Compounds of structure (I), in which R is C₅₋₆alkyl, C₅₋₆alkyl(phenyl), C₂₋₃alkenyl(phenyl)p, C₂₋₃alkynyl(phenyl)p, C₃₋₅cycloalkyl or C₃₋₅cycloalkyl; p is 0 to 2; n is 0 to 6; A is a bond, -CH=CH₂, -C≡C-, oxygen, sulphur or NR₁; R₁ is hydrogen, C₁₋₄alkyl or phenyl(C₁₋₄alkyl; m is 0 to 3; and Ar is aryl or heteroaryl, each of which may be optionally substituted, and their pharmaceutically acceptable salts as calcium channel antagonists. Novel compounds of structure (I), processes for preparing them and pharmaceutical compositions containing them are also described.
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The present invention relates to the use of known and novel 3-substituted pyrrolidine derivatives in therapy, the novel compounds per se, processes for their preparation, and pharmaceutical compositions containing them.

US Patent 3,360,526 describes compounds of the formula:

![Chemical Structure](image)

wherein Y is *inter alia* a pyrrolidino group which may be substituted on the nitrogen atom by lower alkyl or phenyl-lower alkyl. These compounds are said to have antihistamine, antitussive, antinauseant and antifungal activity.

EP 338331 describes as intermediates N-protected (eg benzyl) pyrrolidine derivatives with a 3-position substituent −XA, where X is −OCH₂, CH₂O or 0 and A is aryl or heteroaryl.

US Patent No. 4918073 describes compounds of the formula

\[ R^1-O-(CH₂)ₘA(CH₂)ₙCH(R^2)(R^3) \]

where \( R^1 \) is *inter alia* optionally substituted phenyl or certain bicyclic aryl or heteroaryl groups, \( m \) is 2-4, \( A \) is *inter alia* a group \( \bigwedge (CH₂)₀ \) where \( 0 \) is 4, 5 or 6, \( n \) is 1-4

and \( R^2 \) and \( R^3 \) are each phenyl or phenylalkyl. US Patent No. 4933346 discloses compounds of formula

\[ R^1S(CH₂)ₘA(CH₂)ₙCH(R^2)(R^3) \]

wherein \( R^1 \) is *inter alia* optionally substituted phenyl. The compounds of both these US patents are said to be calcium antagonists.
We have now found a class of substituted pyrrolidine derivatives which are distinct from the compounds described in US Patent No's. 4918073 and 4933346, and which exhibit activity as calcium channel antagonists. They are thus of potential use in the treatment of disorders where calcium channel blockade is indicated, in particular disorders related to an accumulation of calcium in the brain cells of mammals.

The present invention therefore provides, in a first aspect, the use of a compound of structure (I):

\[
\begin{align*}
&\text{Structure (I)} \\
&(\text{CH}_2)_nA(\text{CH}_2)_m\text{Ar} \\
&\text{R}
\end{align*}
\]

in which
- R is C\textsubscript{1-8}alkyl, C\textsubscript{1-8}alkyl(phenyl), C\textsubscript{2-8}alkenyl(phenyl)p, C\textsubscript{2-8}alkynyl(phenyl)p, C\textsubscript{3-8}cycloalkyl or C\textsubscript{1-8}alkylC\textsubscript{3-8}cycloalkyl;
- p is 0 to 2;
- n is 0 to 6;
- A is a bond, -\text{CH=CH}, -\text{C=C}, oxygen, sulphur or N\text{R}^1;
- R\textsuperscript{1} is hydrogen, C\textsubscript{1-8}alkyl or phenylC\textsubscript{1-4}alkyl;
- m is 0 to 3; and
- Ar is aryl or heteroaryl, each of which may be optionally substituted, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated.

Compounds of formula (I) have been found to exhibit high calcium influx blocking activity. As such the compounds are expected to be of use in therapy, particularly in treating conditions and diseases related to an accumulation of calcium
in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal.

In a further aspect of the invention there is therefore also provided a method of treatment of conditions or diseases caused or exacerbated by the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof. Thus for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof.

It will be understood that in the compounds of structure (I) alkylcycloalkyl, alkylphenyl, alkenylphenyl and alkynylphenyl groups are linked to the pyrroldidine nitrogen atom via the alkyl, alkenyl and alkynyl moieties respectively.

In the compounds of structure (I) R is preferably C₁₈alkyl, in particular n-pentyl, or C₂₈alkenyl(phenyl)p where p is 1 eg. cinnamyl.

A is preferably oxygen or sulphur; most preferably A is oxygen.

Preferred values for n and m depend on the group A. In general the length of the chain -(CH₂)ₙA(CH₂)ₘ is from 2 to 5 atoms. Thus for example when A is oxygen n is preferably 1 or 2 and m is preferably zero.
In general n is suitably 0 to 3 eg. 1 or 2; m is suitably 0 or 1.

When Ar represents aryl suitable groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic ring systems of up to 12 carbon atoms or tricyclic ring systems of up to 15 carbon atoms, such as, for example, phenyl, naphthyl, tetrahydronaphthyl, fluorene, fluorenone, dibenzosuberene and dibenzosuberenone. Preferred are optionally substituted phenyl rings.

An aryl group may be substituted, for example, by a C₁₋₂alkylenedioxy group (eg. phenyl substituted by a 3,4-methylenedioxy group) or by 1 to 3 substituents selected from halogen, C₁₋₄alkoxy, nitro, SC₁₋₄alkyl, NR₂R₂a (in which R² and R₂a independently represent H or C₁₋₄alkyl), OCF₃, C₁₋₅alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenoxy, optionally substituted phenylC₁₋₄alkyl, optionally substituted phenylC₂₋₄alkenyl and optionally substituted phenylC₁₋₄alkoxy. Preferably the aryl group is a phenyl ring substituted by one or two substituents, in particular, by a single halogen, trifluoromethyl, unsubstituted phenyl or unsubstituted phenylC₁₋₄alkoxy group; or by two chloro atoms especially in the 3- and 4-positions of the phenyl ring.

Suitable optionally substituted phenylC₁₋₄alkyl groups include, for example benzyl or phenethyl. Suitable optionally substituted phenylC₁₋₄alkoxy groups include, for example benzyloxy groups. Suitable optionally substituted phenylC₂₋₄alkenyl groups include, for example phenethenyl.

Suitable substituents for said optionally substituted phenyl, phenoxy, phenylC₁₋₄alkyl, phenylC₂₋₄alkenyl, and phenylC₁₋₄alkoxy groups include for example halogen, C₁₋₄alkyl, C₁₋₄alkoxy, nitro and trifluoromethyl groups.

