



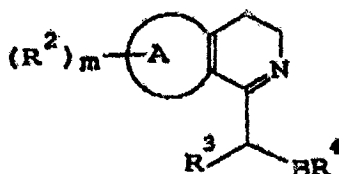
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ANELLATED DIHYDROPYRIDINES AND THEIR USE IN THE PRODUCTION OF PHARMACEUTICAL PREPARATIONS
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INDIAN JOURNAL OF CHEMISTRY VOL 20B NO 10 OCT 1981 P 885-890
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(57) Claim

1. Compound of general formula I



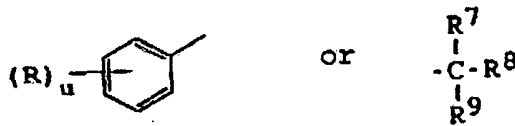
I

wherein

A denotes a benzo, indolo or thieno group;
wherein, if A is benzo, m is 2 or 3 and the substituents R^2 independently of each other denote hydroxy, (C_{1-4}) alkoxy, benzyloxy, halogen (F, Cl, Br, I), (C_{1-4}) alkyl, methanesulphonyloxy or methanesulphonamido, or two adjacent substituents R^2 may together represent -O-CH₂-O- or -O-CH₂-CH₂-O-; and if A is indolo or thieno, m is zero;

B represents the group -O-, -S- or -CHR⁵-, wherein R^5 is hydrogen, (C_{1-4}) alkyl, phenyl or benzyl;

R³ denotes 2- or 3-thienyl, (C₄₋₇)cycloalkyl, (C₄₋₆)-cycloalkyl(C₁₋₅)alkyl or



(wherein

R is (C₁₋₄)alkyl, hydroxy, -N₃, halogen (F, Cl, Br, I), CF₃ or (C₁₋₄)alkoxy,

u is 0, 1, 2 or 3, and

R⁷, R⁸ and R⁹ independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than two of the substituents can simultaneously represent phenyl or benzyl);

R⁴ denotes

- (a) branched or unbranched C₃₋₆-alkenyl which may be substituted by phenyl, or
- (b) branched or unbranched C₃₋₆-alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C₁₋₁₃-alkyl, wherein the alkyl may be substituted by
hydroxy,
(C₁₋₄)alkoxy,
di(C₁₋₄)alkylamino,
furyl,
pyridyl,
pyrrolidinyl, N-methylpyrrolidinyl,
morpholino,
indolyl,
nitrilo,
thienyl,
adamantyl,

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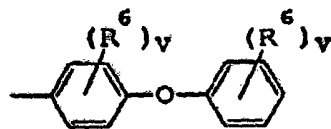
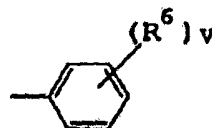
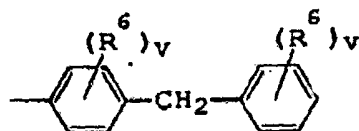
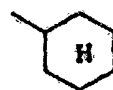
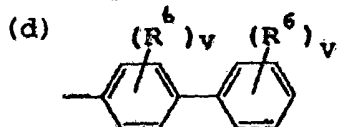
- 3 -

cyclohexyl,
phenoxy,
benzyloxy,
naphthyloxy or
phenyl,

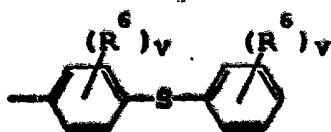
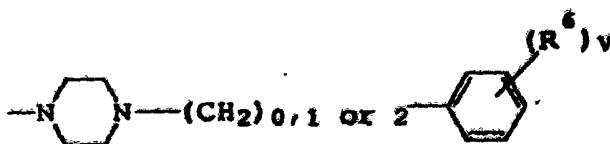
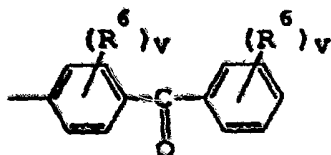
(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by hydroxy, (C₁₋₄)alkoxy, benzyloxy, halogen (F, Cl, Br, I), CF₃, N₃, NO₂, (C₁₋₄)alkyl, adamantyl, -SO₂NH₂, NHCOCH₃, -NHSO₂CH₃ or -C(O)O-R₁₄, [wherein R₁₄ is (C₃₋₇)cycloalkyl or branched or unbranched (C₁₋₆)alkyl, whilst the alkyl may be substituted by phenyl, and this phenyl may be mono- to trisubstituted by halogen (F, Cl, Br, I), CF₃, C₁- or C₂-alkyl, C₁- or C₂-alkoxy]

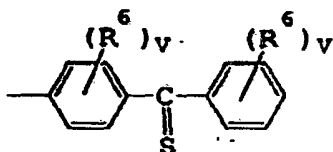
or may be substituted by the bridge -O-CH₂-O-),
or

by 2 unsubstituted phenyl groups;



OR





wherein R^6 is (C_{1-4}) alkyl, hydroxy, $-N_3$, halogen (F, Cl, Br, I), CF_3 , NO_2 or (C_{1-4}) alkoxy and v is 0, 1, 2 or 3,

or the salts thereof with physiologically acceptable acids or complexing agents, with the proviso that when A is benzo and

- (a) if R^2 is methoxy in positions 6 and 7, B is $-CHR^5$ where R^5 is H, and either
- (i) R^4 is CH_2OH , $CH(CH_3)OH$ or $C(CH_3)_2OH$ and R^3 is phenyl, then R cannot be 2-methyl; or
 - (ii) R^4 is phenyl or 4-methoxy, 2,5-dimethoxy or 4-methyl substituted phenyl, then R^3 cannot be unsubstituted phenyl
- or
- (b) if R^2 is hydroxy or C_{1-4} -alkoxy in positions 6 and 7, B is S and R^3 is an unsubstituted or ~~mono~~, di- or tri halogenated or C_{1-4} -alkoxy substituted phenyl, then R^4 cannot be a C_{1-13} -branched or unbranched alkyl, optionally substituted by phenyl, hydroxy or di(C_{1-4})alkylamino or R^4 cannot be a C_{2-6} -alkenyl group.

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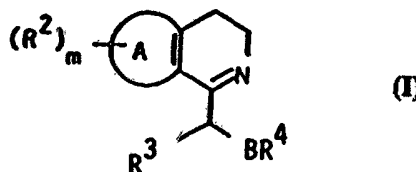
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Veröffentlicht		Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.	

(54) Title: ANELLATED DIHYDROPYRIDINES AND THEIR USE IN THE PRODUCTION OF PHARMACEUTICAL PREPARATIONS

(54a) Bezeichnung: ANELLIERTE DIHYDROPYRIDINE UND DEREN VERWENDUNG FÜR DIE HERSTELLUNG VON PHARMAZEUTISCHEN ZUBEREITUNGEN

(57) Abstract

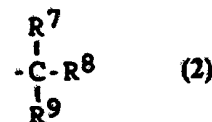
A compound of the general formula (I) in which A is a benzo, indolo or thieno radical, B is the group -O-, -S- or -CHR⁵-, in which R⁵ is hydrogen, (C₁-C₆) alkyl, phenyl or benzyl, R³ is 2- or 3-thienyl, (C₄-C₇) cycloalkyl, (C₄-C₆) cycloalkyl (C₁-C₅) alkyl or (1) or (2) in which R is (C₁-C₄) alkyl, hydroxy, -N₃, halogen (F, Cl, Br, I), CF₃ or (C₁-C₄) alkoxy, u is 0, 1, 2 or 3, and m, R², R⁴, R⁷, R⁸ and R⁹ are as defined in the description, and pharmaceutical preparations containing this compound and their pharmaceutical use.



(I)



(1)



(2)

(57) Zusammenfassung

Verbindung der allgemeinen Formel

(I), worin A einen Benzo, Indolo oder Thienorest bedeutet; B die Gruppe -O-, -S- oder -CHR⁵- bedeutet, worin R⁵ Wasserstoff, (C₁-C₆) Alkyl, Phenyl oder Benzyl ist; R³ 2- oder 3-Thienyl, (C₄-C₇) Cycloalkyl, (C₄-C₆) Cycloalkyl (C₁-C₅) Alkyl oder (1) oder (2) bedeutet, worin R (C₁-C₄) Alkyl, Hydroxy, -N₃, Halogen (F, Cl, Br, I), CF₃ oder (C₁-C₄) Alkoxy ist, u 0, 1, 2 oder 3 ist, und m, R², R⁴, R⁷, R⁸ und R⁹ wie in der Beschreibung definiert sind, und diese Verbindungen enthaltende pharmazeutische Zubereitungen und deren pharmazeutische Verwendung.



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Case 1/978 PCT

Annelated dihydropyridines and the use thereof
for preparing pharmaceutical preparations

The invention relates to new annelated dihydropyridinoacetic acid derivatives, processes for preparing them and pharmaceutical compositions containing these compounds.

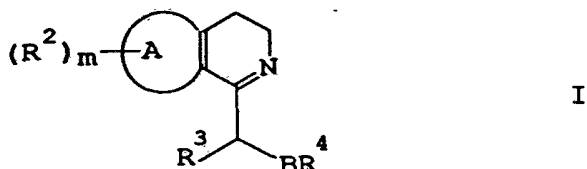
Dihydroisoquinolines are known from EP-A 37 934. The compounds specified therein are cardiotonically active and have the effects of increasing contractility and influencing blood pressure. They have been proposed for improving blood circulation through the tissues and for improving the oxygen supply to the tissues. These possible uses are based on the vascular activity of the compounds. EP-A 251 194 and EP-A 288 048 describe how carbocyclically and heterocyclically annelated dihydropyridines have a cardioprotective or cerebroprotective activity and constitute an entirely new type of Ca-antagonistic compounds. WO 91/11010 describes the use of such compounds for cerebroprotective agents, for treating chronic inflammatory processes and for inhibiting blood clotting and blood platelet aggregation.

The present invention relates to new carbocyclically and heterocyclically annelated dihydropyridines and the pharmaceutical use of these compounds. The new compounds have valuable therapeutically useful properties. They may be used as cardioprotective agents, as cerebroprotective agents (particularly for treating patients who have suffered a stroke or are in danger of suffering a stroke) and as agents for treating chronically inflammatory processes (e.g. bronchial asthma and arthritis). These compounds may also be used as agents with an antiproliferative effect and as agents



for treating ulcerative colitis and Crohn's disease.

