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3-SUBSTITUTED PIPERIDINE DERIVATIVES

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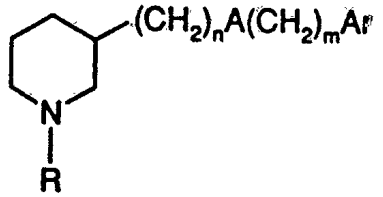
(57) Claim

1. A compound of structure (I):



(I)

in which

R is C_{5-8}alkyl(phenyl)$_p$, C_{2-8}alkenyl(phenyl)$_p$, C_{2-8}alkynyl(phenyl)$_p$, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl;

p is 0 to 1;

n is 0 to 6, and m is 0 to 3 provided that m and n are not both zero;

A is a bond, oxygen, sulphur or NR^1, where

R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

and Ar is optionally substituted phenyl,

or a salt thereof.

.../2

15. A method of treatment of a condition caused or exacerbated by the accumulation of a 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) according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof.

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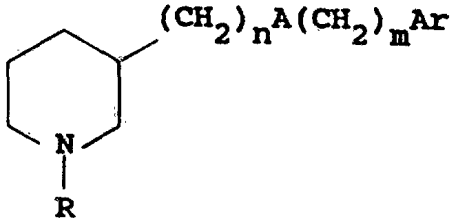
(54) Title: 3-SUBSTITUTED PIPERIDINE DERIVATIVES



(I)

(57) Abstract

Compounds of structure (I) in which R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{2-8}alkynyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl; p is 0 to 2; n is 0 to 6; A is a bond, oxygen, sulphur or NR^1; R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; m is 0 to 3; and Ar is aryl or heteroaryl, each of which may be optionally substituted, and salts thereof; processes for preparing compounds (I), pharmaceutical compositions containing them and their use in medicine, in particular as calcium blocking agents.

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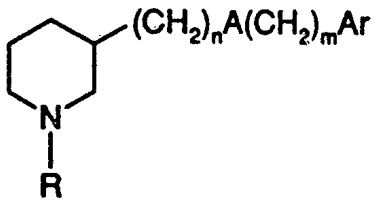
3-SUBSTITUTED PIPERIDINE DERIVATIVES

The present invention relates to 3-substituted piperidine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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



(I)

in which

R is C_{5-8}alkyl(phenyl)$_p$, C_{2-8}alkenyl(phenyl)$_p$, C_{2-8}alkynyl(phenyl)$_p$, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl;

p is 0 to 1;

n is 0 to 6, and m is 0 to 3 provided that m and n are not both zero;

A is a bond, oxygen, sulphur or NR^1, where

R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

and Ar is optionally substituted phenyl,

and salts thereof.

Suitably, R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl-(phenyl)p, C_{2-8}alkynyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl.

It will be understood that the alkylcycloalkyl, alkylphenyl, alkenylphenyl and alkynylphenyl groups are linked to the piperidine nitrogen atom via the alkyl, alkenyl and alkynyl moieties respectively.

Preferably R is C_{1-8}alkyl(phenyl)p in which p is 0 or 1, i.e. C_{1-8}alkyl, such as n-pentyl, or phenylC_{1-8}alkyl such as phenylpropyl, or R is C_{2-8}alkenyl(phenyl)p wherein p is 1, such as cinnamyl.

Suitably, n is 0 to 6; preferably n is 0 to 3; most preferably n is 1.

Suitably, m is 0 to 3; preferably m is 0 or 1; most preferably m is 0.

Suitably, A is a bond, oxygen, sulphur or NR^1; preferably A is oxygen or sulphur; most preferably A is oxygen. When A is oxygen n is preferably 1 and m is preferably 0.

Suitably, Ar is optionally substituted aryl or heteroaryl; preferably Ar is optionally substituted aryl.

Suitable aryl groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic ring systems of up to 10 carbon atoms, such as, for example, phenyl, naphthyl and tetrahydronaphthyl. Preferred are optionally substituted phenyl rings.

Suitable substituted phenyl rings include, for

example, phenyl rings substituted by a C_{1-2}alkylenedioxy group such as a 3,4-methylenedioxy group or by 1 to 3 substituents selected from halogen, C_{1-4}alkoxy, nitro, SC_{1-4}alkyl, NR^2R^2 (in which each R^2 group can be H or C_{1-4}alkyl), OCF_3, C_{1-6}alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy. Preferred are phenyl rings substituted by one or two substituents, in particular, by a single halogen, trifluoromethyl, unsubstituted phenyl or unsubstituted phenylC_{1-4}alkoxy group; or by two chloro atoms especially in the 3- and 4-positions of the phenyl ring.

Suitable optionally substituted phenylC_{1-4}alkyl groups include, for example benzyl. Suitable optionally substituted phenylC_{1-4}alkoxy groups include, for example benzyloxy groups.

Suitable substituents for said optionally substituted phenyl, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy groups include for example halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro and trifluoromethyl groups.

Suitable heteroaryl rings include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic ring systems of up to 10 carbon atoms containing at least one heteroatom, such as pyridyl, thienyl, quinolinyl, tetrahydroquinolinyl and imidazolyl rings. The heteroaryl ring can be linked to the remainder of structure (I) via a carbon atom or via a hetero atom, e.g. a nitrogen 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.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. 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.