When Ar represents heteroaryl suitable groups include, for example, unsaturated or partially saturated bicyclic ring
systems of up to 12 carbon atoms containing at least one heteroatom. A bicyclic ring system preferably contains 8 to 10 ring members such as quinolinyl and tetrahydroquinolinyl. A tricyclic ring system preferably contains from 11 to 14 ring members, and most preferably has the structure:

\[
\begin{array}{c}
\text{Y}^1 \\
\text{Z}
\end{array}
\]

wherein \(Y^1\) represents \((\text{CH}_2)_r\) \(Y\) is O, S or NR\(^3\) (where R\(^3\) is hydrogen or C\(_1-4\)-alkyl), Z is \((\text{CH}_2)_q\) or \(-\text{CH}=\text{CH}-\), q is 0, 1 or 2 and r is 0 or 1, or is a corresponding dehydro ring system. Examples of tricyclic heteroaryl groups include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzoxepine. The heteroaryl ring can be linked to the remainder of structure (I) via any suitable ring atom.

Suitable substituents for said heteroaryl rings include, for example, 1 to 3 substituents selected from halogen, C\(_1-4\)-alkyl and C\(_1-4\)-alkoxy.

Alkyl groups present in the compounds of structure (I) alone or as part of another group, can be straight or branched.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-pharmaceutically acceptable salts may be used, for example, as intermediates and are included within the scope of this invention.

The invention also provides novel compounds of structure (IA):
in which
R\(^{a}\) is C\(_{5}\)-galkyl, C\(_{5}\)-galkyl(phenyl), C\(_{2}\)-galkenyl(phenyl)p,
C\(_{2}\)-galkynyl(phenyl)p, C\(_{3}\)-gcycloalkyl or C\(_{1}\)-galkyl-
C\(_{3}\)-gcycloalkyl;

p is 0 to 2;
n is 0 to 6;
A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR\(^{1}\);
R\(^{1}\) is hydrogen, C\(_{1}\)-galkyl or phenylC\(_{1}\)-galkyl;
m is 0 to 3; and

Ar is aryl or heteroaryl, each of which may be optionally substituted,
and pharmaceutically acceptable salts thereof.

In the compounds of structure (IA) R\(^{a}\) is preferably
C\(_{5}\)-galkyl, in particular n-pentyl or C\(_{2}\)-galkenyl(phenyl)p
where p is 1, eg. cinnamyl. Preferred values for m, n, A and
Ar are as set forth hereinbefore for structure (I).

Particular compounds of the invention include:
3-(4-fluorophenoxy)methyl)-1-pentylpyrrolidine hydrochloride,
3-(3,4-methylenedioxyphenoxy)methyl)-1-pentylpyrrolidine
hydrochloride,
3-(4-benzylphenoxy)methyl)-1-pentylpyrrolidine hydrochloride,
3-(4-fluorobenzyloxy)methyl)-1-pentylpyrrolidine oxalate,
3-[2-(4-fluorobenzyloxy)ethyl]-1-(n-pentyl)-pyrrolidine
oxalate,
3-(3,4-dichlorophenoxy)methyl)-1-pentylpyrrolidine oxalate,
3-(2-phenylphenoxy)methyl)-1-pentylpyrrolidine oxalate,
3-(4-isopropylphenoxy)methyl-1-pentylpyrrolidine oxalate,
3-((3-phenylphenoxy)methyl)-1-pentylpyrrolidine oxalate,
3-((4-chlorophenoxy)methyl)-1-pentylpyrrolidine oxalate,
1-pentyl-3-[4-((2-p-chlorophenylethenyl)phenoxy)methyl-
pyrrolidine oxalate,
1-pentyl-3-[4-((2-phenylethenyl)phenoxy)methyl-pyrrolidine
oxalate,
1-pentyl-3-[4-((2-phenylethyl)phenoxy)methyl-pyrrolidine
oxalate,
1-pentyl-3-(3,4-dichlorobenzylamino)methyl-pyrrolidine
oxalate, and
3-[(N-(3,4-dichlorobenzyl)-N-methylaminomethyl]-1-pentyl-
pyrrolidine dioxalate.

It will be appreciated that the compounds of structure
(I) may contain one or more asymmetric centres. Such
compounds will exist as optical isomers (enantiomers). Both
the pure enantiomers, racemic mixtures (50% of each
enantiomer) and unequal mixtures of the two are included
within the scope of the invention. Further, all
diastereomeric forms possible (pure enantiomers and mixtures
thereof) are within the scope of the invention. In addition
when A represents -CH=CH- the compounds will exist as
geometric isomers and the invention encompasses all such
isomers and mixtures thereof.

The compounds of the present invention can be prepared
by processes analogous to those known in the art. The
present invention therefore provides in a further aspect, a
process for the preparation of a compound of structure (I)
which comprises:

(a) for compounds of structure (I) in which A is O, S or
NR¹, reaction of a compound of structure (II):
in which \( R \) and \( n \) are as described for structure (I) and \( A^1 \) is 0, S or NR\(^1\), with a compound of structure \( L(CH_2)_mAr \) in which \( m \) and \( Ar \) are as described for structure (I), and \( L \) is a leaving group;

(b) for compounds of structure (I) in which \( A \) is 0, S or NR\(^1\), reaction of a compound of structure (III):

in which \( n \) and \( R \) are as described for structure (I) and \( L^1 \) is a group displaceable by a nucleophile, with a compound of structure \( HA^1(CH_2)_mAr \) where \( m \) and \( Ar \) are as described for structure (I) and \( A^1 \) is as described for structure (II); or

(c) for compounds of structure (I) in which \( A \) is NR\(^1\), reduction of a compound of structure (IV):
- 9 -

\[
\begin{align*}
&\text{Structure (IV)} \\
\text{in which } R^4 \text{ represents the group } -(\text{CH}_2)_n\text{N}(\text{R}^1)\text{C(}O)\text{(CH}_2\text{)}_{m-1}\text{Ar or} \\
&\text{ } -(\text{CH}_2)_n\text{C(}O)\text{N}(\text{R}^1)\text{(CH}_2\text{)}_m\text{Ar}, \text{ and } n, m, R \text{ and } \text{Ar are as} \\
&\text{described for structure (I);} \\
\end{align*}
\]

(d) for compounds of structure (I) in which A is a bond, reaction of a compound of structure (V):

\[
\begin{align*}
&(\text{CH}_2)^{n+m}\text{L}^1 \\
&\text{Structure (V)} \\
\text{(wherein } R, \text{ L}^1, n \text{ and } m \text{ are as hereinbefore defined) with a} \\
&\text{compound of structure } X^1\text{Ar in which } \text{Ar is as described for} \\
&\text{structure (I), and } X^1 \text{ is an alkali metal;} \\
\end{align*}
\]

(e) introduction of the group R into a compound of structure (VI):
structure (VI)

by reaction with a compound RL², wherein L² is a leaving group;

(f) Reduction of a compound of structure (VII):