The invention relates to compounds of general formula I

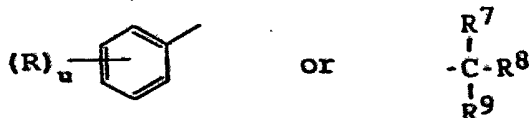


wherein

A denotes a benzo, indolo or thieno group;
 wherein, if A is benzo, m is 2 or 3 (preferably 2,
 whilst the two R²s are in positions 6 and 7) and the
 substituents R² independently of each other denote
 hydroxy, (C₁₋₄)alkoxy, benzoyloxy, halogen (F, Cl, Br, I),
 (C₁₋₄)alkyl, methanesulphonyloxy or methanesulphonamido,
 or two adjacent substituents R² may together represent
 -O-CH₂-O- or -O-CH₂-CH₂-O-; and if A is indolo or thieno,
 m is zero;

B represents the group -O-, -S- or -CHR⁵-, wherein R⁵ is
 hydrogen, (C₁₋₆)alkyl, phenyl or benzyl;

R³ denotes 2- or 3-thienyl, (C₄₋₇)cycloalkyl, (C₄₋₆)-
 cycloalkyl(C₁₋₅)alkyl or



wherein

R is (C₁₋₄)alkyl, hydroxy, -N₃, halogen (F, Cl,
 Br, I), CF₃ or (C₁₋₄)alkoxy,

u is 0, 1, 2 or 3, and



R⁷, R⁸ and R⁹ independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than two of the substituents can simultaneously represent phenyl or benzyl);

R⁴ denotes

- (a) branched or unbranched C₃₋₆-alkenyl which may be substituted by phenyl, or
- (b) branched or unbranched C₃₋₆-alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C₁₋₁₃-alkyl, wherein the alkyl may be substituted by
hydroxy,
(C₁₋₄)alkoxy,
di(C₁₋₄)alkylamino,
furyl,
pyridyl,
pyrrolidinyl, N-methylpyrrolidinyl,
morpholino,
indolyl,
nitrilo,
thienyl,
adamantyl,
cyclohexyl,
phenoxy,
benzyloxy,
naphthyloxy or
phenyl,

(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by hydroxy, (C₁₋₄)alkoxy, benzyloxy, halogen (F, Cl, Br, I), CF₃, N₃, NO₂, (C₁₋₄)alkyl, adamantyl, -SO₂NH₂, NHCOCH₃, -NHSO₂CH₃ or -C(O)O-R₁₄, [wherein R₁₄ is (C₃₋₇)cycloalkyl or branched or unbranched (C₁₋₆)alkyl, whilst the alkyl may be substituted by phenyl, and this phenyl may be



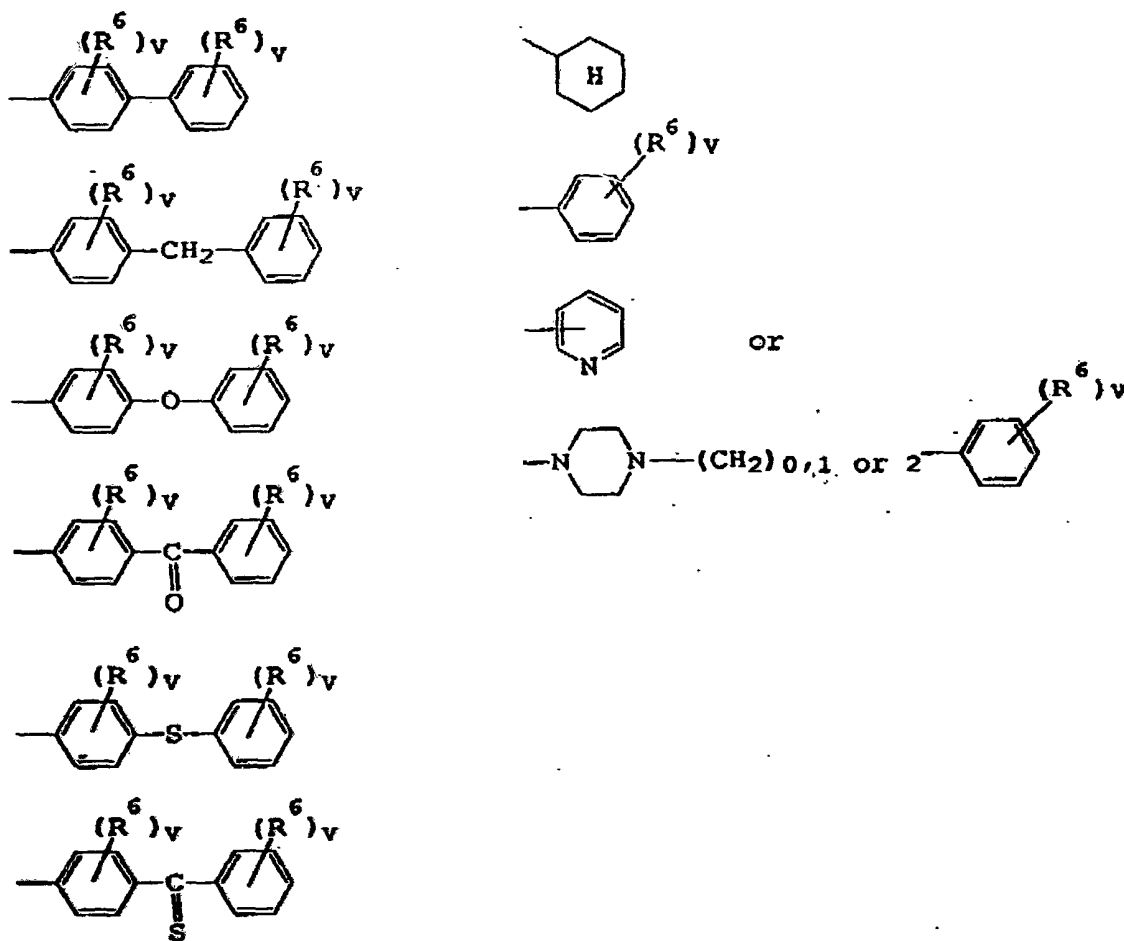
mono- to trisubstituted by halogen (F, Cl, Br, I), CF_3 , C_1 - or C_2 -alkyl, C_1 - or C_2 -alkoxy]

or may be substituted by the bridge $-\text{O}-\text{CH}_2-\text{O}-$),

or

by 2 unsubstituted phenyl groups;

(d)



wherein R^6 is (C_{1-4}) alkyl, hydroxy, $-\text{N}_3$, halogen (F, Cl, Br, I),

CF_3 , NO_2 or (C_{1-4}) alkoxy and

v is 0, 1, 2 or 3,

or the salts thereof with physiologically acceptable acids or complexing agents,



- 5a -

with the proviso that when A is benzo and

(a) if R^2 is methoxy in positions 6 and 7, B is $-CHR^5$ where R^5 is H, and either

(i) R^4 is CH_2OH , $CH(CH_3)OH$ or $C(CH_3)_2OH$ and R^3 is phenyl, then R cannot be 2-methyl; or

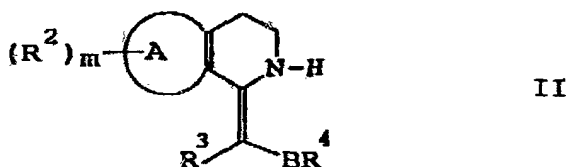
(ii) R^4 is phenyl or 4-methoxy, 2,5-dimethoxy or 4-methyl substituted phenyl, then R^3 cannot be unsubstituted phenyl

or

(b) if R^2 is hydroxy or C_{1-4} -alkoxy in positions 6 and 7, B is S and R^3 is an unsubstituted or mono-, di- or tri halogenated or C_{1-4} -alkoxy substituted phenyl, then R^4 cannot be a C_{1-13} -branched or unbranched alkyl, optionally substituted by phenyl, hydroxy or $di(C_{1-4})$ alkylamino or R^4 cannot be a C_{2-6} -alkenyl group.

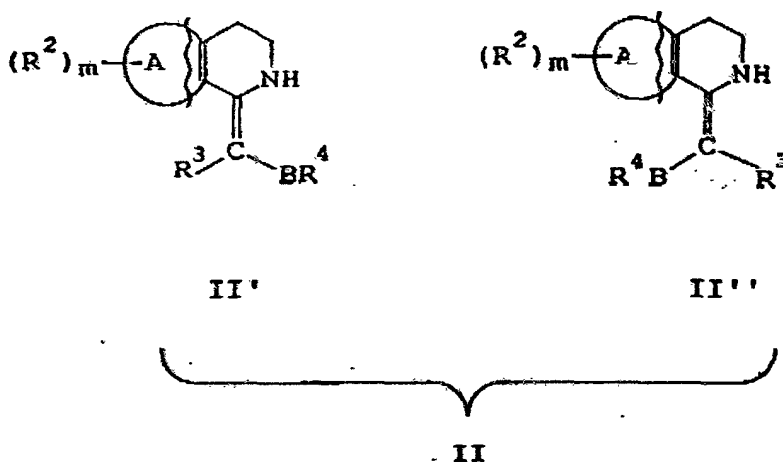


Compounds of formula I form tautomers of formula II



The tautomers can be separated by known methods e.g. by column chromatography or selective reduction (NaBH₄ or catalytic reduction).

The compounds of formula II may occur in cis- and/or trans-form:



If the structure of a compound is not expressly stated, the mention of formula I should be taken as including structure II as well.

In the definitions used in the text the radicals and groups may be identical or different, i.e. if one of the above-mentioned substituents occurs several times in a particular molecule, the meaning can be selected freely within the scope of the definitions provided.

The term alkyl means C₁₋₄-alkyl and C₁₋₄-alkyl radicals which may be substituted or, as alkyl radicals, are part



of a functional group such as alkoxy or alkylthio. The alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl and tert.-butyl radicals as well as the various isomeric pentyl and hexyl radicals, such as e.g. isopentyl, neopentyl, n-pentyl and n-hexyl radical.

Halogens are fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine and to a lesser extent iodine.

C₃₋₇-cycloalkyl denotes cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

C₃₋₆-alkynes are the isomeric hexynes, pentynes, butynes and propynes, propargyl being preferred.

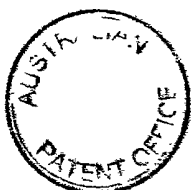
C₃₋₆-alkenes are the isomeric hexenes, pentenes, butenes and propenes, allyl being preferred.

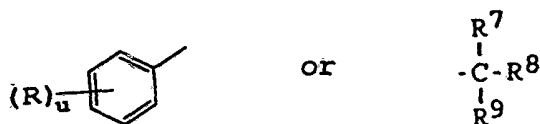
A preferred aspect of the invention consists of compounds of general formula I wherein

A denotes benzo; m is 2 (whilst the two R²s are preferably in positions 6 and 7) and the substituents R² independently of one another represent hydroxy, (C₁₋₄)alkoxy, benzyloxy, halogen (F, Cl, Br, I) or (C₁₋₄)alkyl, or two adjacent substituents R² may together represent -O-CH₂-O;

B denotes the group -O-, -S- or -CHR⁵-, wherein R⁵ is hydrogen, methyl, phenyl or benzyl;

R³ is 2- or 3-thienyl, (C₄₋₇)cycloalkyl, or





wherein

R is (C₁₋₄)alkyl, halogen, (F, Cl, Br, I), CF₃ or (C₁₋₄)alkoxy,

u is 0, 1, 2 or 3, and

R⁷, R⁸ and R⁹ independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than 2 of the substituents may simultaneously represent phenyl or benzyl;

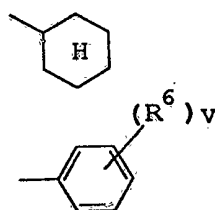
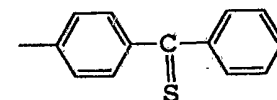
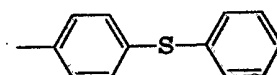
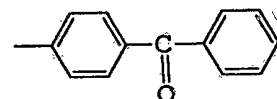
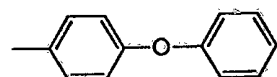
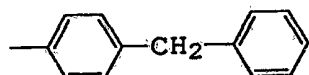
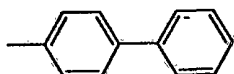
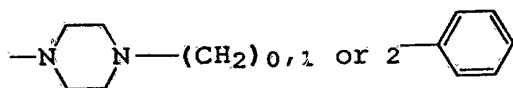
R⁴ denotes

- (a) branched or unbranched C₃₋₆-alkenyl which may be substituted by phenyl or
- (b) branched or unbranched C₃₋₆-alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C₁₋₁₃-alkyl, wherein the alkyl may be substituted by
 - thienyl,
 - adamantyl,
 - cyclohexyl,
 - phenoxy,
 - benzyloxy or
 - phenyl

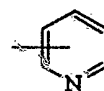
(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by (C₁₋₄)alkoxy, halogen (F, Cl, Br, I), CF₃, N₃, NO₂, (C₁₋₄)alkyl, or -C(O)-O-(CH₂)₁₋₃-CH₃ or by the bridge -O-CH₂-O-), or by 2 unsubstituted phenyl groups;



(d)



or



wherein R^6 denotes (C_{1-4}) alkyl, hydroxy, $-N_3$, halogen, (F, Cl, Br, I), CF_3 , NO_2 or (C_{1-4}) alkoxy and v is 0, 1, 2 or 3,

or the salts thereof with physiologically acceptable acids or complexing agents.