Particular compounds of the invention include:

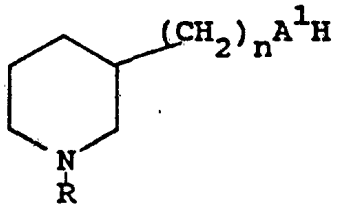
3-(4-fluorophenoxymethyl)-1-pentylpiperidine oxalate,
3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine hydrochloride,
3-(3-trifluoromethylphenoxymethyl)-1-pentylpiperidine hydrochloride,
3-(3-phenylphenoxymethyl)-1-pentylpiperidine oxalate,
3-(2-phenylphenoxymethyl)-1-pentylpiperidine oxalate,
3-(4-phenylphenoxymethyl)-1-pentylpiperidine oxalate,
3-(2-benzylphenoxymethyl)-1-pentylpiperidine oxalate,
3-(4-benzylphenoxymethyl)-1-pentylpiperidine hydrochloride,
3-(4-benzyloxyphenoxymethyl)-1-pentylpiperidine hydrochloride,
1-cinnamyl-3-(3,4-dichlorophenoxymethyl)piperidine oxalate,
3-(4-iso-propylphenoxymethyl)-1-pentylpiperidine hydrochloride, and
3-(3,4-dichlorophenylaminomethyl)-1-pentylpiperidine dihydrochloride.

It will be appreciated that the compounds of structure (I) may contain one or more asymmetric centres, in particular at the 3-position of the piperidine ring. 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.

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:

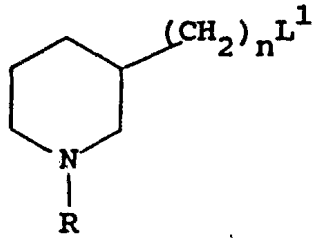
(a) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (II):



(II)

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;

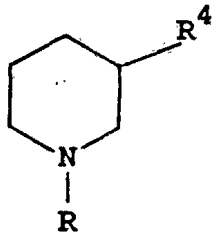
(b) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (III):



(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) :

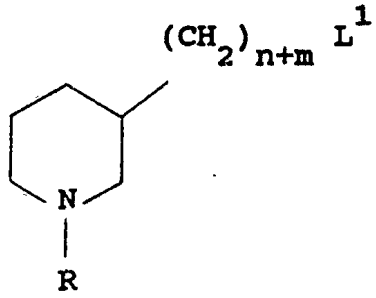


(IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$, 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) :

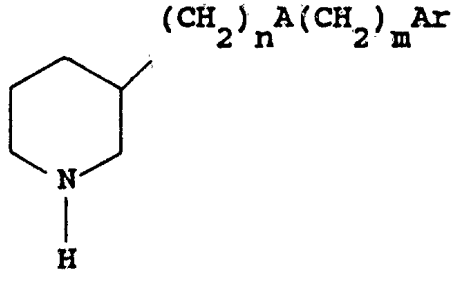


(V)

(wherein R, L^1, m and n are as hereinbefore defined).

with a compound of structure X^1Ar in which Ar is as described for structure (I), and X^1 is an alkali metal;

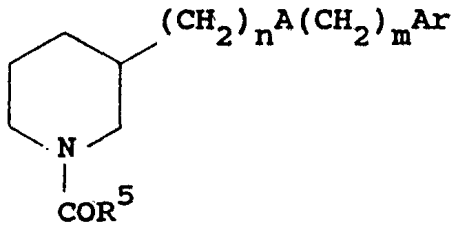
(e) introduction of the group R into a compound of formula (VI) :



(VI)

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

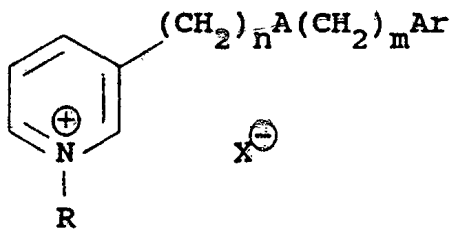
(f) Reduction of a compound of formula (VII) :



(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_{3-8}cycloalkyl;

(g) Reduction of a compound of structure (VIII):



(VIII)

wherein R, A, Ar m and n are as hereinbefore defined and $X^{\ominus}$ is a counter ion;

and optionally thereafter forming a salt.

In process (a) the reaction between a compound of structure (II) and a compound $L(CH_2)_mAr$ can take place under conditions which depend on the nature of the group L. 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), the reaction is effected in the presence of a strong base such as sodium hydride, and in an inert organic solvent such as dimethylformamide. Preferably the aryl group 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 $HA^1(CH_2)_mAr$ 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. methane-sulphonyloxy or p-toluene sulphonyloxy. In this case the reaction may be effected in the presence or absence of solvent and at temperature in the range 0 to 200°C.

The reduction of a compound of structure (IV) 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 X^1Ar 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 RL^2 according to process (e) may be effected in conventional manner, for example in an organic solvent, such as dimethyl formamide. The leaving group L^2 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 L^2 is a halide the reaction is preferably carried out in the presence of a weak base such as potassium carbonate, and when L^2 is sulphonyloxy, a strong base such as sodium hydride or potassium t-butoxide may be employed.