Structure (VII)

wherein R⁵ is C₁₋₇alkyl(phenyl)p, C₂₋₇alkenyl(phenyl)p, C₂₋₇alkynyl(phenyl)p or C₁₋₇alkylC₃₋₈cycloalkyl;

(g) for compounds of structure (I) in which A is NR¹, reduction of a compound of structure (VIII):
- 11 -

Structure (VIII)

5 in which R and R⁴ are as described for structure (IV);

(h) reduction of a compound of structure (IX):

\[
\text{(CH}_2\text{)}_n\text{Ar(CH}_2\text{)}_m\text{R}
\]

Structure (IX)

10 in which n, m, A, R and Ar are as described for structure (I);

(i) for compounds wherein A is -CH=CH- reaction of a compound of structure (X):

\[
\text{(CH}_2\text{)}_n\text{CHO}
\]

Structure (X)

20 (wherein R and n are as hereinbefore defined) with a reagent serving to introduce the group Ar;
(j) interconversion of one compound of structure (I) to a different compound of structure (I), eg. the reduction of a compound wherein A is \(-\text{CH} = \text{CH}-\) to a compound wherein A is \(-\text{CH}_2\text{CH}_2-\), or for compounds in which Ar is substituted by optionally substituted phenylC$_2$-$\text{A}$$\_4$alkyl, reduction of the corresponding phenylC$_2$-$\text{A}$$\_4$alkenyl compound;

and optionally thereafter forming a salt.

In process (a) the reaction between a compound of structure (II) and a compound L(CH$_2$)$_m$Ar can take place under conditions which depend on the nature of the group L and the value of m. For example, when L is halogen or a sulphonic acid residue such as a tosylate or mesylate, the reaction is carried out under standard conditions in a solvent, optionally in the presence of a base. When a fluoro-substituted aryl compound F-Ar is employed in process (a) (to prepare compounds where m is zero) the reaction is effected in the presence of a strong base such as sodium hydride and in an inert organic solvent such as dimethyl formamide. Preferably the aryl ring in the compound F-Ar is substituted by an activating group such as CF$_3$ or NO$_2$.

The reaction between a compound of structure (III) and a compound of structure HA$^1$(CH$_2$)$_m$Ar (process (b)) can take place under conditions which depend on the nature of L$^1$ and A. For example when L$^1$ is hydroxy, m is 0 and A$^1$ is oxygen or sulphur, the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L$^1$ may be for example a halogen atom or a sulphonyloxy group eg. methanesulphonyloxy or p-toluenesulphonyloxy. In this case the reaction may be effected in the presence or absence of solvent and at a temperature in the range 0 to 200°C, optionally in the presence of a base.

The reduction of a compound of structure (IV) according to process (c) can be effected by methods known in the art,
for example using a reducing agent such as lithium aluminium hydride. Conveniently a compound of structure (IV) can be prepared (for example as described below) and reduced in a 'one-pot' reaction, without isolation of compound (IV) itself.

The reaction between a compound of structure (V) and a compound of structure X²Ar in process (d) can take place under standard conditions known to those skilled in the art for the formation of carbon-carbon bonds.

The reaction of a compound of structure (VI) with RL² according to process (e) may be effected in conventional manner, for example in an organic solvent, such as dimethylformamide. The leaving group L² may be for example a halide such as bromide or chloride, an acyloxy group such as acetoxy or chloroacetoxy or a sulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy. When L² is a halide the reaction is preferably carried out in the presence of a weak base such as potassium carbonate, and when L² is sulphonyloxy, a strong base such as sodium hydride or potassium t-butoxide may be employed.

Reduction of a compound of structure (VII) according to process (f) may be effected using standard reducing agents such as lithium aluminium hydride.

The reduction of a compound of structure (VIII) or (IX) can be effected by methods known in the art, for example using a reducing agent such as lithium aluminium hydride in similar manner as hereinbefore described for a compound of structure (IV).

Process (i) may be effected using a Wadsworth–Emmons reagent of the formula \(\text{Ar}(\text{CH}_2)_{m+1}\text{P(O)(Oalk)}_2\), such as a diethylphosphonate, or a Wittig reagent of the formula \(\text{Ar}(\text{CH}_2)_{m+1}\text{PPh}_3\text{X}^-\) (where \(\text{X}^-\) is an anion) which compounds are available commercially or can be prepared by known methods. The reaction may be carried out in a solvent such as tetrahydrofuran optionally containing a crown ether such as
15-crown-5 or 18-crown-6, and in the presence of a strong base such as sodium hydride, or potassium t-butoxide.

Interconversion reactions according to process (j) may be effected by methods well known in the art. Thus for example conversion of a compound (I) wherein A represents -CH=CH- into a compound (I) wherein A represents-CH$_2$-CH$_2$- or the preparation of compounds of the structure (I) in which Ar is substituted by optionally substituted phenylC$_2$-alkyl from the corresponding phenylC$_2$-alkenyl compound, may be effected by the use of catalytic hydrogenation methods.

The compounds of structure (II) wherein A$^1$ is oxygen and n is 1 can be prepared by reaction of dimethylitaconate (H$_2$C=CH-CO$_2$CH$_3$) with a compound of structure RNH$_2$, CH$_2$-CO$_2$CH$_3$

wherein R is as described for structure (I) according to the method of Y-H Wu (J.Org. Chem. 1961, 26, 1519-24), followed by reduction e.g. with lithium aluminium hydride. The cyclisation step is conveniently effected in a solvent such as an alcohol e.g. methanol, and at a temperature in the range of +50 to +150°C, advantageously at reflux temperature of the solvent and the reduction may be effected in a solvent such as ether, conveniently at reflux temperature of the solvent. Compounds of structure (II) wherein A$^1$ is sulphur or NR$^1$ can be prepared from the hydroxy compounds of structure (II), via a corresponding halide, according to methods well known in the art.

Alternatively the compounds of structure (II) can be prepared from the corresponding compounds in which R is hydrogen, by alkylation under standard conditions. For example, compounds of structure (II) in which R is n-pentyl can be prepared from the corresponding precursor in which R is hydrogen by reaction with an n-pentylhalide such as n-pentyl bromide in a suitable solvent, such as a C$_1$-alkanol (e.g. ethanol), in the presence of a base, such as potassium carbonate, or dimethylformamide in the presence of a base such as sodium hydride.
Compounds of structure (III) wherein \( L^1 \) is OH can be prepared as described for compounds of structure (II), and compounds of structure (III) wherein \( L^1 \) is a halogen atom, or a mesyloxy or toslyloxy group can be prepared from the corresponding alcohol in conventional manner.

Compounds of structure (IV) wherein \( R^4 \) is a group \(-(CH_2)_nN(R^1)C(\text{O})(CH_2)_{m-1}Ar\) can be prepared by reacting a compound of structure (II) wherein \( A^1 \) represents \( NR^1 \) with an acylating agent corresponding to the group \-(CH_2)_mAr\), for example an acid chloride \( ClOC(CH_2)_mAr\).

