethoxyphenyl)methyl-4-[(5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl)methyl]piperazine dihydrochloride, m.p. 230°C;

4-(4-fluorophenyl)methyl-1-[(5-(4-methylphenyl)-3-methylfuran-2-yl)methyl]piperidine dihydrochloride, m.p. 210°C;

2,2-di(4-fluorophenyl)-4-[(5-(4-methylphenyl)-3-methylfuran-2-yl)methyl]morpholine dihydrochloride, m.p. 210°C;

1-diphenylmethyl-4-[(5-phenyl-3-methylpyrrol-2-yl)methyl]piperazine, m.p. 60-63°C; maleate salt, m.p. 149-152°C;

1-diphenylmethyl-4-[(5-phenyl-2-methylpyrrol-3-yl)methyl]piperazine maleate, m.p. 180°C;

1-diphenylmethyl-4-[(5-phenyl-1,2-dimethylpyrrol-3-yl)methyl]piperazine dihydrochloride, m.p. 225°C;

1-(2,3,4-trimethoxyphenyl)methyl-4-[(5-phenyl-1,2-dimethylpyrrol-3-yl)methyl]piperazine dihydrochloride, m.p. 205°C;

1-diphenylmethyl-4-[(5-phenyl-1,3-dimethylpyrrol-2-yl)methyl]...
piperazine, m.p. 151-152°C; maleate salt m.p. 159-162°C;
1-(2,3,4-trimethoxyphenyl)methyl-4-[(3-methyl-5-phenylthiophen-2-
yl)methyl]piperazine dihydrochloride, m.p. 180°C;
1-diphenylmethyl-4-[(3-methyl-5-phenylthiophen-2-yl)methyl]piperazine
dihydrochloride, m.p. 179°C;
4-diphenylmethyl-1-[(3-methyl-5-phenylthiophen-2-yl)methyl]piperidine
dihydrochloride, m.p. 250°C;
4-diphenylmethyl-1-[(5-[(4-methylphenyl)-3-methylfuran-2-yl)methyl
piperidine hydrochloride;
4-diphenylmethyl-1-[(5-[(4-methoxyphenyl)-3-methylfuran-2-yl)methyl
piperidine hydrochloride;
4-di(4-fluorophenyl)methyl-1-[(3-methyl-5-phenylthiophen-2-yl)oxy-
methyl]piperidine dihydrochloride, m.p. 135°C;
1-diphenylmethyl-4-[(2-methyl-5-phenylthiophen-3-yl)methyl]piperazine
dihydrochloride, m.p. 179-181°C; and
4-diphenylmethyl-1-[(2-methyl-5-phenylthiophen-3-yl)methyl]piperidine
dihydrochloride, m.p. 155°C.

EXAMPLE 2
Preparation of Compounds of Formula (IB)

A. Preparation of (IB) where m is 0, R¹ is Methyl, -NR²R³ represents
1-(Diphenylmethyl)piperazine, R⁴ is 2-Phenyl, and R⁹ is 4-Methyl
A solution of 2-phenyl-4-methyl-5-formylfuran (1.1 g),
diphenylmethylpiperazine (1.5 g), and titanium(IV)isopropoxide (1.76 g) was
stirred for 1½ hours. Diethyl ether (20 ml) was added, and the resultant
solution was stirred for 30 minutes. Methyl magnesium iodide (6 ml of 3M
in ether) was then added dropwise, and the mixture stirred at room
temperature for 1 hour. Ammonium chloride (20 ml of a saturated solution
in water) was then added, followed by 300 ml of methylene chloride, and the
mixture made basic with a solution of sodium bicarbonate. The residue was
partitioned between methylene chloride/water, the organic layer separated,
dried over anhydrous magnesium sulfate, filtered and evaporated.
The residue was flash-chromatographed on silica gel, eluting with 15% ethyl
acetate in heptane with a trace of ammonia, to yield 0.51 g of
1-(diphenylmethyl)-4-[(2-phenyl-4-methylfuran-5-yl)ethyl-1-yl]piperazine.
Treatment with anhydrous hydrochloric acid in ethanol converted the base to
its dihydrochloride salt, m.p. 205-208°C.
EXAMPLE 3
Preparation of Compounds of Formula (IB)

A. Preparation of (IB) where m is 1, R' is Hydroxy, -NR'R' represents 1-(Diphenylmethyl)piperazine, R' is 3-Phenyl, and R'' is 2-Methyl

1. Preparation of (11) where R' is 3-Phenyl, and R'' is 2-Methyl

A solution of 5-acetyl-2-methyl-3-phenylfuran (3.8 g) in 50 ml of tetrahydrofuran was protected from UV light while pyrrolidone hydrotribromide (9.4 g) was added in small portions with stirring. The mixture was stirred overnight, maintaining protection from the UV light, at room temperature, the crystals filtered off, washed with tetrahydrofuran, and the filtrate evaporated under reduced pressure.