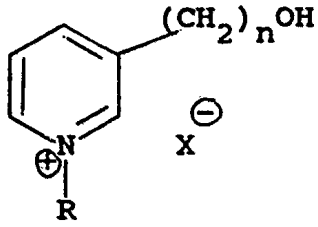
Reduction of a compound of formula (VII) may be effected using standard reducing agents such as lithium aluminium hydride.

Reduction of a compound of formula (VIII) may be effected for example by hydrogenation, using a noble metal catalyst such as platinum, palladium or platinum oxide, suitably in a solvent such as an alcohol eg. ethanol.

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 methyl ethyl ketone, or a C_{1-4}alkanol such as ethanol, in the presence of a base, such as potassium carbonate, or dimethylformamide in the presence of an iodoalkane.

The corresponding compounds of structure (II) in which R is hydrogen are available commercially, known in the literature or can be prepared by standard techniques; for example by reduction of the corresponding 3-hydroxy-alkylpyridine.

Alternatively, the compounds of structure (II) in which A^1 is oxygen can be prepared by reduction of a compound of structure (IX):



(IX)

in which R and n are as described for structure (I) and X^- is a counter ion.

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 tosyloxy group can be prepared from the corresponding alcohol in conventional manner.

Compounds of structure (IV) wherein R^4 is a group $-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ 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 $ClOC(CH_2)_{m-1}Ar$.

Compounds of structure (IV) wherein R^4 is a group $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$ 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 $HN(R^1)(CH_2)_m$ Ar. 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 benzyloxycarbonyl. 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 formula (I) into a different compound of formula (I).

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

A compound of structure (VIII) may be prepared using the general methods described in processes (a) to (e) above.

When compounds of structure (I) are obtained as mixtures 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.

The compounds of the invention have been found to exhibit high calcium influx blocking activity and as such are expected to be of use in therapy 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 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. In addition, the present invention also 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.

In therapeutic use, 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 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, celluloses, 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.

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

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (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 formula (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 100mg per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

DATA

Ca^{2+} 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 Ca^{2+} currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; $MgCl_2$, 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 Ca^{2+} currents.

The external solution for recording Ca^{2+} channel currents contained in mM: $BaCl_2$, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; $MgCl_2$, 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 Ca^{2+} 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^{2+} currents

Peak voltage gated Ca^{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba^{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^{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 μM drug was assessed 3 minutes after drug application.

Compounds of the invention gave percentage inhibition of plateau Ca^{2+} current in the range 30 to 100%.

PHARMACEUTICAL FORMULATIONS

1. Formulation for intravenous infusion

Compound of structure (I)	0.1 - 60 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

2. Formulation for bolus injection

Compound of structure (I)	0.1 - 60 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A toxicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

3. Tablet for oral administration

	mg/tablet
Compound of structure (I)	25
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	255

EXAMPLES

Intermediate Preparations

(i) 3-(Hydroxymethyl)-1-pentylpiperidine

A mixture of 3-(hydroxymethyl)piperidine (20g), 1-bromopentane (26.28g), potassium carbonate (24g) and ethanol (400ml) was heated at reflux for 4 days. The solution was filtered, and the solvent removed under reduced pressure. The residue was treated with acetone, filtered, the solvent removed and the resulting oil was distilled under reduced pressure to give the title compound as an oil. (24.63g, b.p. 103-104°C @ 0.3mmHg.)

(ii) 3-(Hydroxymethyl)-1-propylpiperidine

A mixture of 3-(hydroxymethyl)piperidine (20g), 1-bromopropane (21.4g), potassium carbonate (24g) and ethanol (400ml) was heated at reflux for 1 days. The solution was filtered, and the solvent removed under reduced pressure. The residue was treated with acetone, filtered, the solvent removed and the resulting oil distilled under reduced pressure to give the title compound as an oil. (18.21 g, b.p. 101-103°C @ 0.2mmHg.)

(iii) 1-Cinnamyl-3-(hydroxymethyl)piperidine

A mixture of 3-(hydroxymethyl)piperidine (28g), cinnamyl bromide (47.91g), potassium carbonate (33.6g) and ethanol

(300ml) was heated at reflux for 2 days. The solution was filtered, and the solvent removed under reduced pressure. The residue was distilled under reduced pressure to give the title compound as an oil. (24.63g, b.p. 164-168 °C @ 0.3mmHg.)

Found: C, 77.59; H, 9.18; N, 5.94%
($C_{15}H_{21}NO$) requires: C, 77.88; H, 9.15; N, 6.05%

(iv) 3-Methanesulphonyloxymethyl-1-pentylpiperidine hydrochloride

Methanesulphonyl chloride (5.8ml) in dichloromethane (20ml) was added to a solution of 3-hydroxymethyl-1-pentylpiperidine (10g) in dichloromethane (20ml). The mixture was stirred for 18 hours, treated with hydrogen chloride in ether and recrystallised from ethylacetate to give the title compound (13.2g) m.p. 99-101°C

(v) 3-(3-Hydroxypropyl)-1-pentylpyridinium bromide

A solution of 3-(3-hydroxypropyl)pyridine (20g), 1-bromopentane (22.05g) and acetone (250ml) was refluxed for 72 hours, cooled and poured into diethylether (200ml). The oil which precipitated was collected by decantation then washed by decantation with diethyl ether (5 X 100ml) and dried at 50°C (0.1mmHg) to give the title compound (42g) which was used without further purification.