Of the compounds I wherein A is benzo, the preferred compounds are those wherein m is 2 and the two R^2 's independently of each other represent methoxy, hydroxy, benzyloxy, methyl or chlorine or together represent $-OCH_2O-$, whilst the two R^2 's are in positions 6 and 7,



particularly those compounds wherein R^2 is methoxy, hydroxy, benzyloxy or methyl, and especially those wherein both R^2 's are the same and represent hydroxy or methoxy.

Particular mention should be made of compounds I wherein R^4 has one of the following meanings:

- a) vinyl, preferably substituted by phenyl;
- b) unsubstituted C_{4-9} -alkyl which, if it is branched, contains methyl as a side chain or chains;
- c) substituted C_{1-4} -alkyl (preferably C_{2-3} -alkyl) which, if it is branched, contains a methyl group as side chain,

whilst the alkyl may be substituted by one or 2 phenyl groups,

phenoxy

benzyloxy

thienyl (preferably 3-thienyl)

cyclohexyl or

1- or 2-adamantyl,

whilst if the alkyl is substituted by a phenyl group or by phenoxy or benzyloxy, the appropriate phenyl group may be substituted by

methyl,

methoxy (1 to 3 methoxy groups),

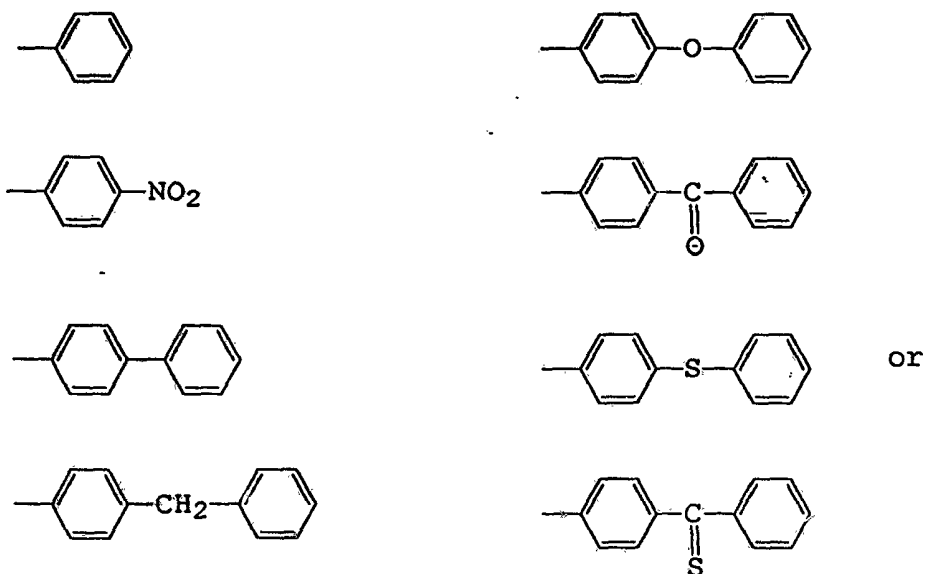
Cl, Br, CF_3 ,

NO_2 or

$C(O)O(CH_2)_3CH_3$.

d)

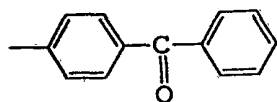
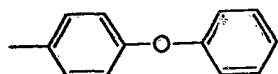
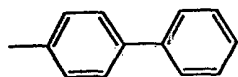
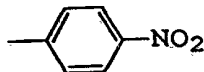
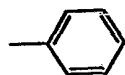




particularly those wherein R^4 has one of the following meanings:

- a) R^4 denotes (C_{4-7}) alkyl;
- b) substituted alkyl having 1 to 4 (preferably 2 or 3) carbon atoms which, if it is branched, contains a methyl group as side chain, whilst the alkyl may be substituted by one or 2 phenyl groups, phenoxy, benzyloxy, thienyl (preferably 3-thienyl) or cyclohexyl, whilst if the alkyl is substituted by phenoxy or benzyloxy or preferably a phenyl group the relevant phenyl group may be substituted by methoxy (1 to 3 methoxy groups), Cl, Br, CF_3 , NO_2 or $C(O)O(CH_2)_3CH_3$;
- c)





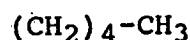
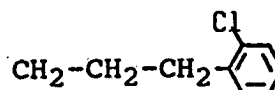
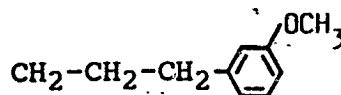
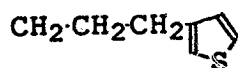
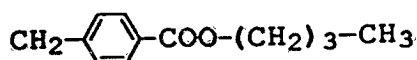
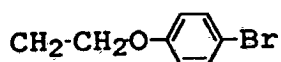
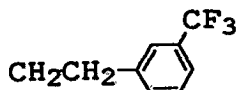
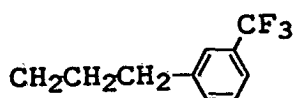
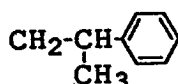
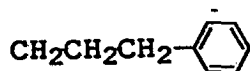
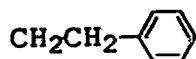
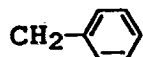
Particular mention should also be made of compounds (I) wherein B is O, S, CH₂ or C(CH₃)H, preferably those wherein B is O.

Special mention should also be made of compounds wherein R³ represents phenyl (which may be mono-, di- or trisubstituted by methoxy, halogen or CF₃), cyclohexyl, thienyl or tert.butyl, especially those compounds wherein R³ is phenyl, methoxyphenyl, Cl-benzyl, di-Cl-benzyl or cyclohexyl. Also worth mentioning are those compounds wherein R³ is thienyl (preferably 3-thienyl) or tert.butyl.

Emphasis should also be placed on those compounds wherein A is benzo which is substituted in positions 6 and 7, wherein the two substituents R² independently of each other represent methoxy, benzyloxy, hydroxy, methyl or chlorine, particularly wherein R² in position 6 represents methoxy, hydroxy or benzyloxy and R² in position 7 represents methoxy or methyl, preferably wherein A is the 6,7-dimethoxybenzo group.



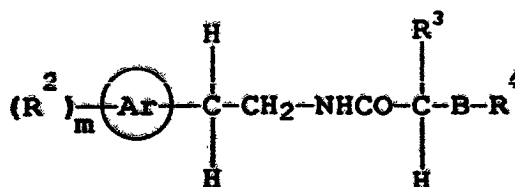
Special mention should be made of compounds wherein R⁴ has one of the following meanings:



particularly those wherein B is O or CH₂ and A is defined as hereinbefore and is preferably 6,7-dimethoxybenzo. Within this group of compounds, those wherein R³ is tert.butyl, thienyl or preferably phenyl or cyclohexyl are preferred.

The compounds of formula I may be prepared by methods known *per se*, preferably analogously to the method described in German Patent Application P 37 18 570.5, EP 358 957, EP 37 934, EP 251 794 and EP 288 048.

In the presence of a condensing agent, a compound of general formula IV



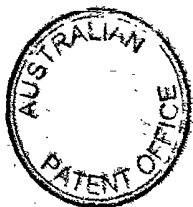
wherein R^2 , R^3 , R^4 and m are as hereinbefore defined and Ar represents phenyl, indolyl or 2- or 3-thienyl, may be cyclised to form the corresponding compounds.

Suitable condensing agents for this process are strong Lewis acids such as phosphorusoxychloride, phosphoruspentachloride, phosphorustrichloride, phosphoruspentoxide, titanium tetrachloride, boron trifluoride, tin tetrachloride, as well as inorganic acids such as polyphosphoric acid, sulphuric acid, fluorosulphonic acid and hydrofluoric acid, or mixtures of condensing agents such as a mixture of phosphorusoxychloride and phosphoruspentachloride, or a mixture of phosphoruspentoxide and (C_{1-4}) alkylsulphonic acid, e.g. with a P_2O_5 - content of about 10% by weight.

The cyclisation may be carried out in the presence or absence of a solvent. Any inert solvents are suitable provided that they have sufficient solubility for the reactants and a high enough boiling point, e.g. benzene, alkylbenzenes (e.g. toluene, xylene), chlorobenzenes, chloroform, acetonitrile and decaline. According to a preferred embodiment of the process the condensing agent used is phosphorusoxychloride in admixture with acetonitrile or a mixture of (C_{1-4}) alkylsulphonic acid and phosphoruspentoxide, without the addition of solvents.

Preferably, the cyclisation is carried out with phosphorusoxychloride/acetonitrile or in difficult cases with a mixture of phosphoruspentoxide and C_{1-4} -alkylsulphonic acid (preferably methanesulphonic acid). The reaction can be carried out in a wide temperature range, preferably with heating to $50^\circ C$ up to the boiling point of the reaction mixture.

The length of reaction required will range from 2 to 15 hours depending on the starting compound IV used.



Starting compounds:

The ethers of general formula IV may be obtained in accordance with the conventional methods described in the literature. It is preferred to use the "mesylate and bromide method", particularly the mesylate method. With the preferred process it should be noted that the usual base must not be added during the reaction, so as to avoid the formation of undesirable non-ethereal by-products.

The thioethers of general formula IV may be obtained in accordance with the conventional methods described in the literature. The "mesylate method" is preferred: converting a mercaptan with the mesylate of N-(2-(3,4-dimethoxyphenyl)ethyl)-mandelic acid amide in solvent-free and base-free medium at 100°C.

The alkanes of general formula IV are obtained by reacting the 2-phenylalkylcarboxylic acids with 2-(3,4-dimethoxyphenylethylamine to obtain the open-ringed amides (preferably using the carbonyldiimidazole method).

The compounds of formula I are bases and can be converted in the usual way with inorganic or organic acids and salts and complex-forming agents into any desired physiologically acceptable adducts (salts).

Acids suitable for salt formation include for example hydrochloric, hydrobromic, hydriodic, hydrofluoric, sulphuric, phosphoric, nitric, acetic, propionic, butyric, caproic, valeric, oxalic, malonic, succinic, maleic, fumaric, lactic, tartaric, citric, malic, benzoic, p-hydroxybenzoic, phthalic, cinnamic, salicylic, ascorbic, methanesulphonic acid and the like.

The compounds may be administered by oral, parenteral or



topical route. The desired therapeutic dose depends on the indication and formulation used and can be determined experimentally. Suitable forms include, for example, tablets, capsules, suppositories, solutions, syrups, emulsions, aerosols or dispersible powders. Tablets may be produced, for example, by mixing the active substance or substances with known excipients, e.g. inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for obtaining delayed release, such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinylacetate. The tablets may also consist of several layers.

Coated tablets may be produced analogously by coating cores made in the same way as the tablets with substances conventionally used for tablet coatings, e.g. collidone or shellack, gum arabic, talc, titanium dioxide or sugar. In order to obtain delayed release or avoid incompatibilities, the core may also consist of several layers. Similarly, the tablet coating may consist of several layers to achieve delayed release, whilst the excipients mentioned for the tablets may be used.

Syrups containing the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar as well as a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethylcellulose, wetting agents, e.g. condensation products of fatty alcohols with ethylene oxide or preservatives such as p-hydroxybenzoates.



Injectable solutions are produced in the usual way, e.g. by adding preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylene diamine tetraacetic acid, and are then transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may be prepared for example by mixing the active substances with inert carriers such as lactose or sorbitol and encapsulating them in gelatine capsules.

Suitable suppositories may be produced for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or derivatives thereof.

The compounds may be administered both enterally and parenterally. A proposed dose for oral use is 0.1 to 500 mg of active substance per dose and from 0.05 to 150 mg per dose for intravenous administration. The desired therapeutic dose depends on the indication and formulation used and can be determined experimentally.