The product was combined with diphenylmethylpiperazine (4.8 g) and potassium carbonate (3 g) in isopropanol (50 ml), and the mixture refluxed for two hours. Solvent was removed under reduced pressure, 100 ml of dichloromethane added to the residue, and the precipitate filtered off. The solid was washed with methylene chloride, the combined organic phases combined and the solvent removed under reduced pressure. The residue was flash chromatographed, eluting with 20% ethyl acetate in heptane, to give 3.8 g of 1-(diphenylmethyl)-4-[(2-methyl-3-phenylfuran-5-yl)acet-2-yl]piperazine, a compound of Formula (11).

2. Preparation of (IB) where R' is Hydroxy, R' is 3-Phenyl, R'' is 2-Methyl, and -NR'R' represents 1-(Diphenylmethyl)piperazine

The compound of Formula (11) (prepared in part 1) was dissolved in 100 ml of ethanol at 5 to 10°C, and 1.3 g of sodium borohydride added. The mixture was stirred for 30 minutes, a further 1.3 g of sodium borohydride added, stirred for a further 30 minutes at 5 to 10°C, then stirred for an further 30 minutes at room temperature. Water (50 ml) was added, and the solvent removed under reduced pressure. The residue was partitioned between methylene chloride and water, the organic layer separated, dried over anhydrous magnesium sulfate, filtered and evaporated. The product, a pale yellow oil, was triturated with isopropylether, to give 2.9 g of a white solid, 1-(diphenylmethyl)-4-[(2-methyl-3-phenylfuran-5-yl)-1-hydroxyethan-2-yl]piperazine. Treatment with anhydrous hydrochloric acid in ethanol converted the base to its dihydrochloride salt, m.p. 190°C.

B. Preparation of (IB) where m is 1, R' is Hydroxy, varying R', R', R', and R''

Similarly, following the procedures of Example 3A, parts 1 and 2 above, but optionally replacing 5-acetyl-2-methyl-3-phenylfuran with other compounds of Formula (10), and optionally replacing diphenylmethyl-piperazine with other amines of formula HNR'R', the following compounds of
Formula (IB) where R' is hydroxy and m is 1 were prepared:

1-(diphenylmethyl)-4-[(2-phenyl-5-methylfuran-4-yl)-1-hydroxyethan-2-yl]piperazine, m.p. 140°C;
1-(diphenylmethyl)-4-[(2-methylfuran-5-yl)-1-hydroxyethan-2-yl]piperazine dihydrochloride, m.p. 197°C;
1-(diphenylmethyl)-4-[(2,5-dimethylfuran-4-yl)-1-hydroxyethan-2-yl]piperazine dihydrochloride, m.p. 195°C; and
1-(diphenylmethyl)-4-[(2-phenyl-4-methylfuran-5-yl)-1-hydroxyethan-2-yl]piperazine dihydrochloride, m.p. 144-154°C.

EXAMPLE 4
Preparation of Compounds of Formula (IB)

A. Preparation of (IDA) where m is 0. R' is Hydrogen, -NR'R'' represents 1-(Diphenylmethyl)piperazine. R'' is 4-Methylphenyl, and R'' is Hydrogen

To a suspension of lithium aluminum hydride (0.13 g) in 50 ml of ether at 0°C was added dropwise a solution of 1-diphenylmethyl-4-(4'-methylbiphenyl-3-carbonyl)piperazine (1 g) in a mixture of ether and tetrahydrofuran. After the addition was complete, the mixture was allowed to slowly rise to room temperature, and stirred for 1½ hours. Excess reagent was hydrolysed with wet sodium sulfate. The mixture was filtered, the solvent evaporated, and the residue flash-chromatographed on silica gel, eluting with 25% ethyl acetate in heptane, to yield 1-diphenylmethyl-4-[4’-methylbiphenyl-3-methyl]piperazine, which was converted to its dihydrochloride salt by treatment with anhydrous hydrochloric acid in ethanol, m.p. 206°C.