(vi) 3-(3-Hydroxypropyl)-1-pentylpiperidine

A mixture of 3-(3-hydroxypropyl)-1-pentylpyridinium bromide (42.g), platinum oxide (1.5g) and ethanol (350ml) was shaken under an atmosphere of hydrogen at 50 p.s.i. for 1 hour. The mixture was filtered and the solvent removed. The residue was dissolved in dilute sodium hydroxide (70ml) and extracted with dichloromethane (3 x 75ml). The organic extracts were combined, dried over magnesium sulphate and the solvent was removed to give the title compound as an oil (18.0g).

Example 1

3-(4-Fluorophenoxymethyl)-1-pentylpiperidine oxalate

A solution of 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 4-fluorophenol (1.21g) and triphenylphosphine (2.62g) in tetrahydrofuran (40ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent was removed and the residue was chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with oxalic acid (0.62g). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.21g), m.p. 126 - 128°C.

Found: C, 61.17; H, 7.79; N, 3.78; F 4.71%.
($C_{17}H_{26}FNO.C_2H_2O_4.3H_2O$) requires: C, 60.80; H, 7.60; N, 3.70; F, 5.06%.

Example 2

3-(3,4-Methylenedioxyphenoxymethyl)-1-pentylpiperidine hydrochloride

A solution of 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), sesamol (1.49g) and triphenylphosphine (2.62g) in tetrahydrofuran (50ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.01g), m.p. 183 - 184°C.

Found: C, 63.27; H, 8.22; N, 4.17; Cl, 10.37%.
($C_{18}H_{27}NO_3$.HCl) requires: C, 63.25; H, 8.20; N, 4.10; Cl, 10.40%.

Example 3

3-(3-Phenylphenoxymethyl)-1-pentylpiperidine oxalate

A solution of 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 3-phenylphenol (1.70g) and triphenylphosphine (2.62g) in tetrahydrofuran (40ml) was treated with diethyl azodicarboxylate (1.66g) in tetrahydrofuran (50ml). The resulting solution was stirred at room temperature for 18 hours, the solvent was removed and the residue was

chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil (1.1g) was dissolved in ethyl acetate (50ml) and treated with oxalic acid (1.1equivalents). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (0.8g), m.p. 148 - 149°C.

Found: C, 70.46; H, 7.80; N, 3.24%.
($C_{23}H_{31}NO.C_2H_2O_4$) requires: C, 70.23; H, 7.78; N, 3.28%

Example 4

3-(2-Phenylphenoxymethyl)-1-pentylpiperidine oxalate

A solution of 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 2-phenylphenol (1.70g) and triphenylphosphine (2.62g) in tetrahydrofuran (50ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with oxalic acid (0.9g). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.10g), m.p. 99 - 101°C.

Found: C, 70.00; H, 7.97; N, 3.28%
($C_{23}H_{31}NO.C_2H_2O_4$) requires: C, 70.23; H, 7.78; N, 3.28%

Example 5

3-(4-Benzyloxyphenoxymethyl)-1-pentylpiperidine hydrochloride

A solution of 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 4-benzyloxyphenol (2.0g) and triphenylphosphine (2.62g) in tetrahydrofuran (50ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate and treated with hydrogen chloride in diethyl ether. The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (0.5g), m.p. 149 - 150°C.

Found: C, 71.56; H, 8.71; N, 3.43; Cl, 8.57%
($C_{24}H_{33}NO_2$.HCl) requires: C, 71.35; H, 8.48; N, 3.47; Cl, 8.78%

Example 6

3-(4-Benzylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 5 starting from 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 4-hydroxydiphenylmethane (1.84g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave

a white solid which was recrystallised from methanol/ethyl acetate (0.51g), m.p. 169 - 171°C.

Found: C, 74.38; H, 8.96; N, 3.68; Cl, 8.22%
($C_{24}H_{33}NO.HCl$) requires: C, 74.30; H, 8.83; N, 3.61; Cl, 9.16%

Example 7

3-(3-Trifluoromethylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 5 starting from 3-(hydroxymethyl)-1-pentylpiperidine (1.85g), 3-trifluoromethylphenol (1.62g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.41g), m.p. 165°C.

Found: C, 59.04; H, 7.40; N, 3.91; Cl, 9.67%
($C_{18}H_{26}F_3NO.HCl$) requires: C, 59.0; H, 7.4; N, 3.8; Cl, 9.7%

Example 8

3-(4-Nitrophenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 5 starting from 3-(hydroxymethyl)-1-pentylpiperidine (1.85g), 4-nitrophenol (1.39g), triphenylphosphine (2.62g) and diethyl azodicarboxylate

(1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.13g), m.p. 220°C.

Found: C, 59.22; H, 7.96; N, 8.08; Cl, 10.31%
($C_{17}H_{26}N_2O_3$.HCl) requires: C, 59.55; H, 7.94; N, 8.17; Cl, 10.35%

Example 9

3-(4-Phenylphenoxymethyl)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 5 starting from 3-(hydroxymethyl)-1-pentylpiperidine (2.0g), 4-phenylphenol (1.70g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.60g), m.p. 173.5 - 174°C.