Compounds of structure (IV) wherein \( R^4 \) is a group \(-(CH_2)_{n-1}C(\text{O})NR^1(CH_2)_mAr\) may be prepared for example by reaction of a corresponding compound wherein \( R^4 \) represents \-(CH_2)_{n-1}CO_2H\ or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula \( HN(R^1)(CH_2)_mAr\). It will be appreciated that when the acid itself is employed, reaction with the amine should be effected in the presence of a coupling agent. The carboxylic acid may itself be prepared for example by oxidation of the corresponding alcohol, ie. a compound of structure (II) wherein \( A^1 \) is oxygen.

Compounds of structure (V) may be prepared in analogous manner to compounds of structure (III); where necessary the chain length may be increased using methods well known in the art.

Compounds of structure (VI) may be prepared for example according to any of processes (a) to (d) above, using intermediates analogous to structures (II) to (IV) wherein \( R \) is replaced by an \( N \)-protecting group, which is subsequently removed by methods well known in the art. Suitable protecting groups include aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl and acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, or benzyloxy carbonyl. An aralkyl group such as benzyl may be cleaved by hydrogenolysis, and an acyl group such as benzoyl
may be cleaved by hydrolysis. It will be appreciated that where the N-protecting group is aralkyl, the compound is of structure (I) and this reaction sequence thus provides a means of converting one compound of structure (I) into a different compound of structure (I).

A compound of structure (VII) may be prepared by reaction of a compound of structure (VI) with an appropriate acid derivative for example an acid chloride, or anhydride.

Compounds of the structure (VIII) wherein \( R^4 \) is a group \(-\text{(CH}_2\text{)}_n\text{N}^1\text{(R}^1\text{)}\text{C}^\text{(O)}\text{(CH}_2\text{)}_{m-1}\text{Ar} \) can be prepared by reacting a compound of structure (XI):

\[
\begin{align*}
\text{Structure (XI)}
\end{align*}
\]

(in which \( n \) and \( R \) are as described for structure (II) and \( A^1 \) is \( NR^1 \)) with an acylating agent as described for preparing the corresponding compound of structure (IV).

Compounds of the structure (VIII) wherein \( R^4 \) is a group \(-\text{(CH}_2\text{)}_{n-1}\text{C}^\text{(O)}\text{N}^1\text{(R}^1\text{)}\text{CH}_2\text{)}_{m\text{Ar}} \) may be prepared for example by reaction of a corresponding compound wherein \( R^4 \) represents \(-\text{(CH}_2\text{)}_{n-1}\text{CO}_2\text{H} \) or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula \( \text{HN}^1\text{(R}^1\text{)}\text{CH}_2\text{)}_{m\text{Ar}} \) in a similar manner as described for the corresponding compound of structure (IV).

Compounds of the structure (IX) can be prepared in similar manner to compounds of the structure (I) except that the appropriate starting material has a 5-oxopyrrolidino ring in place of the pyrrolidino ring. For example a compound of
the structure (IX) can be prepared by reaction of a compound of the structure (XII):

\[
\begin{align*}
\text{Structure (XII)}
\end{align*}
\]

in which \(n, R\) and \(L^1\) are as described for structure (III) with a compound of structure \(HA^1(CH_2)_mAr\) where \(m, A^1\) and \(Ar\) are as described for structure (II).

When \(L^1\) is hydroxy, the Mitsunobu reaction can be used as hereinbefore described for the reaction with a compound of the structure (III).

Compounds of structure (X) may be prepared by conventional methods, for example the oxidation of a compound of structure (II) wherein \(A^1\) is oxygen, or conversion of the corresponding ester, e.g. by reaction with thionyl chloride and \(N, O\)-dimethylhydroxylamine hydrochloride, to give the \(N\)-methyl-\(N\)-methoxycarboxamide, which can be reduced to the aldehyde using diisobutylaluminium hydride. Compounds of structure (X) wherein \(n\) is 1 may be prepared from the corresponding compound wherein \(n\) is zero by various methods. For example the aldehyde wherein \(n\) is zero may be treated with (methoxymethyl) triphenylphosphonium chloride and potassium t-butoxide, followed by a strong acid, e.g. concentrated sulphuric acid, resulting in the aldehyde wherein \(n\) is 1. Alternatively the aldehyde may be converted to the corresponding cyanomethyl derivative as described in EPA 363085 followed by acid hydrolysis, conversion to the \(N\)-methyl-\(N\)-methoxycarboxamide and reduction. These procedures may also be used to form higher homologues.
When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may be administered by any convenient method for example by oral, parenteral, buccal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using
standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, cellulosics, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as cyclodextrins.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg, and each dosage unit for parenteral administration contains preferably from 0.1 to 25 mg of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at
a dose of up to 400 mg per day. Thus the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.
EXAMPLES

Intermediate Preparation

i) 1-Pentyl-3-hydroxymethylpyrrolidine

a) Using the method of Y-H Wu (J.Org. Chem., 1961 26, 1519-24) dimethylitaconate (15.8gms) was reacted with n-pentylamine (8.72gms) in methanol (20ml). After refluxing for two hours, cooling and removal of methanol the residue was vacuum distilled to give methyl 1-pentyl-5-oxopyrrolidine-3-carboxylate 18.9gms, B.P. 100-105°C at 0.02mm.Hg.

Found:  C, 61.83; H, 8.96; N, 6.31%
(C₁₁H₁₉NO₃) requires C, 61.95; H, 8.98; N, 6.57%

b) Lithium aluminium hydride (4.69g) was suspended in dry ether (60ml) under nitrogen and methyl 1-pentyl-5-oxopyrrolidine-3-carboxylate (18.43gms) in dry ether (20ml) was added dropwise at such a rate so as to cause gentle refluxing. The mixture was refluxed for a further hour, cooled to 0°C and water (7ml) carefully added. Further ether was added and the solid salts were filtered off and the ether evaporated (8.98 g-oil). The inorganics were extracted in a Soxhlet with ethanol overnight (6.0gms-oil). The combined oils were vacuum distilled to give the title compound, 11.26gms, B.P. 85-90°C, @ 0.1mmHg.

Found C, 69.78; N, 12.54; H, 7.82%
(C₁₀H₂₁NO) requires C, 70.12; H, 12.36; N,8.18%

ii) 1-Pentyl-3-(2-hydroxyethyl)pyrrolidine

a) Using the method of Y-H Wu (J Org Chem 1961 26 1519-24) 1-pentyl-3-hydroxymethylpyrrolidine (6.54 g) was dissolved in chloroform (10 ml) and the mixture saturated with dry hydrogen chloride gas. The mixture was heated to
reflux and treated with thionyl chloride (5.6 ml) in chloroform (10 ml) over 30 min. The mixture was refluxed for a further 1 hr.