B. Preparation of (IDA) where m is 0. R' is Hydrogen, varying -NR'R'', R'' and R''

Similarly, following the procedures of Example 4A above, but replacing 1-diphenylmethyl-4-(4’-methylbiphenyl-3-carbonyl)piperazine with other compounds of Formula (19), the following compounds of Formula (IDA) are prepared:

1-diphenylmethyl-4-(4,4'-dimethylbiphenyl-3-methyl)piperazine;
1-diphenylmethyl-4-(4-methyl-4'-fluorobiphenyl-3-methyl)piperazine;
1-diphenylmethyl-4-(4-methyl-4'-trifluoromethylbiphenyl-3-methyl)piperazine;
1-diphenylmethyl-4-(4-methyl-4'-methoxybiphenyl-3-methyl)piperazine;
1-diphenylmethyl-4-(4’-methoxybiphenyl-3-methyl)piperazine;
1-diphenylmethyl-4-(4’,4'-dimethylaminobiphenyl-3-methyl)piperazine;

and
1-diphenylmethyl-4-(4-methyl-3’-methoxybiphenyl-3-methyl)piperazine.
EXAMPLE 5
Preparation of Compounds of Formula (ID)

A. Preparation of (IDA) where \( m \) is 0, \( R' \) is Hydrogen, \(-NR^2R'\) is 1-(Diphenylmethyl)piperazinemethyl in the 3-position, \( R'' \) is 4-Methylphenyl, and \( R''^2 \) is 4-Methyl

A solution of 3-hydroxymethyl-4,4'-dimethylbiphenyl (1.3 g) and triethylamine (0.8 g) in methylene chloride (50 ml) was cooled to 0°C, and methanesulfonyl chloride (0.84 g) in methylene chloride was added dropwise. The mixture was allowed to warm to room temperature, and was stirred overnight. Ice/water was then added, the organic layer separated, the aqueous layer washed with methylene chloride, the organic layer washed with brine, dried over sodium sulfate, and the solvent evaporated under reduced pressure, to yield 3-chloromethyl-4,4'-dimethylbiphenyl as an oil.

This product was dissolved in acetonitrile, and added to 1-(diphenylmethyl)piperazine (1.85 g) and potassium carbonate (1 g) in acetonitrile (60 ml). The mixture was refluxed overnight, the solid filtered off, washed with methylene chloride, solvent removed from the filtrate under reduced pressure, and the residue flash-chromatographed on silica gel, eluting with 30% ethyl acetate in heptane, to yield 1-diphenylmethyl-4-[4,4'-dimethylbiphenyl-3-ylmethyl]piperazine, as an off-white solid, which was converted to its dihydrochloride salt by treatment with anhydrous hydrochloric acid in ethanol, m.p. 177°C.

B. Preparation of (IDA) where \( m \) is 0, \( R' \) is Hydrogen, varying \(-NR^2R', R''\) and \( R''^2 \)

Similarly, following the procedures of Example 5A above, but optionally replacing 3-hydroxymethyl-4,4'-dimethylbiphenyl with other compounds of Formula (17), and optionally replacing 1-(diphenylmethyl)piperazine with 1-(2,3,4-trimethoxyphenylmethyl)piperazine, the following compounds of Formula (IDA) were prepared:

- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4,4'-dimethylbiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 193°C;
- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-fluorobiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 198°C;
- 1-diphenylmethyl-4-[4-methyl-4'-trifluoromethylbiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 157;
- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-trifluoromethylbiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 185°C;
- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 230°C;
- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 204°C;
- 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methylbiphenyl-3-ylmethyl]
piperazine dihydrochloride, m.p. 204°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-dimethylamino-biphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 232°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-methyl-3'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 194°C;  
1-(3,4,5-trimethoxyphenylmethyl)-4-[4'-methyl-3'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 220°C;  
N-[4-methyl-4'-methoxybiphenyl-3-methyl]-N-methyl-4,4-diphenylbutylamine hydrochloride, m.p. 93°C;  
N-[4-methyl-4'-methoxybiphenyl-3-methyl]-N-methyl-3-(2,3,4-trimethoxyphenyl)propylamine fumarate, m.p. 185°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[3,4'-dimethylbiphenyl-4-ylmethyl]piperazine dihydrochloride, m.p. 220°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-methylbiphenyl-4-ylmethyl]piperazine dihydrochloride, m.p. 235°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-methylbiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 125°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[3-(3-furanyl)phenylmethyl]piperazine dihydrochloride, m.p. 183°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[3-(4-pyridinyl)phenylmethyl]piperazine trihydrochloride, m.p. 189°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[5-methyl-4'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 230°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4-chloro-4'-methoxybiphenyl-3-ylmethyl]piperazine hydrochloride, m.p. 190°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[4'-chlorobiphenyl-3-ylmethyl]piperazine dihydrochloride, m.p. 201°C;  
2,2-di-(4-fluorophenyl)-4-[4'-methoxybiphenyl-3-ylmethyl]morpholine methanesulfonate, m.p. 202°C;  
1-(4-fluorophenylmethyl)-4-[4'-methoxybiphenyl-3-ylmethyl]piperazine dimethanesulfonate m.p. 202°C;  
1-(2,3,4-trimethoxyphenylmethyl)-4-[(3-(n-butylphenyl)methyl]piperazine dihydrochloride, m.p. 177°C; and  
1-(2,3,4-trimethoxyphenylmethyl)-4-[(3-(3-thiophenyl)phenylmethyl]piperazine dihydrochloride, m.p. 210°C.