Found: C, 70.17; H, 7.74; N, 3.50%
($C_{23}H_{31}NO.C_2H_2O_4$) requires: C, 70.23; H, 7.78; N, 3.28%

Example 10

3-(2-Benzylphenoxymethyl)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 5 starting from 3-hydroxymethyl-1-pentylpiperidine (2.0g), 2-hydroxydiphenylmethane (1.84g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a

white solid which was recrystallised from methanol/ethyl acetate (0.260g), m.p. 120°C.

Found: C, 70.21; H, 7.99; N, 3.20%
($C_{24}H_{33}NO.C_2H_2O_4.0.25H_2O$) requires: C, 69.94; H, 7.96; N, 3.14%

Example 11

3-(4-Chlorophenoxymethyl)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (2.0g), 4-chlorophenol (1.28g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.82g), m.p. 140°C.

Found: C, 59.27; H, 7.26; N, 3.80; Cl, 8.93%
($C_{17}H_{26}ClNO.C_2H_2O_4$) requires: C, 59.14; H, 7.31; N, 3.63; Cl, 9.19%

Example 12

3-(4-Cyanophenoxymethyl)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (2.0g), 4-cyanophenol (1.19g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was

recrystallised from methanol/ethyl acetate (0.79g), m.p. 104°C.

Found: C, 63.83; H, 7.59; N, 7.47%
($C_{18}H_{26}N_2O.C_2H_2O_4$) requires: C, 63.81; H, 7.50; N, 7.44%

Example 13

3-Phenoxymethyl-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (2.0g), phenol (0.94g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (1.02g), m.p. 144.5°C.

Found: C, 65.15; H, 8.43; N, 4.02%
($C_{17}H_{27}NO.C_2H_2O_4$) requires: C, 64.93; H, 8.32; N, 3.99%

Example 14

3-(4-Fluorobenzyloxymethyl)-1-pentylpiperidine oxalate

A solution of 3-hydroxymethyl-1-pentylpiperidine (3.0g) in dimethylformamide (30 ml) was treated with sodium hydride (0.0162 mole) and then stirred for 0.5 hour when 4-fluorobenzyl chloride (2.35g) was added. The mixture was stirred for 2 days and the solvent removed. Water (100 ml) and dichloromethane (100 ml) were added and the organic layer was separated, washed with saturated sodium chloride (150 ml) and dried over magnesium sulphate. The

solvent was removed and the residue chromatographed on silica gel using methanol/dichloromethane as eluent. The resulting oil was dissolved in ethyl acetate and treated with oxalic acid (1.1 mole equivalent). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.2g), m.p. 126 - 127°C.

Found: C, 62.64; H, 7.97; N, 3.66%.
($C_{18}H_{28}FNO.C_2H_2O_4$) requires: C, 62.64; H, 7.89; N, 3.65%

Example 15

3-(3,4-Methylenedioxyphenoxymethyl)-1-propylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 5 starting from 3-(hydroxymethyl)-1-propyl-piperidine (1.57g), sesamol (1.38g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.30g), m.p. 154°C.

Found: C, 59.14; H, 7.63; N, 4.62; Cl, 10.77%
($C_{16}H_{23}NO_3.HCl.0.5H_2O$) requires: C, 59.47; H, 7.74; N, 4.34; Cl, 10.84%

Example 16

1-Cinnamyl-3-(3,4-dichlorophenoxymethyl)piperidine oxalate

The title compound was prepared in a similar manner to example 1 from 1-cinnamyl-3-hydroxymethylpiperidine (2.00g), 3,4-dichlorophenol (1.41g), triphenylphosphine (2.27g) and diethyl azodicarboxylate (1.51g). Treating the product with oxalic acid in ethyl acetate gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.27g), m.p.206°C.

Found: C, 59.37; H, 5.46; N, 3.16; Cl, 15.16%
($C_{21}H_{23}Cl_2NO.C_2H_2O_4$) requires: C, 59.24; H, 5.40; N, 3.00; Cl, 15.16%

Example 17

1-Cinnamyl-3-(4-fluorophenoxymethyl)piperidine oxalate

The title compound was prepared in a similar manner to example 1 from 1-cinnamyl-3-hydroxymethylpiperidine (2.00g), 4-fluorophenol (0.971g), triphenylphosphine (2.27g) and diethyl azodicarboxylate (1.51g). Treating the product with oxalic acid in ethyl acetate gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.7g), m.p.123°C.

Found: C, 66.51; H, 6.31; N, 3.44%
($C_{21}H_{24}FNO.C_2H_2O_4$) requires: C, 66.49; H, 6.31; N, 3.37%

Example 18

3-(3,4-Dichlorophenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (2.00g), 3,4-dichlorophenol (1.63g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride in ether gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.10g), m.p.188-190°C.

Found: C, 55.92; H, 7.18; N, 3.86; Cl^-, 9.64%
($C_{17}H_{25}Cl_2NO.HCl$) requires: C, 55.67; H, 7.15; N, 3.82; Cl^-, 9.68%

Example 19

3-(4-iso-Propylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (2.00g), 4-iso-propylphenol (1.36g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride in ether gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.18g), m.p.172-174°C.