Excess thionyl chloride was removed by co-distillation with ethanol. The product was obtained by evaporation and extraction of the basified residue with ether. Evaporation of the ether solution gave an oil which was purified by Kugelrohr distillation. 1-Pentyl-3-chloromethylpyrrolidine was obtained as an oil (5.79 g).

Found: C, 62.99; H, 10.78; N, 6.99; Cl, 18.72%.
(C_{10}H_{20}ClN) requires C, 63.31; H, 10.63; N, 7.38;
Cl, 18.68%.

b) 1-Pentyl-3-chloromethylpyrrolidine (5.42 g), sodium cyanide (7.25 g), aliquot 336 (375 mg) and water (12.5 ml) were vigorously stirred together at 100°C for 24 hrs.

Extraction of the cooled reaction mixture with ethyl acetate followed by evaporation gave an oil (5.03 g) which on distillation gave 1-pentyl-3-cyanomethyl-pyrrolidine (2.98 g).

Found: C, 60.32; H, 9.72; N, 12.31%.
(C_{11}H_{20}N_{2}HCl) requires C, 60.67; H, 10.18; N, 12.23%.

c) Using the method of A E Fadia (J Med Chem 1985 28 653-60), 1-pentyl-3-cyanomethyl-pyrrolidine (2.982 g) was added to methanol (60 ml) which had been saturated with dry hydrogen chloride gas. The mixture was allowed to stand at room temperature for 16 hrs.

The solvent was evaporated in vacuo and the residue partitioned between sodium hydroxide solution and ether. Evaporation of the washed (H_2O) and dried (Na_2SO_4) ether phase gave an oil which on Kugelrohr distillation gave methyl 3-(1-pentyl-pyrrolidino) acetate (2.13 g) bp 100°C @ 0.2 mmHg.
d) Methyl 3-\((1\text{-}pentylypyrrolidino)\) acetate (1.967 g) was added to a suspension of lithium aluminium hydride (0.7 g) in diethyl ether (40 ml) over 30 min. The mixture was refluxed for 4 hr and then allowed to cool to room temperature.

Water (5 ml) was added and the inorganics filtered off. Evaporation of the filtrate gave an oil (1.918 g) which on Kugelrohr distillation gave 1-pentyl-3-[2-hydroxyethyl]-pyrrolidine (1.48 g) bp 150°C @ 1.0 mmHg.

Accurate Mass Spectrum M⁺ 185.1780 C₁₁H₂₃OH.

iii) \(3-\left[N-(3,4\text{-Dichlorophenyl})\text{methylaminocarboxy}\right]-5\text{-oxo-1-pentylpyrrolidine}\)

Methyl 1-pentyl-5-oxopyrrolidine-3-carboxylate (2.13 g) and 3,4-dichlorobenzylamine (1.76 g) were fused together at 150°C under nitrogen for 1 hr.

The reaction mixture was dissolved in ethyl acetate and eluted down a silica column with ethyl acetate, methanol mixtures. The resulting oil was stirred with diethyl ether until it crystallised yielding the title compound (1.84 g) mp = 69-73°C.

Found C, 56.82; H, 6.14; N, 7.54; Cl, 20.26%.
(C₁₇H₂₂Cl₂N₂O₂) requires C, 57.15; H, 6.21; N, 7.84; Cl, 19.85%.

iv) \(3\text{-Chloromethyl-1-pentyl-5-pyrrolidinone}\)

a) Using the method of P A Zoretic (J Org Chem 45 810 (1980)) sodium borohydride (37.83 g) was added in small portions to methyl 1-pentyl-5-oxopyrrolidine-3-carboxylate (21.30 g) in ethanol (600 ml) under dry nitrogen over 6 hrs. The mixture was stirred at room temperature for 16 hrs.

The solvent was removed in vacuo and the residue partitioned between aqueous sodium hydroxide and ether. The
ether phase was washed (brine), dried (Na₂SO₄) and evaporated to give an oil which on distillation gave 3-hydroxymethyl-1-pentyl-5-pyrrolidinone (7.46 g) bp = 150-160°C 0.8 mBar.

Found: C, 64.31; H, 10.98; N, 7.56%.
[B₁₀H₁₉NO₂] requires C, 64.83; H, 10.34; N, 7.56%.

b) 3-Hydroxymethyl-1-pentyl-5-pyrrolidinone (1.85 g) was dissolved in ether (50 ml). Thionyl chloride (1.6 ml) was added and the mixture stirred at room temperature for 24 hrs.

Solid anhydrous potassium carbonate was added and the mixture stirred for 10 mins. The mixture was filtered and the solvent removed from the filtrate in vacuo. Excess thionyl chloride was removed by co-distillation with toluene.

Purification of the residue by silica chromatography with ethyl acetate as eluant gave the title compound (1.674 g) as an oil.

Found: C, 58.77; H, 8.87; N, 6.75%.
(C₁₀H₁₈ClNO) requires C, 58.96; H, 8.91; N, 6.88%.

v) 3-[N-(3,4-Dichlorophenyl)methyl-N-methylamino carboxy]-5-oxo-1-pentylpyrrolidine

Méthyl 1-pentyl-5-oxopyrrolidine-3-carboxylate (4.26 g) and N-methyl-3,4-dichlorobenzylamine (3.80 g) were fused together at 150°C for 4 hrs. On cooling to room temperature, the product was purified by silica chromatography using ethyl acetate, methanol mixtures. The title compound (oil) thus obtained, (1.49 g) was used directly.
Example 1

3-(4-Fluorophenoxymethyl)-1-pentylpyrrolidine hydrochloride

3-Hydroxymethyl-1-pentylpyrrolidine (0.853g), 4-fluorophenol (0.56g) and triphenylphosphine (1.31g) were stirred together in dry THF (25ml) under nitrogen. The mixture was cooled in an ice-bath and diethylazodicarboxylate (0.79ml) was injected. The mixture was allowed to stand at room temperature overnight, the THF evaporated off and the residue subjected to flash chromatography on silica gel using ethyl acetate as eluent. The resulting oil was dissolved in ether and extracted with 10% hydrochloric acid. The aqueous phase was basified with 2N.NaOH and extracted with ether. The ether was washed with H2O, dried and evaporated to give an oil which was free from tri-phenylphosphine oxide. This oil was treated with 1M HCl in Et2O to give the title compound, which was crystallised from isopropylacetate (0.155gms), M.P. = 92-94°C.