**EXAMPLES 6-12**

The following examples illustrate the preparation of representative pharmaceutical formulations containing an active compound of Formula (I), e.g., (+)-1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride. Other compounds and salts of Formula (I), such as those prepared in accordance with Examples 1-5, can be used as the active compound in the formulations of Examples 6-12.
EXAMPLE 6
I.V. Formulation

Active compound: 0.14 g
Propylene glycol: 20.0 g
Polyethylene glycol 400: 20.0 g
Tween 80: 1.0 g
0.9% Saline solution: 100.0 ml

Other compounds of Formula (I) and the pharmaceutically acceptable salts thereof may be substituted therein.

EXAMPLE 7

Ingredients | Quantity per tablet, mgs.
--- | ---
Active compound | 25
Cornstarch | 20
Lactose, spray-dried | 153
Magnesium stearate | 2

The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 8

Ingredients | Quantity per capsule, mgs.
--- | ---
Active compound | 100
Lactose, spray-dried | 148
Magnesium stearate | 2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 9

Ingredients | Quantity per tablet, mgs.
--- | ---
Active compound | 1
Cornstarch | 50
Lactose | 145
Magnesium stearate | 5

The above ingredients are mixed intimately and pressed into single scored tablets.
EXAMPLE 10

Ingredients

<table>
<thead>
<tr>
<th>Active compound</th>
<th>150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactose</td>
<td>92</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 11

An injectable preparation buffered to a pH of 7 is prepared having the following composition:

Ingredients

<table>
<thead>
<tr>
<th>Active compound</th>
<th>0.2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH$_2$PO$_4$ buffer (0.4 M solution)</td>
<td>2 ml</td>
</tr>
<tr>
<td>KOH (1 N)</td>
<td>q.s. to pH 7</td>
</tr>
<tr>
<td>water (distilled, sterile)</td>
<td>q.s. to 20 ml</td>
</tr>
</tbody>
</table>

EXAMPLE 12

An oral suspension is prepared having the following composition:

Ingredients

<table>
<thead>
<tr>
<th>Active compound</th>
<th>0.1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>fumaric acid</td>
<td>0.5 g</td>
</tr>
<tr>
<td>sodium chloride</td>
<td>2.0 g</td>
</tr>
<tr>
<td>methyl paraben</td>
<td>0.1 g</td>
</tr>
<tr>
<td>granulated sugar</td>
<td>25.5 g</td>
</tr>
<tr>
<td>sorbitol (70% solution)</td>
<td>12.85 g</td>
</tr>
<tr>
<td>Veegum K (Vanderbilt Co.)</td>
<td>1.0 g</td>
</tr>
<tr>
<td>flavoring</td>
<td>0.035 ml</td>
</tr>
<tr>
<td>colorings</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>distilled water</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

EXAMPLE 13

Determination of Na$^+$ Channel Binding Site Affinity

([H]-batrachotoxin)

Washed rat brain synaptosomal homogenates are incubated with [H]-batrachotoxin ([H] BTX, 2nM) with and without the test compound over a concentration range of 10$^{-10}$-10$^{-4}$ M in Hepes buffer (potassium chloride 5.4 mM, MgSO$_4$ 0.8 mM, glucose 5.5 mM, Hepes 50 mM, choline 130 mM, pH 7.4), containing tetrodotoxin (final assay concentration 1µM) and scorpion toxin (final assay concentration 100 µg) in a final volume of 500 µl. Non-specific binding is defined using a saturating concentration of veratridine
(0.3 mM). The assay tubes are incubated at 25°C for 90 min then filtered over Whatman GF/B glass fibre filters and using a Brandel cell harvester. Bound radioactivity is assessed by liquid scintillation spectrometry. The affinity of the test compounds for the Na⁺ channel were compared as pIC₅₀ values.

The compounds of Formula (I) show affinity for the Na⁺ channel as shown below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>pIC₅₀ vs [³H]-BTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.47 ± 0.1</td>
</tr>
<tr>
<td>B</td>
<td>7.76 ± 0.09</td>
</tr>
</tbody>
</table>

A = 1-(2,3,4-trimethoxyphenethylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3ylmethyl]piperazine dihydrochloride

B = 4-diphenylmethyl-1-[5-(4-trifluoromethylphenyl)-3-methylfuran-2-y1)methyl]piperidine hydrochloride

**EXAMPLE 14**

Whole cell voltage clamp recordings of Sodium currents (Iₘ) from NIE 115 neuroblastoma cells

This is a whole cell variant of the patch clamp technique (Hamill et al., Pflugers Arch. (1981) 391, 85-100).