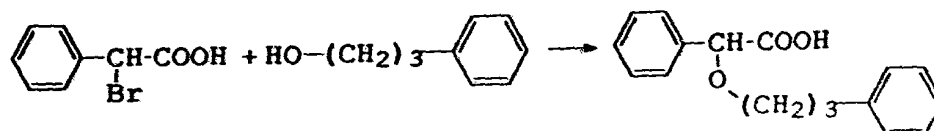
The pharmaceutical compositions are suitable for oral or parenteral and possibly topical application. The chief formulations used are plain or coated tablets, ampoules and syrups. The single dose using these formulations is between 1.0 and 200 mg, preferably 20 to 50 mg per 75 kg of body weight. Generally, 1 to 3 single doses are required per day, depending on the gravity of the case.

The following Examples serve to illustrate the invention:



Example 1:

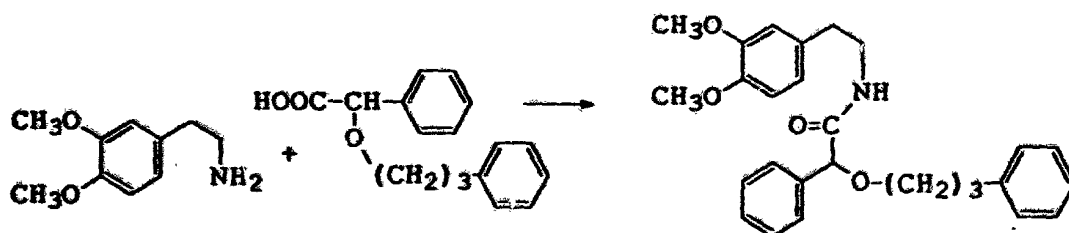
O-(3-Phenylpropyl)-phenylacetic acid



7.8 g (0.2 mol) of potassium are dissolved in 136 g (1 Mol) of 3-phenyl-1-propanol by heating to 100° and after cooling to ambient temperature a solution of 21.5 g (0.1 Mol) of α-bromophenylacetic acid in 20 ml of 3-phenyl-1-propanol is added dropwise.

After 2½ hours heating to 110°C, 500 ml of diethylether are added at ambient temperature and the solution is extracted 3 times with 100 ml of water. The combined aqueous extracts are acidified with 30 ml of 4N HCl whilst cooling with ice; the oil precipitated is taken up in ether, washed with water and dried over MgSO₄. After the solvent has been distilled off, 23.4 g (86.6% of theory) of the desired carboxylic acid ether are left as an oily residue which can be used for the following reaction without any further purification.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-O-(3-phenylpropyl)-phenylacetic acid amide



30.3 g (112 mmol) of O-(3-phenylpropyl)-phenylacetic

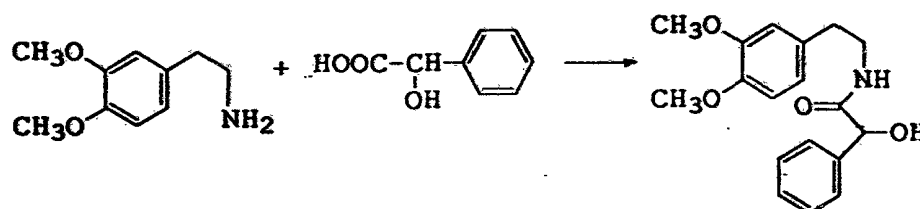


acid are dissolved in 250 ml of absolute tetrahydrofuran, combined with 18.14 g (112 mmol) of carbonyldiimidazole and stirred for 2 hours at ambient temperature. Whilst cooling with ice, 20.27 g (112 mmol) of 2-(3,4-dimethoxyphenyl)-ethylamine in 50 ml of absolute tetrahydrofuran are added dropwise to this reaction solution and the resulting mixture is stirred for a further 15 hours at ambient temperature. Then the solvent is distilled off in vacuo, the residue is dissolved in 250 ml of ethyl acetate, washed 3 times with 100 ml of 1N HCl, twice with 75 ml of saturated NaHCO₃ solution and twice with 50 ml of saturated NaCl solution. The ethyl acetate solution is dried over MgSO₄ and evaporated down in vacuo.

The oily reaction product 44.28 g (91.3% of theory) can be processed without any further purification.

Alternative embodiment:

N-[2-(3,4-Dimethoxyphenyl)ethyl]-mandelic acid amide



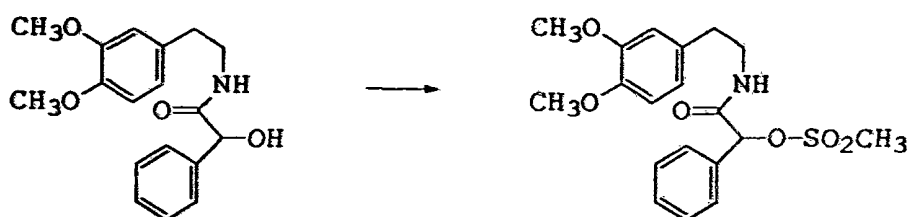
33.2 g (0.2 Mol) of methyl mandelate and 72 g (0.4 Mol) of 2-(3,4-dimethoxyphenyl)-ethylamine are heated to 160-165°C under an N₂ atmosphere with stirring, for 5 hours using a descending condenser (to remove the methanol released). The cooled residue is dissolved in 300 ml of ethyl acetate, washed twice with 100 ml of 2N HCl, once with saturated NaHCO₃ solution and saturated NaCl solution, dried over MgSO₄ and distilled off from the solvent.



The crystalline residue is dissolved in 200 ml of ethyl acetate and the reaction product is precipitated with 160 ml of n-hexane.

Yield: 51.2 g (80.95% of theory), m.p.: 89-91°.

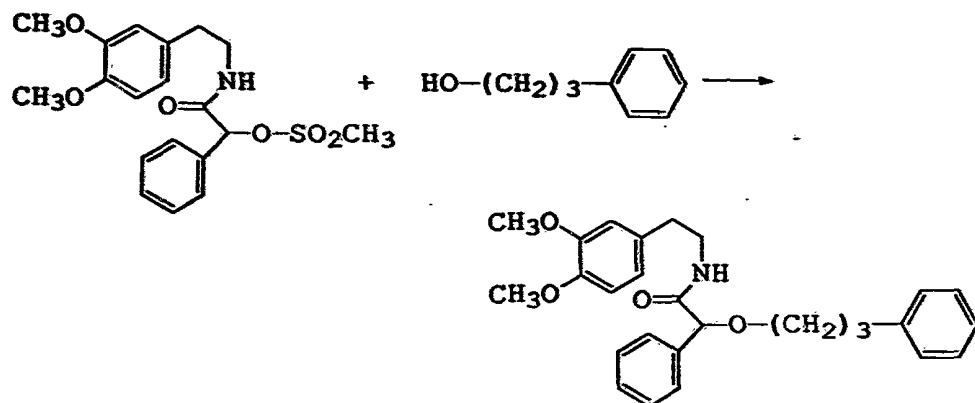
N-[2-(3,4-Dimethoxyphenyl)ethyl]-O-mesylmandelic acid
amide



To a solution of 19.6 g (62.2 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-mandelic acid amide in 60 ml of absolute pyridine are added dropwise, with stirring and cooling, 7.8 (69 mmol) of methanesulphonic acid chloride, the reaction solution being maintained at -15 to -5°. After 5 hours' stirring at ambient temperature, 200 g of ice are added and the mixture is acidified with 180 ml of 4N HCl, whilst cooling with ice. The acid solution is extracted twice with 400 ml of ethyl acetate and the organic phase is washed twice with 50 ml of H₂O and twice with saturated NaCl solution, dried over MgSO₄ and the solvent is distilled off in vacuo. The crystalline residue is re-precipitated with 100 ml of ethyl acetate and 50 ml of n-heptane and 16.3 g (66.6% of theory) of the reaction product are obtained, m.p. 89-90°C.



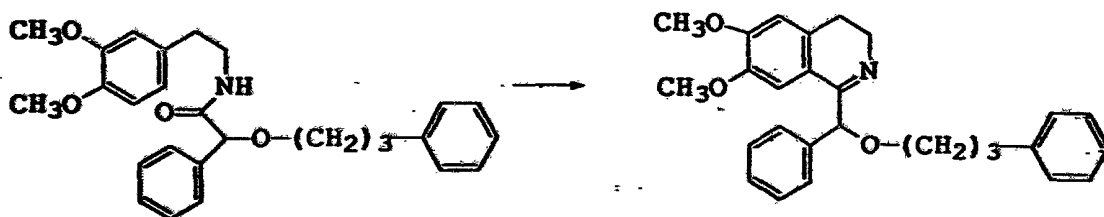
N-[2-(3,4-Dimethoxyphenyl)ethyl]-O-(3-phenylpropyl)-phenylacetic acid amide



1.95 g (5 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-O-mesylmandelic acid amide are dissolved in 3.4 g (25 mmol) of 3-phenyl-1-propanol and heated to 100°C for 30 minutes with stirring. After cooling to ambient temperature the reaction product is dissolved in 100 ml of ethyl acetate, washed twice with saturated NaHCO₃ solution and once with NaCl solution, dried over MgSO₄ and the solvent is distilled off in vacuo.

The oily reaction product is purified by chromatography over a silica gel column using ethyl acetate/n-heptane 1:1 and 1.54 g (71.5% of theory) of the desired ether are obtained in the form of an oil.

(R,S)-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)-2-phenyl-2-(3-phenylpropyl)-ether



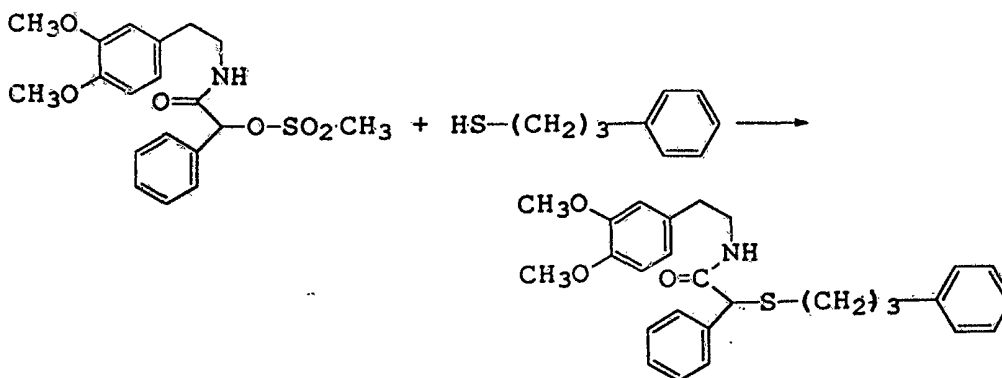
A solution of 44.28 g (102.3 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-O-(3-phenylpropyl)phenylacetic



acid amide and 46.93 g (307 mmol) of phosphorus-oxychloride in 300 ml of acetonitrile is refluxed for 1 hour in an N₂ atmosphere. After cooling to room temperature the reaction mixture is dissolved in 1 litre of ethyl acetate, washed twice with 150 ml of ice water, 3 times with 150 ml of saturated NaHCO₃ solution and twice with 100 ml of saturated NaCl solution, dried over MgSO₄ and the solvent is distilled off in vacuo. The residue is dissolved in 110 ml of acetone and acidified with ethereal HCl, with stirring and cooling with ice whereupon 17.6 g (38.68% of theory) of the desired reaction product crystallise out in the form of the hydrochloride; m.p.: 176-178°C.