Found C, 63.34; H, 8.39; N, 4.56; Cl., 11.77%
(C16H24FNO.HCl) requires C, 63.67; H, 8.35; N, 4.64; Cl, 11.70%

Example 2

3-(3,4-Methylenedioxyphenoxy methyl)-1-pentyl pyrrolidine hydrochloride

Substituting 3,4-methylenedioxyphenol (0.695gms) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil following first acid/base extraction as described and then flash chromatography (silica gel-ethyl acetate). This oil was dissolved in ether and treated with 1M. HCl in ether. The resulting solid was crystallised twice from ethyl acetate to give the title compound (0.653gms), M.P. = 133-134°C.
Found C, 62.15; H, 8.13; N, 4.24; Cl, 10.61%
(C_{17}H_{25}NO_{2}.HCl) requires C, 62.28; H, 7.99; N, 4.27;
Cl, 10.81%

Example 3

3-(4-Benzylloxophenoxy)methyl)-1-pentyloxyrrolidine hydrochloride

Substituting 4-benzylloxphenol (1.00g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil which was subjected to acid-base extraction followed by flash chromatography (silica gel - ethyl acetate). The residue was dissolved in ether and treated with a slight excess of HCl in ether to give a solid which was washed with ether and dried. This solid was then crystallised from ethyl acetate to give the title compound as white microcrystals (0.481gms), M.P. = 155-156°C.

Found C, 70.85; H, 8.43; N, 3.59; Cl, 9.18%
(C_{21}H_{31}NO_{2}.HCl) requires C, 70.84; H, 8.31; N, 3.73; Cl, 9.09%

Example 4

3-(4-Fluorobenzylloxophenoxy)methyl)-1-pentyloxyrrolidine oxalate

Sodium hydride (60% oil dispersion, 0.44gms) was suspended, under nitrogen, in anhydrous dimethylformamide (20ml). 3-Hydroxymethyl-1-pentyloxyrrolidine (1.72g) in DMF (20ml) was added and the mixture stirred for 10 minutes. 4-Fluorobenzyl chloride (1.2ml) was added and the mixture stirred at room temperature for 48 hours. The reaction mixture was partitioned between water and ether. The ether
phase was washed, dried and evaporated to give an oil (2.45g). Vacuum distillation (150°C, 0.2mmHg) did not give pure product. The distilled material (1.98g) was flash chromatographed on silica gel (CH₂Cl₂/MeOH) to give an oil (1.47g). This was added to a solution of oxalic acid (0.67g) in hot ethyl acetate to give, on cooling, a solid which was collected, washed with ether and dried. The resulting solid was re-crystallised from ethyl acetate to give the title compound as a white solid (1.31gms), M.P. = 110-114°C.

 Found C, 61.66; H, 7.64; N, 3.99%
(C₁₇H₂₆FNO.C₂H₂O₄) requires C, 61.77; H, 7.64; N, 3.79%

Example 5

3-[2-(4-Fluorobenzylxyloxy)ethyl]-1-(n-pentyl)-pyrrolidine oxalate

Sodium hydride (80% oil dispersion 0.32 g) was suspended in anhydrous dimethylformamide (40 ml) under dry nitrogen. 3-[2-Hydroxyethyl]-1-pentylpyrrolidine (1.83 g) was added and the mixture stirred for 10 mins.

4-Fluorobenzylchloride (1.22 ml) was added and the mixture stirred for 1 hr at room temperature and then at 60°C for 6 hrs. The mixture was allowed to come to room temperature over 16 hrs.

The solvent was evaporated under vacuum and the residue treated with water. The product was obtained by extraction into ether. The ether phase was extracted with hydrochloric acid. The acid solution was basified with a 50% (W/W) solution of sodium hydroxide in water. The resulting oil was extracted into ether. The ether phase on washing (H₂O) drying (Na₂SO₄) and evaporating yielded an oil (1.763 g).
The product was purified as its hydrochloride by column chromatography on silica using dichloromethane/methanol mixtures. The product was reconverted to its free base and then to its oxalate salt using oxalic acid in THF. The product was purified by treatment with ethyl acetate to give a white microcrystalline solid (0.746 g) mp = 80-82°C.

Found: C, 62.39; H, 7.82; N, 3.83%.

$\text{C}_{18}\text{H}_{28}\text{FNO} \cdot (\text{CO}_2\text{H})_2$ requires C, 62.65; H, 7.89; N, 3.65%.

Example 6

3-(3, 4-Dichlorophenoxy)methyl)-1-pentylpyrrolidine oxalate

Substituting 3, 4-dichlorophenol (1.22 g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil. This oil when treated with an equimolar quantity of oxalic acid dihydrate in warm ethyl acetate gave a solid which on recrystallisation from ethyl acetate gave the title compound (0.746 g) mp = 116-117°C.

Found: C, 52.94; H, 6.09; N, 3.54%.

$(\text{C}_{16}\text{H}_{23}\text{Cl}_2\text{NO} \cdot (\text{CO}_2\text{H})_2)$ requires C, 53.21; H, 6.20; N, 3.45%.

Example 7

3-(2-Phenylphenoxy)methyl)-1-pentylpyrrolidine oxalate

Substituting 2-phenylphenol (1.28 g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil which was purified by chromatography on silica using ethyl acetate, methanol ammonia mixtures as elutant. The purified product was converted to its oxalate by treating it with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The resulting solid was recrystallised from ethyl acetate and then treated with charcoal in methanol. Filtration and treatment of the
filtrate with diethyl ether gave the title compound (0.278 g) mp = 119-121°C.

Found: C, 68.42; H, 7.44; N, 3.77%

\[ \text{C}_{22}\text{H}_{29}\text{NO} \cdot \text{(CO}_2\text{H})_2 \cdot 0.5\text{H}_2\text{O} \text{ requires C, 68.22; H, 7.63; N, 3.31%}. \]

Example 8

3-(4-isopropylphenoxy)methyl-1-pentylpyrrolidine oxalate

Substituting 4-isopropylphenol (1.02 g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil which was purified to silica chromatography with ethyl acetate, methanol, ammonia mixtures as eluant. The purified oil was treated with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The resulting solid on recrystallisation from ethyl acetate gave the title compound (0.342 g) mp = 103-105°C.

Found: C, 66.37; H, 8.73; N, 3.95%.

\[ \text{(C}_{19}\text{H}_{31}\text{NO} \cdot \text{(CO}_2\text{H})_2 \text{ requires C, 66.46; H, 8.76; N, 3.69%}. \]

Example 9

3-(3-Phenylphenoxyethyl)-1-pentylpyrrolidine oxalate

Substituting 3-phenylphenol (1.28 g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil which was purified by silica chromatography using ethyl acetate, methanol, ammonia mixtures as eluant. The purified product was converted to its oxalate salt by treatment with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The resulting solid, on recrystallisation from ethyl acetate gave the title compound (0.515 g) mp = 100-103°C.

Found C, 69.64; H, 7.55; N, 3.64%.

\[ \text{(C}_{22}\text{H}_{29}\text{NO} \cdot \text{(CO}_2\text{H})_2 \text{ requires C, 69.71; H, 7.56; N, 3.39%}. \]
Example 10

3-(4-Chlorophenoxyethyl)-1-pentylpyrrolidine oxalate

Substituting 4-chlorophenol (0.96 g) for 4-fluorophenol and using corresponding molar proportions of the other reagents in Example 1 gave an oil. Treatment of this oil with a 10% excess of oxalic acid dihydrate in warm ethyl acetate gave a solid which on recrystallisation from ethyl acetate and water (charcoal) gave the title compound (0.308 g) mp = 132°C.