The ionic composition of the internal solution was (in mM): 120 CsF, 10 NaCl, 11 EGTA, 10 HEPES, 10 tetraethylammonium Cl, 1 CaCl₂, 1 MgCl₂ (pH to 7.3 with CsOH) and the external solution contained 145 NaCl, 3 KCl, 10 HEPES, 1 CaCl₂, 1 MgCl₂, 0.5 CdCl₂, 5 glucose (pH to 7.3 with NaOH).

Cells were held at a membrane potential of -80mV and Iₘ was evoked by 10ms depolarizing steps to OmV until a stable current was recorded. A current/voltage curve was then constructed by applying a series of depolarizing steps to membrane potentials ranging from -60 to +70mV (increments of 10mV). Test compounds were then applied at 1μM, 3μM or 10μM for 10 minutes after which a second current/voltage curve was recorded.

The compounds of Formula (I) produce an inhibition of the peak inward sodium current (Iₘ) (measured from the current/voltage curve) as shown below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc'n[μM]</th>
<th>% Inhibition of Na current</th>
<th>n</th>
<th>IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>12.9 ± 7.7</td>
<td>3</td>
<td>3μM</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>51.2 ± 6.1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>A =</td>
<td>10</td>
<td>100</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

n = number of cells tested

A = 1-(2,3,4-trimethoxyphenethylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3ylmethyl]piperazine dihydrochloride

n = number of cells tested
EXAMPLE 15
Whole cell voltage clamp recordings of
T-type Calcium currents (I\textsubscript{Ca})

This is a whole cell variant of the patch clamp technique (Hammill et al., Pflugers Arch. (1981) 391, 85-100).

The ionic composition of the internal solution was (in mM): 120 CsCl, 10 NaCl, 11 EGTA, 10 HEPES, 10 tetraethylammonium Cl, 1 CaCl\textsubscript{2}, 1 MgCl\textsubscript{2}, 40 sucrose (pH adjusted to 7.4 with CsOH) and the external solution contained 110 Tris base, 20 BaCl\textsubscript{2}, 5 CsCl, 5 KCl, 20 HEPES, 30 Glucose (pH adjusted to 7.4 with HCl).

Cells were clamped at a membrane potential of -80mV and I\textsubscript{Ca,W} was evoked by 200ms depolarizing steps to -10mV until a stable current was elicited. A current/voltage curve was then constructed by applying a series of depolarizing steps to membrane potentials ranging from -60 to +40mV (in increments of 10mV). A test compound was then introduced into the superfusing medium to give a final concentration of 3\muM or 10\muM. Drug was applied for 10 minutes after which a second current/voltage curve was recorded.

The compounds of Formula (I) inhibit T-type calcium currents, as shown below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration</th>
<th>% Inhibition of T\textsubscript{type Ca current}</th>
<th>n</th>
<th>IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3 \muM</td>
<td>30 ± 3.3</td>
<td>3</td>
<td>8 \muM</td>
</tr>
<tr>
<td></td>
<td>10 \muM</td>
<td>59.2 ± 5.8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4′-methoxybiphenyl-3-ylmethyl]piperazine dihydrochloride \]

\[ n = \text{number of cells tested} \]

EXAMPLE 16
Determination of Activity Utilizing
The MCA Model

Adult male mice (CD, strain), weighing 30 to 40 g, were anaesthetized by 5% halothane in a 70%:30% nitrous oxide:oxygen gas mixture.

The left middle cerebral artery was exposed through a curved incision midway between the eye and the external auditory meatus, the artery was sealed by thermocautery.

The dosing schedule was as follows. The first dose of test compound (0.05 to 1.0 mg/kg intraperitoneally) was administered 15 minutes following ischaemia. The mice then recovered for seven days, during which they were dosed with the same amount of test compound twice daily at approximately 9 am and 4 pm.

The animals were sacrificed 4 h after the last dose. The infarcted
area was dissected from the ischemic left hemisphere and the contralateral right hemispherical area was also taken as control non-ischemic tissue.

Damage in the ischemic hemisphere was quantified by measuring the binding of [³H] PK 11195, which provides an index of ischemic damage insofar as an increase in binding of [³H] PK 11195 (assessed by B_{max}) indirectly reflects neuronal damage. Compounds which prevent the increase in the number of binding sites are considered to be neuroprotective.