Example 2:

N-[2-(3,4-Dimethoxyphenyl)ethyl]-S-(3-phenylpropyl)-phenylacetic acid amide

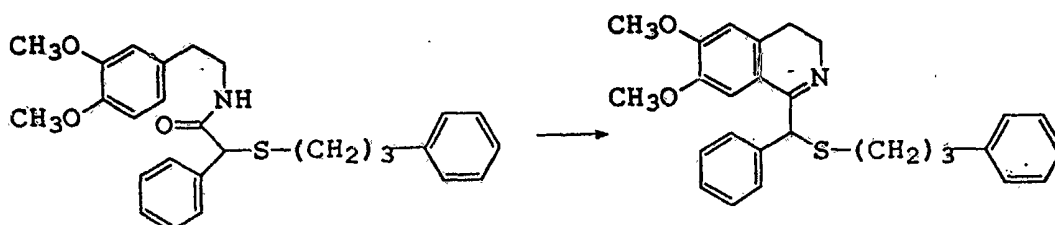


3.93 g (10 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-O-mesylmandelic acid amide and 4.56 g (30 mmol) of 3-phenyl-n-propylmercaptan are heated to 100°C for 30 minutes, with stirring. The cooled reaction product is dissolved in 100 ml of ethyl acetate, washed twice with 20 ml of saturated NaHCO₃ solution and once with saturated NaCl solution. After drying over MgSO₄ the solvent is distilled off in vacuo. The oily residue is purified by chromatography over a silica gel column using ethyl acetate/n-heptane 1:1 as eluant.

Yield: 2.55 g (56.8% of theory)



(R,S)-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)-2-phenyl-2-(3-phenylpropyl)-thioether

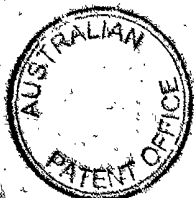
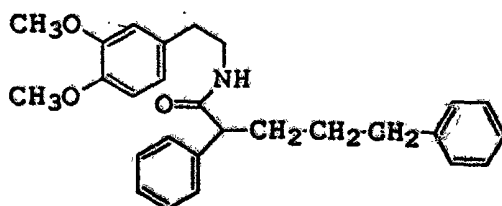


2.55 g (5.67 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-S-(3-phenylpropyl)phenylacetamide and 2.6 g (17 mmol) of phosphorus oxychloride are heated to 100° in 35 ml of acetonitrile for 1.5 hours under an N₂ atmosphere, with stirring. The reaction solution is combined with 125 ml of ethyl acetate at ambient temperature, washed 3 times with 25 ml of ice water, 3 times with 25 ml of saturated NaHCO₃ solution and once with saturated NaCl solution and dried over MgSO₄.

After the organic phase has been distilled off in vacuo the oily residue is purified over a silica gel column with ethyl acetate as eluant and 1.18 g of the desired reaction product are obtained in amorphous form.

Example 3:

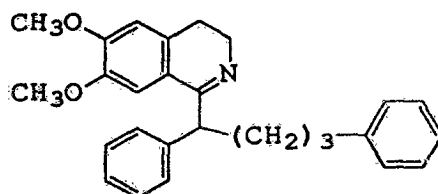
N-[2-(3,4-Dimethoxyphenyl)ethyl]-2,5-diphenylpentane-carboxylic acid amide



A solution of 3.0 g (11.8 mmol) of 2,5-diphenylpentane

carboxylic acid and 1.91 g (11.8 mmol) of carbonyldiimidazole is stirred at ambient temperature for one hour and then mixed with a solution of 2.13 g (11.8 mmol) of 2-(3,4-dimethylethoxyphenyl)ethylamine in 20 ml of tetrahydrofuran, stirred overnight at ambient temperature and, after the solvent has been distilled off, the residue is dissolved in ethyl acetate. The organic phase is washed twice with 15 ml of 1N HCl, twice with 20 ml of saturated NaHCO₃ solution and then with a saturated NaCl solution. After drying over MgSO₄ and distilling off the solvent, 4.9 g (100% of theory) of the desired end product are left, and this end product is further processed in the form of an oil without any more purification.

(R,S)-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)-1,4-diphenylbutane



A solution of 4.9 g (11.75 mmol) of N-[2-(3,4-dimethoxyphenyl)ethyl]-2,5-diphenylpentanecarboxylic acid amide and 5.39 g (35.2 mmol) of phosphorus oxychloride in 40 ml of absolute acetonitrile is refluxed for 1.5 hours under an N₂ atmosphere, with stirring. The reaction solution is diluted with 150 ml of ethyl acetate and washed successively twice with 40 ml of ice water, three times with 30 ml of saturated NaHCO₃ solution and with saturated NaCl solution and the organic phase is dried over MgSO₄. After the solvent has been distilled off in vacuo, the oily residue is dissolved in acetone and acidified with ethereal hydrochloric acid.



- 25 -

The desired reaction product is obtained as an amorphous solid substance in the form of the hydrochloride salt.

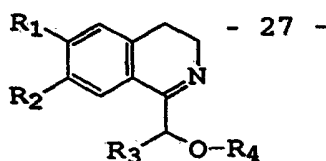
Yield: 2.6 g (50.8% of theory)



The following Tables list examples of compounds according to the invention. These compounds may be prepared analogously to the processes described hereinbefore.

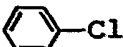
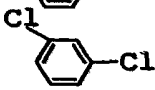
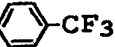
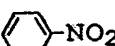
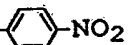
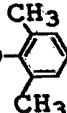
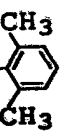


Table 1:



No.	R ₁	R ₂	R ₃	R ₄	Mp. °C	Salt form
1	OCH ₃	OCH ₃	C ₆ H ₅		amorph	OX
2	OCH ₃	OCH ₃	C ₆ H ₅		142-145	OX
3	OCH ₃	OCH ₃	C ₆ H ₅		165-168	CL
4	OCH ₃	OCH ₃	C ₆ H ₅		176-178	CL
5	OCH ₃	OCH ₃	C ₆ H ₅		57-60	OX
6	OCH ₃	OCH ₃	C ₆ H ₅		112-114	OX
7	OCH ₃	OCH ₃	C ₆ H ₅			
8	OCH ₃	OCH ₃	C ₆ H ₅			
9	OCH ₃	OCH ₃	C ₆ H ₅			
10	OCH ₃	OCH ₃	C ₆ H ₅		123-126	CL
11	OCH ₃	OCH ₃	C ₆ H ₅		70-80	OX
12	OCH ₃	OCH ₃	C ₆ H ₅		amorph	CL
13	OCH ₃	OCH ₃	C ₆ H ₅		amorph	OX
14	OCH ₃	OCH ₃			amorph	OX
15	OCH ₃	OCH ₃			amorph	OX
16	OCH ₃	OCH ₃	C ₆ H ₅			
17	OCH ₃	OCH ₃	C ₆ H ₅			
18	OCH ₃	OCH ₃	C ₆ H ₅		141-143	OX
19	OCH ₃	OCH ₃	C ₆ H ₅		143-145	MA
20	OCH ₃	OCH ₃	C ₆ H ₅		75-80	OX

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No.	R ₁	R ₂	R ₃	R ₄	Mp. °C	Salt form
21	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ - 	139-142	OX
22	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ - 	159-163	OX
23	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ - 		
24	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ - 	108-110	CL
25	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ - 		
26	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ - 	amorph	OX
27	OCH ₃	OCH ₃	C ₆ H ₅		138-140	OX
28	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ - 		
29	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ - 	157-159	MA
30	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ - 		
31	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ - 	180-182	CL
32	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O- 	amorph	CL
33	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O-CH ₂ - 	amorph	OX
34	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O- 		
35	OCH ₃	OCH ₃	C ₆ H ₅	CH-CH ₂ -O-  CH ₃		
36	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O- 	120-122	MA
37	OCH ₃	OCH ₃	C ₆ H ₅		80-100 (Decomposition)	OX
38	OCH ₃	OCH ₃	C ₆ H ₅	 -CH ₂ - 		
39	OCH ₃	OCH ₃	C ₆ H ₅	 -O- 	50-75 (Decomposition)	OX
40	OCH ₃	OCH ₃	C ₆ H ₅	 -S- 		
41	OCH ₃	OCH ₃	C ₆ H ₅	 -C(=O)- 	60-80 (Decomposition)	OX



No.	R ₁	R ₂	R ₃	R ₄	Mp. °C	Salt form
42	OCH ₃	OCH ₃	C ₆ H ₅			
43	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ --C(=O)-O-CH ₂ -CH ₂ -CH ₃	amorph	OX
44	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -	amorph	OX
45	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	60-70 (Decomposition)	OX
46	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -	124-127	OX
47	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	145-147	OX
48	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ -	138-140	OX
50	OH	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	65-80 (Decomposition)	OX
51	OCH ₂ -	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	amorph	OX
52	OH	CH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	75-120 (Decomposition)	OX
53	OCH ₂ -	CH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	amorph	OX
54	OH	Cl	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
55	OCH ₂ -	Cl	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
56	OH	Cl		CH ₂ -CH ₂ -CH ₂ -		
57	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ -		
58	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH() ₂	amorph	CL
59	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₃		
60	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	105-110	OX
61	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	82-85	OX



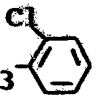
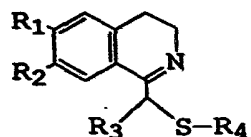
No.	R ₁	R ₂	R ₃	R ₄	Mp. °C	Salt form
62	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	96-100	OX
63	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	60-65	OX
64	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH(CH ₃)-CH ₂ -CH ₂ -CH ₃	~ 60 (decomposition)	OX
65	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH(CH ₃)-CH ₂ -CH ₃		
66	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH(CH ₃)-CH ₃		
67	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -C(CH ₃) ₂ -CH ₃	150-152	OX
68	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -C(CH ₃) ₂ -CH ₃	105-110	OX
69	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -C(CH ₃) ₂ -CH ₃		
70	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -1-Adamantane	155-158	OX
71	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -2-Adamantane		
72	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -1-Adamantane		
73	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -2-Adamantane		
74a	OCH ₃	OCH ₃	C ₆ H ₅	(CH ₂) ₃ - 	135-136	OX



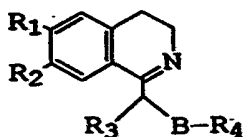
Table 2:



No.	R ₁	R ₂	R ₃	R ₄	Mp. °C	Salt form
74	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
75	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH()-CH ₃		
76	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -		
77	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O-		
78	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ --CO-O-(CH ₂) ₃ -CH ₃		
79	OH	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
80	OH	CH ₃		CH ₂ -CH ₂ -CH ₂ -		
81	OH	CH ₃		CH ₂ -CH ₂ -CH ₂ -		
82	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
83	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ -		
84	OH	Cl		CH ₂ -CH ₂ -CH ₂ -		
85	OH	Cl		CH ₂ -CH ₂ -CH ₂ -		
86	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ -		
	OH	CH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		



Table 3:



NO.	R ₁	R ₂	R ₃	BR ₄	Mp. °C	Salt form
88	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -	190-192	CL
89	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -	amorph	CL
90	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -	185-195	CL
91	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH()-CH ₃		
92	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH()-CH ₃		
93	OCH ₃	OCH ₃	C ₆ H ₅	CH-CH ₂ -CH ₂ -		
94	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -		
95	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -O-		
96	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ --CO-O-(CH ₂) ₃ -CH ₃		
97	OCH ₃	OCH ₃	C ₆ H ₅	-CH ₂ -CH ₂ -CH ₂ -		
98	OCH ₃	OCH ₃		-CH ₂ -CH ₂ -CH ₂ -CH ₂ -		
99	OCH ₃	OCH ₃		-CH ₂ -CH ₂ -CH ₂ -CH ₂ -		
100	OCH ₃	OCH ₃		-CH ₂ -CH ₂ -CH ₂ -		
101	OCH ₃	OCH ₃	t-Butyl	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -		
102	OCH ₃	OCH ₃	t-Butyl	-CH ₂ -CH ₂ -CH ₂ -		



No.	R ₁	R ₂	R ₃	BR ₄		
103	OH	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ - 		
104	OH	OCH ₃		CH ₂ -CH ₂ -CH ₂ -CH ₂ - 		
105	OH	CH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ - 		
106	OH	CH ₃		CH ₂ -CH ₂ -CH ₂ - 		
107	OH	CH ₃		CH ₂ -CH ₂ -CH- 		
108	OH	CH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ - 		
109	OH	Cl	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ - 		
110	OH	Cl		CH ₂ -CH ₂ -CH ₂ - 		
111	OH	Cl		CH ₂ -CH ₂ -CH ₂ - 		
112	OH	Cl	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ - 		
113	OCH ₃	OCH ₃	t-Butyl	CH ₂ -CH ₂ -CH ₂ - 		
114	OCH ₃	OCH ₃	t-Butyl	CH ₂ -CH ₂ -CH ₂ - 		
115	OCH ₃	OCH ₃		CH ₂ -CH ₂ -CH ₂ - 		
116	OH	OCH ₃		CH ₂ -CH ₂ -CH ₂ - 		
117	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ =CH- 	amorph	CL
118	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	105-110	OX
119	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH-CH ₂ -CH ₂ -CH ₂ -CH ₃	90-93	OX
120	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -(CH ₂) ₅ -CH ₃	96-100	
121	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -(CH ₂) ₆ -CH ₃	amorph	OX
122	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -(CH ₂) ₈ -CH ₃	45-53 (decomposition)	OX
123	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₂ -1-Adamantane		
124	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -1-Adamantane	156-159	OX



- 33a -

No.	R ₁	R ₂	R ₃	B R ₄	Mp. °C	Salt form
125	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -(CH ₂) ₁₀ -CH ₃	amorph	OX
126	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH-CH ₃ CH ₃	178-180	CL
127	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH / \ CH ₃ CH ₃	198-202	Cl
128	OCH ₃	OCH ₃	C ₆ H ₅	CH ₂ -CH ₂ -CH ₃	144-147	OX
129	OCH ₃	OCH ₃		CH ₂ -CH ₂ - 	121-124	OX



The present invention also relates to the use of these new compounds.