Found: C, 58.13; H, 7.00; N, 3.89%.
C₁₆H₂₄ClNO.(CO₂H)₂ requires C, 58.14; H, 7.05; N, 3.77%.

Example 11

1-Pentyl-3-[4-(2-p-chlorophenylethenyl)phenoxy]-methylpyrrolidine oxalate

Substituting 4-chloro-4′-hydroxystilbene (4.60 g) for 4-fluorophenol, using the corresponding molar proportions of other reagents and washing with dilute sulphuric rather than hydrochloric acid at the appropriate stage in Example 1 gave an oil. A portion of this oil was converted to its oxalate salt by treatment with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The salt, on recrystallisation from ethanol/water gave the title compound (0.233 g) mp = 201-202°C dcv.

Found: C, 65.66; H, 6.68; N, 3.06; Cl, 7.21%.
(C₂₄H₃₀ClNO.(CO₂H)₂) requires C, 65.88; H, 6.80; N, 2.96; Cl, 7.48%.
Example 12

1-Pentyl-3-[4-(2-phenylethyl)phenoxy]methyl-pyrrolidine oxalate

Substituting 4-hydroxy-trans-stilbene (3.925 g) for 4-fluorophenol and using the corresponding molar proportions of other reagents in Example 1 gave an oil. A portion of this oil was converted to its oxalate with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The salt was recrystallised first from ethanol and then from acetonitrile, water mixtures to give the title compound (0.126 g) mp = 198-199°C.

Found C, 70.98; H, 7.53; N, 3.23%.
(C₂₄H₃₁NO₇(CO₂H)₂) requires C, 71.05; H, 7.57; N, 3.19%.

Example 13

1-Pentyl-3-[4-(2-phenylethyl)phenoxy]methyl-pyrrolidine oxalate

1-Pentyl-3-[4-(2-phenylethene)phenoxy]-methyl-pyrrolidine (2.00 g) prepared as in Example 12, was suspended in ethanol (100 ml) and a slight excess of hydrochloric acid added. 5% Palladium on carbon (0.1 g) was added and the mixture hydrogenated at 40 psi and room temperature for 16 hrs.

The catalyst was filtered off and the filtrate reduced in bulk under vacuum. The residue was partitioned between aqueous sodium hydroxide and ether. The ether phase on washing (H₂O), drying (Na₂SO₄) and evaporation gave an oil. The oil was converted to its oxalate salt with a 10% excess of oxalic acid dihydrate in warm ethyl acetate. The salt on recrystallisation from acetonitrile gave the title compound (1.41 g) mp = 143-144°C.

Found: C, 70.34; H, 7.92; N, 3.56%.
(C₂₄H₃₃NO₇(CO₂H)₂) requires C, 70.72; H, 7.99; N, 3.17%
Example 14

1-Pentyl-3-(3,4-dichlorobenzylamino)methyl-pyrrolidine dioxalate

Lithium aluminium hydride (0.14 g) was suspended in dry tetrahydrofuran (10 ml). 3-[N-(3,4-Dichlorophenyl)methylamino-carboxy]-5-oxo-1-pentylpyrrolidine (0.50 g) dissolved in dry tetrahydrofuran (30 ml) was added at ice temperature over 15 minutes.

The reaction mixture was refluxed for 1 hr and left to stand at room temperature for 16 hrs. Water was carefully added to the reaction mixture until the reaction ceased. The mixture was extracted with ether. The ether phase on washing (H₂O), drying (Na₂SO₄) and evaporating gave an oil.

The oil was converted into its oxalate by treatment with two equivalents of oxalic acid dihydrate in warm ethyl acetate. The resulting solid was purified by stirring with dimethylformamide giving the title compound. (0.214 g) mp = 217-218°C.

Found: C, 49.79; H, 6.05; N, 5.80; Cl, 13.17%.
(C₁₇H₂₆Cl₂N₂.2(CO₂H)₂) requires C, 49.52; H, 5.94; N, 5.50; Cl, 13.92%.

Example 15

3-[N-(3,4-Dichlorobenzyl)-N-methylaminomethyl]-1-pentylpyrrolidine dioxalate

A solution of 3-[N-3,4-dichlorophenyl)methyl-N-methylamino carboxy]-5-oxo-1-pentyl-pyrrolidine (1.49 g) in tetrahydrofuran (30 ml) was added to a suspension of lithium aluminium hydride (0.4 g) in tetrahydrofuran (10 ml) over 30 mins. The mixture was stirred at room temperature for 1 hr and then refluxed for 1 hr.
The mixture was cooled in an ice bath and sufficient water added to decompose the complex. Ether (100 ml) was added and the mixture dried with anhydrous sodium sulphate. The mixture was filtered and the filtrate evaporated to give an oil. The oil was converted to its salt by treatment with two equivalents of oxalate acid dihydrate in warm ethyl acetate.

The resulting solid on recrystallisation from ethanol gave the title compound (1.265 g) mp = 163-165°C.

Found: C, 50.63; H, 6.06; N, 5.35; Cl, 13.99%.
(C_{18}H_{28}Cl_{2}N_{2}.2(CO_{2}H))_{2} requires C, 50.48; H, 6.16; N, 5.35; Cl, 13.55%.

Example 16

3-[4-(2-p-Chlorophenylethyl)phenoxy]methyl-1-pentylpyrrolidine oxalate

Substituting 1-(p-chlorophenyl)-2-(p-hydroxyphenyl) ethane (2.00g) for 4-fluorophenol and using corresponding molar proportions of other reagents in Example 1 gave a solid which was purified on a silica gel column using ethyl acetate/methanol mixtures as elutant.

The product, a white solid, was converted to its oxalate salt with a 10% excess of oxalate acid dihydrate in warm ethyl acetate. The salt, on recrystallisation from ethanol gave the title compound (0.73g), m.p. = 121-123°C.
BIOLOGICAL DATA

Ca²⁺ Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Forda et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca²⁺ currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; MgCl₂, 4; ATP, 2; buffered to pH 7.2 with CsOH.

Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca²⁺ currents.

The external solution for recording Ca²⁺ channel currents contained in mM: BaCl₂, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; MgCl₂, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided.

Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca²⁺ currents.

All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for later analysis using PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), 404, 767-784).
RESULTS

Ca\textsuperscript{2+} currents

Peak voltage gated Ca\textsuperscript{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba\textsuperscript{2+} as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow rundown of current as is commonly seen when recording Ca\textsuperscript{2+} currents. The rundown rate was measured in control conditions and extrapolated through the time of drug application to derive a control value to relate the drug affected current to. Block by 20 \textmu M drug was assessed 3 minutes after drug application.