Animals treated with placebo showed an increase in the B_{max} of [³H] PK 11195 binding in the ischemic hemisphere resulting in an increase in the ratio of binding of the left (ischemic) hemisphere:right (non-ischemic) hemisphere. This was taken as 100% damage against which the effect of test compounds could be calculated.

There were no changes in the affinity of [³H] PK 11195 for its binding sites in the study.

The compounds of Formula (I) exhibited neuroprotective effects in this model as shown below.

a. Efficacy Dose Ranging

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose ip 15 min post-ischaemia</th>
<th>Dose ip bid 7 days</th>
<th>% Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50 μg/kg</td>
<td>50 μg/kg</td>
<td>59% compared with control</td>
</tr>
<tr>
<td></td>
<td>500 μg/kg</td>
<td>500 μg/kg</td>
<td>73% compared with control</td>
</tr>
<tr>
<td>B</td>
<td>50 μg/kg</td>
<td>50 μg/kg</td>
<td>63% compared with control</td>
</tr>
<tr>
<td></td>
<td>500 μg/kg</td>
<td>500 μg/kg</td>
<td>66% compared with control</td>
</tr>
</tbody>
</table>

b. Dose Response Curve

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose μg/kg</th>
<th>% Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50</td>
<td>52 n.s.</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>62 p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>87</td>
</tr>
</tbody>
</table>

\[
A = 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3ylmethyl]piperazine dihydrochloride
\]

\[
B = 4-diphenylmethyl-1-[5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl]methyl]piperidine hydrochloride
\]

**EXAMPLE 17**

**Intravenous Toxicity in Rats**

Adult male and female rats (Hsd Ola:Sprague Dawley SD, strain) weighing 150 to 180 g were intravenously dosed via the tail vein once a day for up to 5 days. The doses of compound A (1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-methoxybiphenyl-3ylmethyl]piperazine dihydrochloride) used were 6 and 10 mg/kg/day.

The clinical status of the animals was assessed daily and no adverse effects were seen. Post mortem examination showed no evidence of systemic toxicity.
While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.
WHAT WE CLAIM IS:

1. A compound represented by the Formula:

\[
A \quad \text{(CH}_2\text{)}_m \quad -N^+_{R^3} \quad \text{(I)}
\]

wherein:
- \( m \) is 0 or 1;
- \( R^1 \) is hydrogen, hydroxy, or lower alkyl;
- \( R^2 \) is hydrogen, or lower alkyl;
- \( R^3 \) is

\[
-X\quad \text{(CH}_2\text{)}_n \quad R^4
\]

or \( R^2 \) and \( R^3 \) taken together with the nitrogen atom to which they are attached represent a group of the formula:

\[
\text{or } \text{(II)}
\]

wherein:
- \( n \) is 0 or 1;
- \( p \) is 0, 1, 2 or 3;
- \( q \) is 0 or 1;
- \( R^4 \) is hydrogen, lower alkyl, cycloalkyl, or optionally substituted phenyl;
- \( R^5 \) is optionally substituted phenyl;
- \( X \) is \((\text{CH}_2)_n\), or 4-piperidin-1-yl;
- \( Y \) is \(\text{CH}, \text{CH}-0-, \text{CH}-S-, \text{or nitrogen};\)
- \( Z \) is \(\text{CH}_2, \text{NH}, \text{sulfur, or oxygen};\) and
- \( A \) is chosen from the group consisting of:

1. \( R^9 \)

\[
\text{(B)}
\]

and

1. \( R^{12} \)

\[
\text{(DA)}
\]
wherein:
R' is lower alkyl, or optionally substituted phenyl;
R'^10 is hydrogen, or lower alkyl;
R'^11 is lower alkyl or optionally substituted aryl;
R'^12 is hydrogen, lower alkyl, lower alkoxy, halo, or trifluoromethyl; and
W is oxygen, sulfur, or NR'^15;
wherein R'^15 is hydrogen or lower alkyl;
with the proviso that R', R'^10, R'^12, and the sidechain cannot be attached to a hetero atom; or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of Claim 1, wherein A is:

or a pharmaceutically acceptable acid addition salt thereof.

3. The compound of Claim 2, wherein R'^2 and R'^3 taken together with the nitrogen atom to which they are attached represent a group of the formula:

or a pharmaceutically acceptable acid addition salt thereof.

4. The compound of Claim 3, wherein W is oxygen, Y is CH, R'^9 is 5-(4-trifluoromethylphenyl), R'^10 is 3-methyl, and the sidechain is in the 2-position, namely 4-diphenylmethyl-1-[[5-(4-trifluoromethylphenyl)-3-methylfuran-2-yl)methyl]piperidine, or a pharmaceutically acceptable acid addition salt thereof.