The compounds are valuable in the treatment of degenerative and necrotic diseases of the brain. It is also possible to provide preventative treatment for patients who are at risk from such diseases. The effect of the compounds is not based on an improvement in the blood flow through the tissues. The compounds are therefore suitable for a new kind of treatment of epilepsy and Alzheimer's disease and particularly for treating patients who have suffered a stroke or are at risk of suffering a stroke.

The present invention further relates to the use of the above compounds for preparing agents for the treatment of chronic inflammatory processes, ulcerative colitis and Crohn's disease and agents with an antiproliferative activity. The effect of the compounds can be explained by their inhibition of the unselective cation channels (UCC).

The pathophysiology of chronic bronchial asthma is based on inflammatory processes which are mediated by the activation of inflammatory cells. (BARNES, 1987; SEIFERT and SCHULTZ, 1991).

The receptor-regulated activation of inflammatory cells (e.g. neutrophilic granulocytes and mast cells or the permanent cell lines HL-60 cells or sensitised RBL cells, i.e. those charged with gammaglobulin E) is inhibited, irrespective of the nature of the stimulating agonists (e.g. endothelin, PAF, leukotrienes, chemotactical peptide fMLP or antigen against sensitised mast cells) by blockers of unselective cation channels (UCC) (RINK, 1990). Through these channels extracellular calcium, which is responsible for the



persistence of receptor-mediated cell activations, enters the cells (PUTNEY, 1990). If this supply of calcium is interrupted this results in a blockade of the activation of inflammatory cells.

Conventional calcium antagonists of the dihydropyridine or phenylalkylamine type do not inhibit either UCCs or inflammatory processes (WELLS et al., 1986).

As a measurement of the cell activation or as a measurement of the inhibition thereof by UCC blockers, the kinetics of the cytoplasmic calcium ion concentration in fura-2-charged cells is quantified fluorometrically using the method described by GRYNKIEWICZ et al. (1985). This procedure has proved a reliable screening method, within the scope of the invention, for detecting UCC blockers.

So-called functional THAPSIGARGIN inhibition has proved suitable for the specific characterisation of blockers of the unselective cation channels. THAPSIGARGIN is a tumour promoter described by THASTRUP et al. (Proc. Natl. Acad. Sci. (USA), 87, 2466-2470, 1990) which selectively and irreversibly inhibits the Ca^{2+} -ATPase of intracellular IP_3 -sensitive Ca^{2+} -stores. Consequently the Ca^{2+} -stores are rapidly depleted. As described by J. PUTNEY (Calcium, 11, 611-624, 1990) the depletion of these stores constitutes the physiological stimulation for opening up unselective cation channels in the cell membrane. The result of this is a massive influx of Na^+ and Ca^{2+} into the cell. Because of these properties, Thapsigargin is suitable as an indirect stimulator for agonist- and IP_3 -independent opening up of the unselective cation channels.

Within the scope of the present invention the Thapsigargin stimulation of unselective cation channels



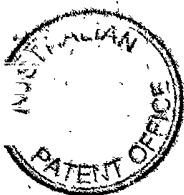
has been carried out successfully on HL 60 cells (human leukaemia cells), on hippocampal and cortical neurone cells and on RBL-cells (rat basophilic lymphoma cells) and in this way the existence of these channels in particular cell lines was demonstrated.

The cytoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) plays an important part in the cell proliferation and in tumour growth (for a summary see L.R. ZACHARSKI, Journal of Medicine 19: 145-177, 1988). In particular, the Ca^{2+} -influx into the cell stimulated by receptor activation with consecutive inositoltriphosphate- (IP_3) -mediation would appear to be of crucial importance for oncogenic cell proliferation (U. KIKKAWA and Y. NISHIZUKA, Ann. REV. CELL. BIOL. 2: 149-178, 1986). This mechanism also plays a part in the formation of metastases and in "Multi-Drug Resistance". (For a summary see the above-mentioned publication by L.R. ZACHARSKI, J. MED. 19: 145-177, 1980).

This hypothesis is supported by the fact that Thapsigargin, as an indirect stimulator of the unselective cation channels (UCC) not only leads to a Ca^{2+} -overload in the cell but is also a highly effective tumour promoter. (V. THASTRUP et al. Proceedings of the NATL. Acad. Sci: (USA) 87: 2466-2470, 1990). The blockade of the Ca^{2+} -influx by the UCC leads to normalisation of the intracellular Ca-ion concentration and hence to inhibition of tumour growth etc.

Conventional calcium antagonists do not inhibit these UCC. It has been found, surprisingly, that the compounds according to this invention inhibit the influx of calcium into the cell through the UCC.

As shown by S. H. MURCH et al. (Lancet 339 : 381-385, 15. Febr. 1992) endothelin I plays an important



pathophysiological role in inflammatory intestinal diseases such as ulcerative colitis and Crohn's disease. Using immunohistochemical methods it has been shown that patients with Crohn's disease in the region of the submucosa and patients with ulcerative colitis in the region of the lamina propria of the epithelium of the large intestine show significantly and greatly increased concentrations of endothelin I compared with healthy normal people. It is assumed that the local secretion of endothelin causes massive vasospasms with consecutive disseminated ischaemia with microinfarcts which are regarded as the actual cause of the above diseases. The vasospasmogenic effectiveness of endothelin is explained by a Ca^{2+} -overload of vascular myocytes. Endothelin primarily triggers an IP_3 -mediated intracellular release of Ca^{2+} which is followed by a massive transmembranal Ca^{2+} -entry through dihydropyridine-insensitive channels. (M. S. Simonson et al. Clin. Invest. Med. 14: 499-507, 1991; T. Masakai, J. Cardiovasc. Pharmacol. 13:Suppl. 5, S1-S4, 1989; D. W. Hay, R. J. Pharmacol. 100: 383-392, 1990). These channels are unselective cation channels which have also been briefly described as existing in cells of the large intestine mucosa. (Chr. Siemer and H. Gögelein, Europ. J. Physiol. 420: 319-328, 1992).

The endothelin-stimulated activation of fura-2-charged human leukaemia cells (HL 60 cells) has proved a suitable screening model for detecting functional endothelin antagonists. In conformity with G. GRYNKIEWICZ et al. (J. Biol. Chem. 260:3440-3450, 1985) the intracellular Ca^{2+} -concentration in the cytoplasm of HL 60 cells (suspensions) can be monitored by spectrofluorometry and quantified as a measurement of cell activation by endothelin. The stimulation was effected by adding 0.1 mM endothelin and could be inhibited in a dosage-dependent manner by means of the substances according to the invention.



The functional endothelin antagonism of the substances according to the invention is mediated through a blockade of the unselective cation channels. Consequently, detection of a functional Thapsigargin-antagonism on RBL-hm1 cells is also a suitable screening method for functional endothelin antagonists.

Carrying out the investigation:

For screening purposes, fura-2-charged adhesive RBL-hm 1 cells are stimulated with 0.1 μ M Thapsigargin in a Ca^{2+} -free incubation medium. After 2 minutes, extracellular Ca^{2+} is restored to a concentration of 1.5 mM and, using the fura-2-fluorescence, the excessive increase in the cytoplasmic Ca^{2+} -concentration caused by a massive transmembranal Ca^{2+} -entry through unselective cation channels is recorded.

This entry is to be inhibited solely by unselective cation channel blockers in a dosage-dependent manner. Neither conventional calcium antagonists nor specific blockers of agonists which stimulate the IP_3 -turnover are able to inhibit the transmembranal Ca^{2+} -entry triggered indirectly by Thapsigargin. The compounds of the present invention are distinguished by their inhibition of UCC.

The fluorometric calcium measurement in the cytoplasm of individual adhering RBL-hm1 cells is carried out analogously to the method described by KUDO and OGURA (1986) for neuronal cells. An AXIOVERT 35 fluorescence microscope made by ZEISS is used in conjunction with an imaging system made by HAMAMATSU, consisting of the ICMS-image processing system, residual light camera with control unit and image intensifier DVS 3000.

The kinetics of the cytoplasmic Ca^{2+} -concentration is



recorded continuously as a concentration/time curve after the cell activation stimulated by Thapsigargin (0.1 μ M). The curves of two activated cell cultures are compared in the presence and absence of 10 μ M test substance. The area under these curves (area under the curve = AUC) is integrated and recorded as a measurement of cell activation. The inhibitory potency of the UCC-blockers tested is determined using the following equation:

$$\%H = 100 - \frac{AUC_{inh} \times 100}{AUC_{(control)}}$$

%H = the percentage inhibition of the calcium entry through unselective cation channels which is stimulated and inhibited by 10 μ M of test substance.

AUC_{inh} = area under the curve recorded in the presence of the stimulant plus 10 μ M inhibitory test substance.

AUC control = area under the curve which is recorded only after the addition of the stimulant.

Literature relating to the above explanations:

BARNES P.J., I.W. RODGER and N.C. THOMSON

Pathogenesis of asthma, in "ASTHMA, basic mechanisms and clinical management"

ED by P.J. BARNES; ACADEMIC PRESS, LONDON, 1988

GRYNKIEWICZ G., M. POENIE and R.Y. TSIEN

A new generation of Ca²⁺-indicators with greatly improved fluorescence properties

J. BIOL. CHEM. 260: 3440-3450, 1985

HIDE, M. and M.A. BEAVEN

Calcium influx in a rat mast cell (RBL-2H3) line



J. BIOL. CHEM. 266 15221-15229, 1991

KUDO, Y. and A. OGURA

Glutamate-induced increase in intracellular Ca^{2+} -
concentration in isolated hippocampal neurones

BR. J. PHARMACOL. 89: 191-198; 1986

PUTNEY, J.W., jr.

Capacitative Calcium entry revised

CELL CALCIUM 11: 611-624, 1990

RINK, T.J.

Receptor-mediated calcium entry

FEBS LETT. 268: 381-385, 1990

SEIFERT, R. and G. SCHULTZ

The superoxide forming NADPH oxidase of phagocytes: An
enzyme system regulated by multiple mechanism

REV. PHYSIOL. BIOCHEM. PHARMACOL., Vol. 117,

SPRINGER VERL., 1991

WELLS, E., C.G. JACKSON, S.T. HARPER, J. MANN and R.P.
BAOY

Characterization of primate bronchoalveolar mast cells
II, inhibition of histamine, LTC_4 and PGF_{2a} release from
primate bronchoalveolar mast cells and a comparison with
rat peritoneal mast cells

J. IMMUNOL. 137: 3941-3945, 1986.

Results of measurement:

The percentage inhibition of UCC after Thapsigargin
stimulation ($0.1 \mu\text{M}$ Thapsigargin) in RBL-hm 1 cells is
given. The uniform concentration of the test substances
is 10^{-5} mol).