The compounds of Examples 1 to 16 exhibited percentage inhibition of plateau Ca\textsuperscript{2+} current in the range 36 to 99\%.
Claims:

1. Use of a compound of structure (I):

\[
\begin{align*}
\text{Structure (I)} \quad (\text{CH}_2)_n A (\text{CH}_2)_m \text{Ar} \\
\text{R}
\end{align*}
\]

in which

- R is C₁-alkyl, C₁-alkyl(phenyl), C₂-alkenyl(phenyl)p, C₂-alkynyl(phenyl)p, C₃-cycloalkyl or C₁-alkylC₃-cycloalkyl;
- p is 0 to 2;
- n is 0 to 6;
- A is a bond, -CH=CH-, -C=O-, oxygen, sulphur or NR²;
- R¹ is hydrogen, C₁-alkyl or phenylC₁-alkyl;
- m is 0 to 3; and
- Ar is aryl or heteroaryl, each of which may be optionally substituted,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated.

2. Use of a compound according to claim 1 wherein the disorder is a condition or disease related to an accumulation of calcium in the brain cells of a mammal.

3. A method of treatment of a condition or disease caused or exacerbated by the accumulation of calcium in the brain cells of a mammal which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

4. A compound of structure (IA):
Structure (IA)

5 in which
Ra is C5-8alkyl, C5-8alkyl(phenyl), C2-8alkenyl(phenyl)p,
C1-8alkynyl(phenyl)p, C3-8cycloalkyl or C1-8alkylC3-
cycloalkyl;
p is 0 to 2;
n is 0 to 6;
A is a bond, oxygen, sulphur or NR1;
R1 is hydrogen, C1-8alkyl or phenylC1-4alkyl;
m is 0 to 3; and
Ar is aryl or heteroaryl, each of which may be
optionally substituted,
or a salt thereof.

5. A compound according to claim 4 wherein Ra is
C5-8alkyl or C2-8alkenyl(phenyl)p wherein p is 1.

6. A compound according to claim 4 or claim 5 in which
A is oxygen.

7. A compound according to any of claims 4 to 6 in
which the length of the chain -(CH2)nA(CH2)m is from 2 to 5
atoms.

8. A compound according to any of claims 4 to 7 in
which Ar is optionally substituted phenyl.

9. A compound according to claim 4 which is:
3-(4-fluorophenoxy)methyl)-1-pentylpyrrolidine;
3-(3,4-methyleneoxyphenoxy)methyl)-1-pentylpyrrolidine;
3-(4-benzylphenoxy)methyl)-1-pentylpyrrolidine;
3-(4-fluorobenzyl)oxy)methyl)-1-pentylpyrrolidine;
3-(3,4-dichlorophenoxy)methyl)-1-pentylpyrrolidine;
3-(2-phenylphenoxy)methyl-1-pentylpyrroolidine;
3-(4-isopropylphenoxy)methyl-1-pentylpyrroolidine;
3-(3-phenylphenoxy)methyl-1-pentylpyrroolidine;
3-(4-chlorophenoxy)methyl-1-pentylpyrroolidine;

1-pentyl-3-[4-(2-p-chlorophenylethenyl)phenoxy]methyl-
pyrroolidine;
1-pentyl-3-[4-(2-phenylethenyl)phenoxy]methyl-
pyrroolidine;
1-pentyl-3-[4-(2-phenylethyl)phenoxy]methyl-
pyrroolidine;
1-pentyl-3-(3,4-dichlorobenzylamino)methyl-
pyrroolidine; or

3-[N-(3,4-dichlorobenzyl)-N-methylaminomethyl]-1-pentyl-
pyrroolidine;
or a pharmaceutically acceptable salt thereof.

10. A process for preparing a novel compound of
structure (I) which comprises:

(a) for compounds of structure (I) in which A is O, S
or NR\(^1\), reaction of a compound of structure (II):

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\[ \text{Structure (II)} \]
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in which R and \( n \) are as described for structure (I) and \( A^1 \) is
O, S or NR\(^1\), with a compound of structure \( L(CH_2)_mAr \) in which \( m \)
and Ar are as described for structure (I), and \( L \) is a leaving
group;

(b) for compounds of structure (I) in which A is O, S
or NR\(^1\), reaction of a compound of structure (III):
in which n and R are as described for structure (I) and L\(^1\) is a group displaceable by a nucleophile, with a compound of structure HA\(^1\)(CH\(_2\))\(_m\)Ar where m and Ar are as described for structure (I) and A\(^1\) is as described for structure (II); or

(c) for compounds of structure (I) in which A is NR\(^1\), reduction of a compound of structure (IV):

in which R\(^4\) represents the group -(CH\(_2\))\(_n\)N(R\(^1\))C(O)(CH\(_2\))\(_m\)-Ar or -(CH\(_2\))\(_n\)-C(O)N(R\(^1\))(CH\(_2\))\(_m\)-Ar, and n, m, R and Ar are as described for structure (I);

(d) for compounds of structure (I) in which A is a bond, reaction of a compound of structure (V):
with a compound of structure $X^1\text{Ar}$ in which Ar is as described for structure (I), and $X^1$ is an alkali metal;

(e) introduction of the group R into a compound of structure (VI):

by reaction with a compound $RL^2$, wherein $L^2$ is a leaving group;

(f) Reduction of a compound of structure (VII):

wherein $R^5$ is $C_{1-7}$alkyl(phenyl)p, $C_{2-7}$alkenyl(phenyl)p, $C_{2-7}$alkynyl(phenyl)p or $C_{1-7}$alkylC$_3$-8cycloalkyl;
and optionally thereafter forming a salt.

(g) for compounds of structure (I) in which A is NR¹,

reduction of a compound of structure (VIII):

![Structure (VIII)](image)

Structure (VIII)

in which R and R⁴ are as described for structure (IV);

(h) reduction of a compound of structure (IX):

![Structure (IX)](image)

Structure (IX)

in which n, m, A, R and Ar are as described for structure (I);

(i) for compounds wherein A is -CH=CH- reaction of a compound of structure (X):
(wherein R and n are as hereinbefore defined) with a reagent serving to introduce the group Ar;

(j) interconversion of one compound of structure (I) to a different compound of structure (I), e.g. the reduction of a compound wherein A is \(-\text{CH}=\text{CH}-\) to a compound wherein A is \(-\text{CH}_2\text{CH}_2-\), or for compounds in which Ar is substituted by optionally substituted phenylC\(_2\)-alkyl, reduction of the corresponding phenylC\(_2\)-alkenyl compound;

and optionally thereafter forming a salt.

11. A pharmaceutical composition comprising a compound as defined in claim 1 or claims 4 to 9, in association with a pharmaceutically acceptable carrier.