5. The compound of Claim 1, wherein A is:

or a pharmaceutically acceptable acid addition salt thereof.
6. The compound of Claim 5, wherein R² and R¹ taken together with the nitrogen atom to which they are attached represent a group of the formula:

\[
\text{N} - \left(\text{CH}_2\right)_n \rightarrow \left(\text{CH}_2\right)_q \text{R}^4 \rightarrow \text{R}^5
\]

or a pharmaceutically acceptable acid addition salt thereof.

7. The compound of Claim 6, wherein Y is nitrogen, R¹ is hydrogen, R² is 2,3,4-trimethoxyphenyl, and the sidechain is in the 3-position, namely 1-(2,3,4-trimethoxyphenylmethyl)-4-[4-methyl-4'-methylbiphenyl-3-ylmethyl]piperazine, or a pharmaceutically acceptable acid addition salt thereof.

8. Use of a compound of Claim 1 for treating a mammal having a disease selected from the group consisting of:

- ischaemia including focal and global cerebral ischaemia,
- cerebral ischaemia including ischaemia-induced neurodegeneration,
- perinatal asphyxia, spinal injuries, peripheral nerve ischaemia,
- peripheral nerve damage, neuropathic pain, head trauma, primary intracerebral hemorrhage, encephalopathy, epilepsy or epileptic psychotic symptoms, and neurological diseases such as Alzheimer's,
- Huntington's chorea, Parkinson's and dementias; or
- migraine, stroke, vasospasm due to subarachnoid hemorrhage, and cerebrovascular ischaemia induced by cocaine abuse;
- cerebral oedema and hyponatraemic encephalopathy;
- hypertension, angina, stable and unstable angina, Prinzmetal angina, arrhythmia, thrombosis, embolism, and congestive heart failure, including chronic or acute cardiac failure;
- intermittent claudication;
- reversible airways obstruction, asthma, spasms of the ureter, spasms of the bladder; uterine cramps, and irritable bowel syndrome;
- vasoconstriction and/or ischemic tissue damage during a surgical procedure, selected from the group: bypass grafts, angiography, angioplasty, organ preservation during transplant, hypertensive crisis, or post-operative hypertension;
- a disease treated by diuresis; and
- uraemic encephalopathy.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with one or more pharmaceutically acceptable
10. A process for the preparation of a compound represented by the formula:

\[ A \text{-(CH}_2)_m \text{--N}^1 \text{--R}^2 \text{--(CH}_2)_n \text{--R}^4 \text{--R}^5 \]

wherein:
- \( m \) is 0 or 1;
- \( R^1 \) is hydrogen, hydroxy, or lower alkyl;
- \( R^2 \) is hydrogen, or lower alkyl;
- \( R^4 \) is

\[ \text{or } R^2 \text{ and } R^3 \text{ taken together with the nitrogen atom to which they are attached represent a group of the formula:} \]

\[ \text{or} \text{---N}^1 \text{--(CH}_2)_p \text{--(CH}_2)_q \text{--R}^4 \text{--R}^5 \text{---} \]

wherein:
- \( n \) is 0 or 1;
- \( p \) is 0, 1, 2 or 3;
- \( q \) is 0 or 1;
- \( R^4 \) is hydrogen, lower alkyl, cycloalkyl, or optionally substituted phenyl;
- \( R^5 \) is optionally substituted phenyl;
- \( X \) is \((\text{CH}_2)_n\), or 4-piperid-1-yl;
- \( Y \) is CH, CH-O-, CH-S-, or nitrogen;
- \( Z \) is CH, NH, sulfur, or oxygen; and
- \( A \) is chosen from the group consisting of:

\[ \text{and} \text{---R}^{11} \text{---} \]

[(B) and (DA)]
wherein:

- $R^9$ is lower alkyl, or optionally substituted phenyl;
- $R^0$ is hydrogen, or lower alkyl;
- $R^{10}$ is lower alkyl or optionally substituted aryl;
- $R^{12}$ is hydrogen, lower alkyl, lower alkoxy, halo, or trifluoromethyl; and
- $W$ is oxygen, sulfur, or NR$^{15}$;

wherein $R^{15}$ is hydrogen or lower alkyl;

with the proviso that $R^9$, $R^0$, $R^{12}$, and the sidechain cannot be attached to a hetero atom; or a pharmaceutically acceptable acid addition salt thereof, which comprises

a) reacting a compound of the formula

\[
\begin{array}{c}
\text{R}^9 \\
\text{R}^{10} \text{W} \\
\text{N} \\
\text{R}^2 \\
\text{R}^3
\end{array}
\]