The functional antiinflammatory effectiveness can be
demonstrated by means of the following test:



Individual RBL-2H3-cells (a tumour cell line related to the mast cells) adhering to glass slides are used.

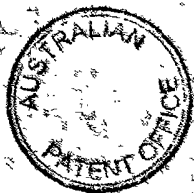
The cultivation and attachment of the RBL-2H3-cells are carried out by the method described by HIDE and BRAVEN (1991). In order to sensitise the adhesive RBL-2H3-cells the cells are incubated for 2 hours at ambient temperature with a 1:2000 diluted commercial gammaglobulin E-solution against a dinitrophenol-bovine serum albumin complex (DNP-BSA-antigen). The cells are then washed. By the addition of 0.1 ml of DNP-BSA-solution (10 µg/ml) there is a massive immunological cell activation which is mediated by a cytoplasmic Ca^{2+} -overload. The fluorometric calcium measurement in the cytoplasm of individual adhering RBL-2H3-cells is carried out analogously to the method described by KUDO and OGURA (1986) for neuronal cells, which is also explained hereinbefore in this specification.

The comparison used in these investigations is (10 µM) chromoglycate which brings about an approximately 50% inhibition of the antigen-induced cell activation.

In this test the above-mentioned compounds demonstrate IC_{50} values which are comparable with the values specified hereinbefore.

Tests on microcultures of various human tumour cell lines using the tetrazolium assay in order to determine the antiproliferative effect of the substances according to the invention surprisingly showed that the compound tested was 5 to 100 times more potent than the comparison substance Verapamil.

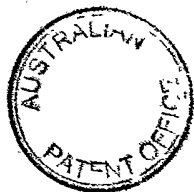
The antiproliferative effectiveness of the test substances was determined by means of the MTT test described by MOSMANN (J. IMMUNOL. METH. 65: 55-63,



1983), DENIZOT et al. (J. IMMUNOL. METH. 89: 271-277, 1986) and J. ELIASON et al. (INT. J. CANCER 46: 113-117, 1990). (MTT = [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl-tetrazolium bromide] produced by CHEMICON Inc. El Segundo, Ca, USA). This indicator is metabolised only by living cells with intact mitochondria into a blue formazane product. The following human tumour cell lines were used in our test: A 549 (adenocarcinoma of the lung), A 431 (epidermal carcinoma of the vulva), PC 3 (adenocarcinoma of the prostate), SK BR 3 (adenocarcinoma of the breast), HT 29 (CX1 1) (adenocarcinoma of the colon) and K 562 (chronic myeloid leukaemia cell).

The test was carried out on microtitre plates. Each well contained 100 μ l of a cell suspension (0.2×10^6 cells per ml). The incubation medium used was RPMI 1640 with 10% heat-inactivated foetal calves' serum and 50 μ g/ml of gentamycin. The cell suspensions were incubated for 0, 24, 48 or 72 hours in air with a humidity at saturation point in a CO₂ (5%)/air (95%) mixture at 37°C, incubated in the presence and absence of variable concentrations of antiproliferative test substances. The test substances were dissolved in DMSO (final dilution: 0.1%). Then 10 μ l of MTT-solution (3 mg/ml) were added, followed after 3 hours by 100 μ l of an isopropanol solution containing 0.08 N HCl. After a further hour, the light absorption at 570 nm (comparative wavelength 630 nm) was determined in a microplate reader. The light absorption is directly proportional to the number of living cells. The half-maximum inhibitory concentrations of the substances tested were 1 μ g/ml.

The vasospasmolytic effectiveness of the above-mentioned functional endothelin and Thapsigargin antagonists were confirmed on an isolated blood vessel preparation:



coronary perfusion was continuously quantified, on retrogressively perfused, spontaneously beating LANDENDORFF hearts taken from rats, by means of electromagnetic flow measurement (apparatus supplied by Hugo Sachs Elektronik, MARCH). This measuring apparatus could be used to record the extent, duration and pattern of vascular spasms with a high degree of accuracy. If perfusion is carried out with 100 nM endothelin concentration, the coronary perfusion flow is reduced from 11 to 5 ml/min. The restriction in perfusion can be reversed by means of the substances according to the invention. The potencies of the compounds according to the invention with regard to Thapsigargin inhibition on fura-2-charged RBL-hm1-cells or the effectiveness of endothelin-inhibition on fura-2-charged HL 60 cells correlates clearly with the vasospasmolytic effectiveness of the test substances detected on the Langendorff preparation. It can be concluded from this that, underlying the vasospasmolytic endothelin antagonism of the substances tested, there is a blockade of the unselective cation channels.



Examples of Pharmaceutical Preparations

a) Coated tablets

1 tablet core contains:

Active substance of general formula I	30.0 mg
Lactose	100.0 mg
Corn starch	75.0 mg
Gelatine	3.0 mg
Magnesium stearate	2.0 mg
	210.0 mg

Preparation

The active substance mixed with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a 1 mm mesh screen, dried at 40°C and rubbed through a screen once more. The granules thus obtained are mixed with magnesium stearate and compressed. The cores produced in this way are coated in the usual manner with a coating consisting of an aqueous suspension of sugar, titanium dioxide, talc and gum arabic. The finished coated tablets are polished with beeswax.

b) Tablets

Active substance of general formula I	30.0 mg
Lactose	100.0 mg
Corn starch	70.0 mg
Soluble starch	7.0 mg
Magnesium stearate	3.0 mg
	210.0 mg

Preparation

The active substance and magnesium stearate are granulated with an aqueous solution of the soluble starch, the granules are dried and intimately mixed with



lactose and corn starch. The mixture is then compressed into tablets weighing 210 mg.

c) Capsules

Active substance according to formula I	20.0 mg
Lactose	230.0 mg
Corn starch	40.0 mg
Talc	10.0 mg
	300.0 mg

Preparation

The active substance, lactose and corn starch are first combined in a mixer and then in a grinding machine. The mixture is returned to the mixer, thoroughly combined with the talc and mechanically packed into hard gelatine capsules.

d) Tablets

Active substance according to the invention	40.0 mg
Lactose	100.0 mg
Corn starch	50.0 mg
Colloidal silica	2.0 mg
Magnesium stearate	3.0 mg
total	195.0 mg

Preparation

The active substance is mixed with some of the excipients and granulated with a solution of the soluble starch in water. After the granules have dried the remaining excipients are added and the mixture is compressed to form tablets.



e) Coated tablets

Active substance according to the invention	20.0 mg
Lactose	100.0 mg
Corn starch	65.0 mg
Colloidal silica	2.0 mg
So'uble starch	5.0 mg
Magnesium stearate	3.0 mg
total	195.0 mg

Preparation

The active substance and excipients are compressed to form tablet cores as described in Example a) and these are then coated in the usual way with sugar, talc and gum arabic.

f) Suppositories

Active substance according to the invention	50.0 mg
Lactose	250.0 mg
Suppository mass q.s. <u>ad</u>	1.7 g

Preparation

The active substance and lactose are mixed together and the mixture is uniformly suspended in the molten suppository mass. The suspensions are poured into chilled moulds to form suppositories weighing 1.7 g.

g) Ampoules

Active substance according to the invention	20.0 mg
Sodium chloride	5.0 mg
Twice distilled water q.s. <u>ad</u>	2.0 ml

Preparation

The active substance and the sodium chloride are dissolved in twice distilled water and the solution is transferred under sterile conditions into ampoules.



h) Ampoules

Active substance according to the invention	10.0 mg
Sodium chloride	7.0 mg
Twice distilled water q.s. ad	1.0 ml

i) Drops

Active substance according to the invention	0.70 g
Methyl p-hydroxybenzoate	0.07 g
Propyl p-hydroxybenzoate	0.03 g
Demineralised water q.s. ad	100.00 ml

Preparation

The active substance and preservatives are dissolved in demineralised water, the solution is filtered and transferred into 100 ml vials.

Example 4 - Antiproliferative Effect

The new activity of the compounds of the present invention as antiproliferative agents is shown by the following experimental data. The inhibition of cell proliferation in human neuroblastoma cells was tested using the MTT test (see description, last paragraph, page 41). The results for compound 4 (Table 1, page 27) and compound 90 (Table 3, page 32) together with a further compound according to the present invention of a general formula shown in Table 3 (page 32) where R_1 and R_2 are methoxy, R_3 is phenyl and the group BR_4 is $-CH_2-CH_2=CH-C_6H_5$ are shown in the table below.

Substance	IC ₅₀
Compound 4	4.65 μ M
Compound 90	6.46 μ M
Further compound	8.76 μ M

These test results show that the compounds according to the invention have an antiproliferative effect.



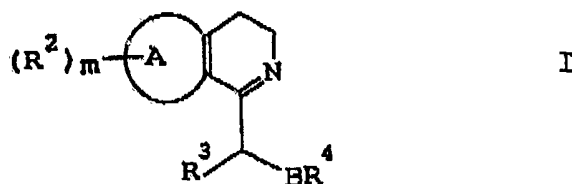






THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. Compound of general formula I

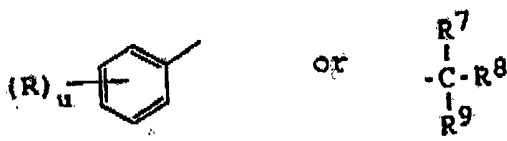


wherein

A denotes a benzo, indolo or thieno group;
 wherein, if A is benzo, m is 2 or 3 and the substituents R^2 independently of each other denote hydroxy, (C_{1-4}) alkoxy, benzyloxy, halogen (F, Cl, Br, I), (C_{1-4}) alkyl, methanesulphonyloxy or methanesulphonamido, or two adjacent substituents R^2 may together represent $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$; and if A is indolo or thieno, m is zero;

B represents the group $-O-$, $-S-$ or $-CHR^5-$, wherein R^5 is hydrogen, (C_{1-6}) alkyl, phenyl or benzyl;

R^3 denotes 2- or 3-thienyl, (C_{4-7}) cycloalkyl, (C_{4-6}) -cycloalkyl (C_{1-5}) alkyl or



(wherein

R is (C_{1-4}) alkyl, hydroxy, $-N_3$, halogen (F, Cl, Br, I), CF_3 or (C_{1-4}) alkoxy,

u is 0, 1, 2 or 3, and



R^7 , R^8 and R^9 independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than two of the substituents can simultaneously represent phenyl or benzyl);