Found: C, 70.41; H, 9.95; N, 4.34%

($C_{20}H_{33}NO.HCl$) requires: C, 70.66; H, 10.08; N, 4.12%

Example 20

3-(3-iso-Propylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (1.5g), 3-iso-propylphenol (1.1g), triphenylphosphine (2.12g) and diethyl azodicarboxylate (1.41g). Treating the product with hydrogen chloride in ether gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.8g), m.p.138-140°C.

Found: C, 69.89; H, 9.91; N, 4.10; Cl^-, 10.33%
($C_{20}H_{33}NO.HCl.0.25\ H_2O$) requires: C, 69.74; H, 9.95; N, 4.07; Cl^-, 10.29%

Example 21

3-(3-tert-Butylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (1.50g), 3-tert-butylphenol (1.22g), triphenylphosphine (2.12g) and diethyl azodicarboxylate (1.41g). Treating the product with hydrogen chloride in ether gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.035g), m.p.185-187°C.

Found: C, 71.39; H, 10.33; N, 4.09; Cl, 9.92%
($C_{21}H_{35}NO.HCl$) requires: C, 71.26; H, 10.25; N, 3.96; Cl,10.02%

Example 22

3-(4-Fluorobenzylaminomethyl)-pentylpiperidine dihydrochloride

A mixture of 4-fluorobenzylamine (2.49g) and 3-methanesulphonyloxymethyl-1-pentylpiperidine hydrochloride (2g) was heated at 150°C for 2.5 hours. The mixture was dissolved in dichloromethane and the dichloromethane solution washed with dilute sodium hydroxide solution, dried over sodium sulphate and the solvent removed. The residue was chromatographed on silica gel with dichloromethane - methanol as eluent and treated with hydrogen chloride in ether to give a solid. Recrystallisation from ethyl acetate gave the title compound (0.92g), m.p. 207-209°C.

Found: C, 58.12; H, 8.55; N, 7.67; Cl, 19.41%
($C_{18}H_{29}FN_2.2HCl.0.3H_2O$) requires: C, 58.26; H, 8.57; N, 7.54; Cl, 19.09%

Example 23

3-(4-Fluorophenylaminomethyl)-pentylpiperidine dihydrochloride

Substituting 4-fluoroaniline for 4-fluorobenzylamine (9.12g) in example 22 gave the title compound (0.593g) as a white microcrystaline solid. m.p. 196-198°C

Found: C, 56.77; H, 8.12; N, 7.83; Cl, 19.63%
($C_{17}H_{27}FN_2.2HCl.0.5H_2O$) requires: C, 56.66; H, 8.39; N, 7.77; Cl, 19.68%

Example 24

3-(3,4-Dichlorophenylaminomethyl)-pentylpiperidine dihydrochloride

Substituting 3,4-dichloroaniline for 4-fluorobenzylamine (4.04g) in example 22 gave the title compound (0.38g) as a white microcrystaline solid. m.p. 185-187°C

Found: C, 50.99; H, 7.02; N, 6.99%
($C_{17}H_{26}Cl_2N_2.2HCl$) requires: C, 50.76; H, 7.02; N, 6.96%

Example 25

3-(4-tert-Butylphenoxymethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 3-hydroxymethyl-1-pentylpiperidine (1.50g), 4-tert-butylphenol (1.22g), triphenylphosphine (2.12g) and diethyl azodicarboxylate (1.41g). Treating the product with hydrogen chloride in ether gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.205g), m.p.197-199°C.

Found: C, 70.98; H, 10.21; N, 4.00; Cl, 9.82%

($C_{21}H_{35}NO.HCl$) requires: C, 71.26; H, 10.25; N, 3.96; Cl,10.02%

Example 26

3-[3-(4-Fluorophenoxy)propyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 1-pentyl-3-(3-hydroxypropyl)piperidine (2.13g), 4-fluorophenol (1.12g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (1.10g), m.p. 115 - 118°C.

Found: C, 63.53; H, 8.11; N, 3.80%

($C_{19}H_{30}FNO.C_2H_2O_4$) requires: C, 63.48; H, 8.06; N, 3.53%

Example 27

3-[3-(3,4-Dichlorophenoxy)propyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 1-pentyl-3-(3-hydroxypropyl)piperidine (2.13g), 3,4-dichlorophenol (1.63g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.5g), m.p. 127-130°C.

Found: C, 56.35; H, 6.90; N, 3.25%

($C_{19}H_{29}Cl_2NO.C_2H_2O_4$) requires: C, 56.25; H, 6.97; N, 3.12%

Example 28

a) (-)-3-(4-Benzyloxyphenoxymethyl)-1-pentylpiperidine

b) (+)-3-(4-Benzyloxyphenoxymethyl)-1-pentylpiperidine

The product from example 5 (55mg) was partitioned between diethyl ether and dilute sodium bicarbonate solution. The ether phase was separated, dried and the solvent removed. The residue was chromatographed on a Chiralcel OJ h.p.l.c. chromatography column using ethanol/hexane as eluent. The two enantiomers were collected. The (-) enantiomer being eluted first. Yield (8.0mg) rotation (-1.38° @ 22°C in methanol). The second peak gave the (+) enantiomer, yield (7.2mg) rotation (+1.24° @ 22°C in methanol).