wherein $R^9$ and $R^{10}$ are as defined above, with an amine of the formula $\text{HN}R^2R^3$, wherein $R^2$ and $R^3$ are as defined above, in the presence of a titanium (IV) catalyst, followed by the addition of a reducing agent (if $R^1$ is hydrogen) or a Grignard reagent (if $R^1$ is lower alkyl) to form a compound of Formula I; or

b) reacting a compound of the formula

\[
\begin{array}{c}
\text{R}^9 \\
\text{R}^{10} \text{W} \\
\text{N} \\
\text{R}^2 \\
\text{R}^3
\end{array}
\] \quad (11)

wherein $R^9$, $R^{10}$, $R^2$, and $R^3$ are as defined above, with a reducing agent to form a compound of Formula I wherein $R^1$ is hydroxy; or

c) reacting a compound of the formula

\[
\begin{array}{c}
\text{R}^{11} \\
\text{R}^{12} \\
\text{N} \\
\text{R}^2 \\
\text{R}^3
\end{array}
\] \quad (19)

wherein $R^{11}$, $R^{12}$, $R^2$, and $R^3$ are as defined above, with a reducing agent to form a compound of Formula I; or

d) reacting a compound of the formula

\[
\begin{array}{c}
\text{R}^{11} \\
\text{L}
\end{array}
\]
wherein $R^a$ and $R^b$ are as defined above, and $L$ is a leaving group with an amine of the formula $HN=NR^b$ wherein $R^c$ and $R^d$ are as defined above to form a compound of Formula I; or

e) reacting the free base of a compound of Formula I with an acid to give a pharmaceutically acceptable acid addition salt; or
f) reacting an acid addition salt of a compound of Formula I with a base to give the corresponding free base; or
g) converting an acid addition salt of a compound of Formula I to another pharmaceutically acceptable acid addition salt.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/01085

A. CLASSIFICATION OF SUBJECT MATTER

 IPC 5 C07D295/073 C07D295/096 C07D295/135 C07D307/52 C07D333/20
       C07D207/32 A61K31/445 A61K31/495 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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          | Week 8829,
          | Derwent Publications Ltd., London, GB;
          | AN 88-202980 & JP,A,63 141 966 (SANTEN SEIYAKU KK) 14
          | June 1988 see abstract ---
|          | GB,A,705 979 (H. MORREN) 24 March 1954 see the whole document --- /---       | 1,5-7                 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
28 July 1994

Date of mailing of the international search report
12.08.94

Name and mailing address of the ISA
European Patent Office, P.B. 3818 Patentlaan 2
NL - 2280 HV Rijswijk
Tld. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer
Paisdor, B

Form PCT/ISA/318 (second sheet) (July 1992)
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<td>JPN. J. PHARMACOL., vol.48, no.2, 1988, pages 241 - 247 T. IWAMOTO ET AL. 'Effects of KB-2796, a new calcium antagonist, and other diphenylpiperazines on [3H]nitrendipine binding' see the whole document, and in particular 3-[(4-chlorophenyl)[4-(3-methylphenyl)methyl]-1-piperazinyl]methyl]-phenol</td>
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<td>EP,A,0 152 799 (PULITZER ITALIANA S.P.A.) 28 August 1985 see page 1, line 1 - line 18; claim 1</td>
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# INTERNATIONAL SEARCH REPORT

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

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

1. **X** Claims No.: 8  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   
   **Remark:** Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: 1-5, 8-10  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
   
   See annexed sheet.

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

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

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

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

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

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

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

**Remark on Protest**  
□ The additional search fees were accompanied by the applicant’s protest.

□ No protest accompanied the payment of additional search fees.
Claims 1-5 and 8-10 do not meet the requirements of Art. 6 PCT; these claims encompass such an enormous amount of possible compounds that a complete search, even by means of on-line searching techniques was found to be impossible on economic grounds.

The general formula I of claim 1 of the present application consists of different groups \( A, R^2, R^3, R^4, \) and \( R^5 \) which do not only possess variable connection points to the basic structure, but also include "open definitions" such as "optionally substituted phenyl" or "optionally substituted aryl". Such definitions are not concise and are regarded as violations of Rule 6.3 (b) PCT; within the scope of claim 1 are simple compounds such as \( N,N'\text{-benzyl-(4-methylbenzyl)}\text{-amine} \) and a characteristic distinguishing feature of such a compound with regard to the prior art is not evident from the wording of the principal claim 1.

Consequently the search has been limited on economic grounds on the basis of claim 6, on the majority of the examples (which are piperazines), and in particular on the basis of claim 7; the piperazine derivatives of claim 7, being the test compound applied in all pharmacological tests disclosed in the present application.
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