Example 29

3-(3,4-Dichlorobenzylaminomethyl)-1-pentylpiperidine dihydrochloride

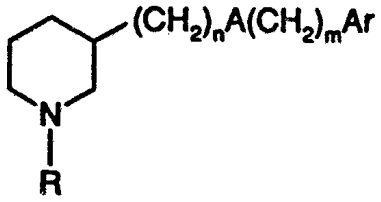
Substituting 3,4-dichlorobenzylamine for 4-fluorobenzylamine (0.587g) in example 22 gave the title compound (0.46g) as a white microcrystaline solid. m.p. 254-256°C

Found: C, 51.55; H, 7.09; N, 6.73; Cl, 16.85%
($C_{18}H_{28}Cl_2N_2.2HCl$) requires: C, 51.94; H, 7.26; N, 6.73; Cl, 17.04%

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of structure (I):



(I)

in which

R is C_{5-8}alkyl(phenyl)$_p$, C_{2-8}alkenyl(phenyl)$_p$, C_{2-8}alkynyl(phenyl)$_p$, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl;

p is 0 to 1;

n is 0 to 6, and m is 0 to 3 provided that m and n are not both zero;

A is a bond, oxygen, sulphur or NR^1, where R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

and Ar is optionally substituted phenyl,

or a salt thereof.

2. A compound according to claim 1 wherein R is C_{5-8}alkyl, or phenyl(C_{2-8})alkenyl.

3. A compound according to claim 2 wherein R is n-pentyl.

4. A compound according to any one of claims 1 to 3 in which A is oxygen.

5. A compound according to any one of claims 1 to 4 wherein n is 0 to 3.

6. A compound according to any one of claims 1 to 5 wherein m is 0 or 1.

7. A compound according to any one of claims 1 to 6 in which Ar is phenyl, optionally substituted by a C_{1-2}alkylene-dioxy group or by 1 to 3 substituents selected from halogen,

C_{1-4}alkoxy, nitro, SC_{1-4}alkyl, NR^2R^2 (in which each R^2 group can be H or C_{1-4}alkyl), OCF_3, C_{1-6}alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy.

8. A compound according to any one of claims 1 to 6 wherein Ar is phenyl optionally substituted by one or two substituents selected from a single halogen, trifluoromethyl, unsubstituted phenyl or unsubstituted phenyl C_{1-4}alkoxy group; or by two chloro atoms.

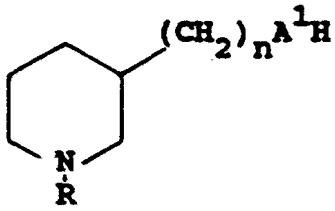
9. A compound according to any one of claims 1 to 6 in which Ar is unsubstituted phenyl or phenyl substituted by fluoro, chloro, dichloro, trifluoromethyl, nitro, cyano, isopropyl, t-butyl, methylenedioxy, phenyl, benzyloxy or benzyl.

10. A compound according to any one of claims 1 to 6 wherein Ar is phenyl substituted by optionally substituted phenyl, optionally substituted phenyl C_{1-4}alkyl or optionally substituted phenyl C_{1-4}alkoxy.

11. A compound according to claim 1 which is:
3-(4-fluorophenoxymethyl)-1-pentylpiperidine,
3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine,
3-(3-trifluoromethylphenoxymethyl)-1-pentylpiperidine,
3-(3-phenylphenoxymethyl)-1-pentylpiperidine,
3-(2-phenylphenoxymethyl)-1-pentylpiperidine,
3-(4-phenylphenoxymethyl)-1-pentylpiperidine,
3-(2-benzylphenoxymethyl)-1-pentylpiperidine,
3-(4-benzylphenoxymethyl)-1-pentylpiperidine,
3-(4-benzyloxyphenoxymethyl)-1-pentylpiperidine,
1-cinnamyl-3-(3,4-dichlorophenoxymethyl)piperidine,
3-(4-iso-propylphenoxymethyl)-1-pentylpiperidine; or
3-(3,4-dichlorophenylaminomethyl)-1-pentylpiperidine; or
a pharmaceutically acceptable salt thereof.

12. A process for preparing a compound of structure (I) as claimed in any one of claims 1 to 11 which comprises:

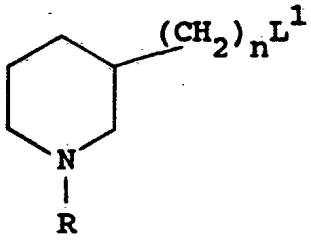
(a) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (II):



(II)

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;

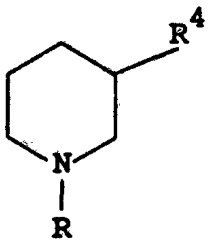
(b) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (III):



(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) :



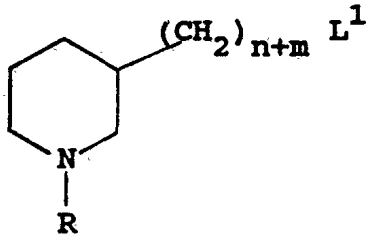
(IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$,

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) :

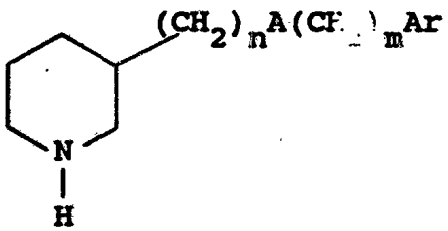


(V)

(wherein R, L^1, m and n are as hereinbefore defined).

with a compound of structure X^1Ar in which Ar is as described for structure (I), and X^1 is an alkali metal;

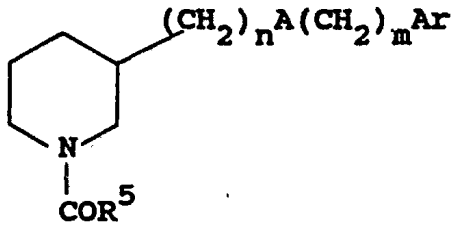
(e) introduction of the group R into a compound of formula (VI) :



(VI)

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

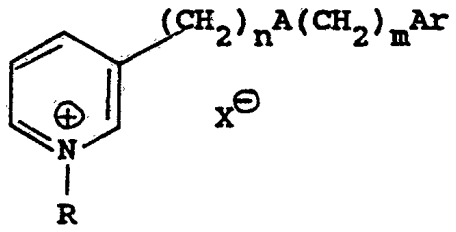
(f) Reduction of a compound of formula (VII) :



(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_{3-8}cycloalkyl;

(g) Reduction of a compound of structure (VIII):



(VIII)

wherein R, A, Ar m and n are as hereinbefore defined and $X^{\ominus}$ is a counter ion;

and optionally thereafter forming a salt.

13. A pharmaceutical composition comprising a compound of structure (I) as claimed in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

14. Use of a compound of structure (I) according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions caused or exacerbated by the accumulation of calcium in the brain cells of mammals.

15. A method of treatment of a condition caused or exacerbated by the accumulation of a 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) according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof.

16. A method according to claim 15 wherein the condition is stroke.

17. A method according to claim 15 or claim 16 wherein the mammal is a human.

18. Compounds of structure (I) or processes for their preparation, substantially as hereinbefore described with reference to Examples 1 to 29.

DATED this 18th day of March, 1994
Smith Kline & French Laboratories Limited
By Its Patent Attorneys
DAVIES COLLISON CAVE

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01339

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 211/18, 405/12, A 61 K 31/445

II FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Chemical Abstracts, vol. 106, no. 7, 16 February 1987, (Columbus, Ohio, US) Balsamo A. et al: "3-((2-Ethoxyphenoxy)methyl) piperidine derivatives. Synthesis and antidepressant activity", page 622, abstract no. 49983u, & J. Med. Chem. 1987, 30(1), 222-5, see reg.no. 104778-59-8 and 104778-62-3	1-11
X	Chemical Abstracts, vol. 89, no. 1, 3 July 1978, (Columbus, Ohio, US), Arya V.P. et al: "Psychoactive agents. Part V. Synthesis and CNS depressant activity of some pyridyl and piperidyl ethers", page 529, abstract 6187a, & Indian J. Chem., Sect. B, 1977, 15B(12), 1125-8, see reg.no. 66496-76-z and 61472-15-9	1-10

* Special categories of cited documents:[10]

"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
7th November 1991	03. 12. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	DE, A1, 3834860 (BASF AG) 19 April 1990, see page 4, lines 19-21 and compound 17	1-6,8-11
X	DE, A1, 2950135 (MERCK PATENT GMBH) 19 June 1981, see pages 8-9 and examples 146-148, 191-193, 247 and 295	1-6,8-11
X	EP, A2, 0071521 (ROUSSEL-UCLAF) 9 February 1983, see pages 6-7 and 11 and examples 3-5	1-2,4-5, 8-11
X	DE, A1, 2621536 (ROUSSEL-UCLAF S.A.) 25 November 1976, see pages 6 and 22-26	1-2,4-6, 8-11
X	EP, A2, 0259621 (A/S FERROSAN) 16 March 1988, see pages 1 and 7 and examples 3-5	1-2,4-5, 8-11
X	EP, A2, 0239309 (MERCK SHARP & DOHME LTD.) 30 September 1987, see pages 1-4 and examples 8-9, 26	1-2,4-5, 8-11
X	EP, A1, 0184257 (JANSSEN PHARMACEUTICA N.V.) 11 June 1986, see page 1 and page 50 lines 13-14	1-2,4-5, 8-11
X	EP, A2, 0307141 (MERCK SHARP & DOHME LTD.) 15 March 1989, see page 3 and example 14	1-2,4-5, 8-11
X	Chemical Abstracts, vol. 56, 1962, (Columbus, Ohio, US), V. Carelli et al: "Substituted N-(pyridylmethyl)anilides with local anesthetic action", columns 5921f-5922e & Farmaco (Pavia) Ed. Sci. 16, 375-86 (1961), see compound IX	1-2,4-5, 8-10

III DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A1, 0149088 (DEGUSSA AKTIENGESELLSCHAFT) 24 July 1985, see page 32, compound 6 --	1-5,8-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01339

SA 50352

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The members are as contained in the European Patent Office EDP file on 27/09/91
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For more details about this annex : see Official Journal of the European patent Office, No. 12/82

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		SU-A-	1428203	30/09/88
		US-A-	4861785	29/08/89
		US-A-	5010198	23/04/91
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		DE-A-	3443968	31/10/85
		GB-A-B-	2152048	31/07/85
		JP-A-	60169476	02/09/85
		SU-A-	1417796	15/08/88
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