R^4 denotes

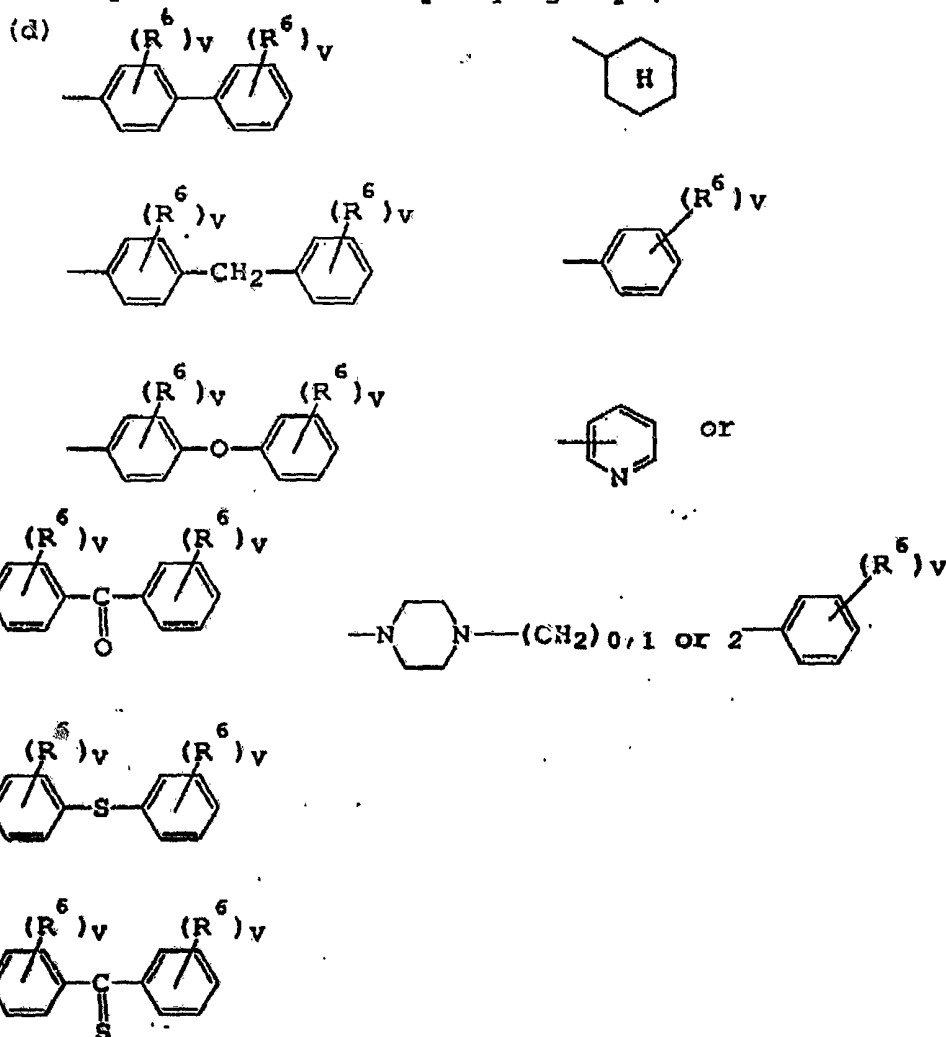
- (a) branched or unbranched C_{3-6} -alkenyl which may be substituted by phenyl, or
- (b) branched or unbranched C_{3-6} -alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C_{1-13} -alkyl, wherein the alkyl may be substituted by
hydroxy,
(C_{1-4})alkoxy,
di(C_{1-4})alkylamino,
furyl,
pyridyl,
pyrrolidinyl, N-methylpyrrolidinyl,
morpholino,
indolyl,
nitrilo,
thienyl,
adamantyl,
cyclohexyl,
phenoxy,
benzyloxy,
naphthyloxy or
phenyl,
(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by hydroxy,
(C_{1-4})alkoxy, benzyloxy, halogen (F, Cl, Br, I), CF_3 , N_3 , NO_2 , (C_{1-4})alkyl, adamantyl,
 $-SO_2NH_2$, $NHCOCH_3$, $-NHSO_2CH_3$ or $-C(O)C-R_{14}$,
[wherein R_{14} is (C_{3-7})cycloalkyl or branched or unbranched (C_{1-6})alkyl, whilst the alkyl may be



substituted by phenyl, and this phenyl may be mono- to trisubstituted by halogen (F, Cl, Br, I), CF_3 , C_1 - or C_2 -alkyl, C_1 - or C_2 -alkoxy]

or may be substituted by the bridge $-\text{O}-\text{CH}_2-\text{O}-$,
or

by 2 unsubstituted phenyl groups;



wherein R^6 is (C_{1-4}) alkyl, hydroxy, $-\text{N}_3$, halogen (F, Cl, Br, I), CF_3 , NO_2 or (C_{1-4}) alkoxy and v is 0, 1, 2 or 3,

or the salts thereof with physiologically acceptable acids or complexing agents,



with the proviso that when A is benzo and

(a) if R^2 is methoxy in positions 6 and 7, B is $-CHR^5$ where R^5 is H, and either

(i) R^4 is CH_2OH , $CH(CH_3)OH$ or $C(CH_3)_2OH$ and R^3 is phenyl, then R cannot be 2-methyl; or

(ii) R^4 is phenyl or 4-methoxy, 2,5-dimethoxy or 4-methyl substituted phenyl, then R^3 cannot be unsubstituted phenyl

or

(b) if R^2 is hydroxy or C_{1-4} -alkoxy in positions 6 and 7, B is S and R^3 is an unsubstituted or mono-, di- or tri halogenated or C_{1-4} -alkoxy substituted phenyl, then R^4 cannot be a C_{1-13} -branched or unbranched alkyl, optionally substituted by phenyl, hydroxy or di(C_{1-4})alkylamino or R^4 cannot be a C_{2-6} -alkenyl group.

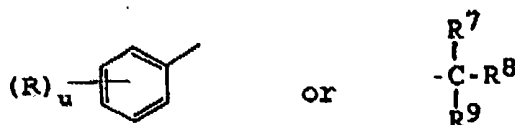
2. Compound according to claim 1, wherein

A denotes benzo; m is 2 and the substituents R^2 independently of one another represent hydroxy, (C_{1-4})alkoxy, benzyloxy, halogen (F, Cl, Br, I) or (C_{1-4})alkyl, or two adjacent substituents R^2 may together represent $-O-CH_2-O$;

B denotes the group $-O-$, $-S-$ or $-CHR^5-$, wherein R^5 is hydrogen, methyl, phenyl or benzyl;

R^3 is 2- or 3-thienyl, (C_{4-7})cycloalkyl, or





(wherein

R is (C₁₋₄)alkyl, halogen (F, Cl, Br, I), CF₃ or (C₁₋₄)alkoxy,

u is 0, 1, 2 or 3, and

R⁷, R⁸ and R⁹ independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than 2 of the substituents may simultaneously represent phenyl or benzyl);

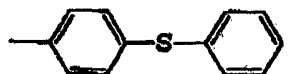
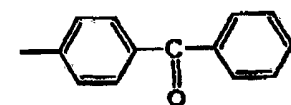
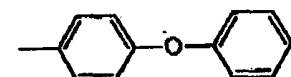
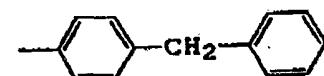
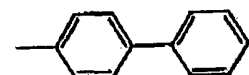
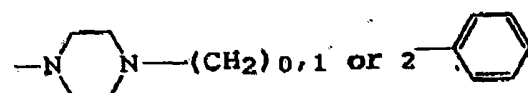
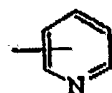
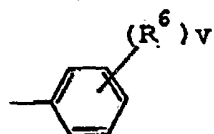
R⁴ denotes

- (a) branched or unbranched C₃₋₆-alkenyl which may be substituted by phenyl or
- (b) branched or unbranched C₃₋₆-alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C₁₋₁₃-alkyl, wherein the alkyl may be substituted by thienyl, adamantyl, cyclohexyl, phenoxy, benzyloxy or phenyl
(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by (C₁₋₄)alkoxy, halogen (F, Cl, Br, I), CF₃, N₃, NO₂, (C₁₋₄)alkyl, or -C(O)-O-(CH₂)₁₋₃-CH₃ or by the bridge -O-CH₂-O-), or

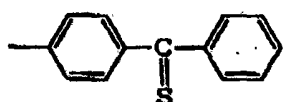


by 2 unsubstituted phenyl groups;

(d)



or



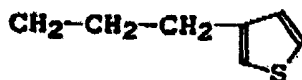
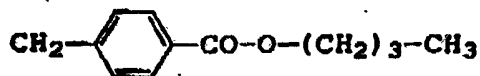
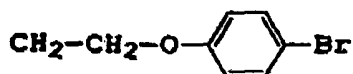
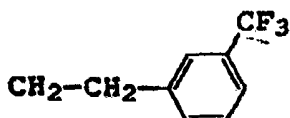
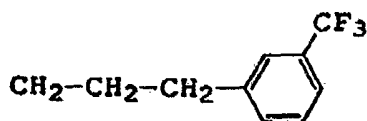
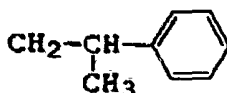
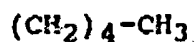
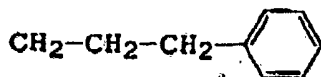
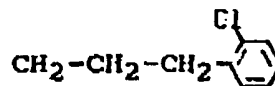
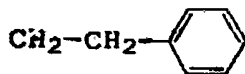
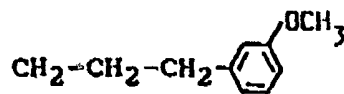
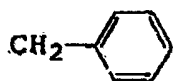
wherein R^6 denotes (C_{1-4}) alkyl, hydroxy, $-N_3$, halogen (F, Cl, Br, I), CF_3 , NO_2 or (C_{1-4}) alkoxy and v is 0, 1, 2 or 3,

or the salts thereof with physiologically acceptable acids or complexing agents.



3. Compound according to claim 1 or claim 2 wherein when A is benzo and m is 2, the two R² substituents are in positions 6 and 7.

4. Compound according to any of claims 1 to 3, wherein R¹ has one of the following meanings:



5. Compound according to one of claims 1 to 4, wherein A is 6,7-dimethoxybenzo.

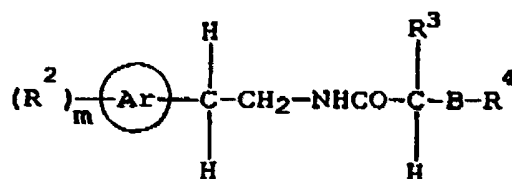
6. Compound according to one of claims 1 to 5, wherein R³ is phenyl or cyclohexyl.

7. Compound according to one of claims 1 to 6, wherein B is O or CH₂.



8. Compound according to one of claims 1 to 3 wherein A is 6,7-dimethoxybenzo, B is CH₂, R₁ is 1-pentenyl and R₂ is phenyl.

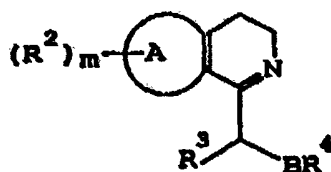
9. Process for preparing a compound according to one of claims 1 to 8, characterised in that a compound of general formula IV



wherein R², R³, R⁴, m and B are defined as in one of claims 1 to 8 and Ar denotes phenyl, indolyl or 2- or 3-thienyl, is cyclised in the presence of a condensing agent and, if desired, converted into a salt thereof.

10. Pharmaceutical preparation containing a compound according to one of claims 1 to 6 in combination with a pharmaceutically acceptable and/carrier or excipient.

11. Method of treatment of ulcerative colitis, Crohn's disease, inflammatory processes or of providing an antiproliferative or cerebroprotective effect in a subject comprising the administration of a compound of general formula I



I

wherein

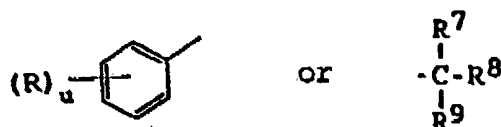
A denotes a benzo, indolo or thieno group;
wherein, if A is benzo, m is 2 or 3 (preferably 2,
whilst the two R²'s are in positions 6 and 7) and the
substituents R² independently of each other denote



hydroxy, (C₁₋₄)alkoxy, benzyloxy, halogen (F, Cl, Br, I), (C₁₋₄)alkyl, methanesulphonyloxy or methanesulphonamido, or two adjacent substituents R² may together represent -O-CH₂-O- or -O-CH₂-CH₂-O-; and if A is indolo or thieno, m is zero;

B represents the group -O-, -S- or -CHR⁵-, wherein R⁵ is hydrogen, (C₁₋₆)alkyl, phenyl or benzyl;

R³ denotes 2- or 3-thienyl, (C₄₋₇)cycloalkyl, (C₄₋₆)-cycloalkyl(C₁₋₅)alkyl or



(wherein

R is (C₁₋₄)alkyl, hydroxy, -N₃, halogen (F, Cl, Br, I), CF₃ or (C₁₋₄)alkoxy,

u is 0, 1, 2 or 3, and

R⁷, R⁸ and R⁹ independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, but not more than two of the substituents can simultaneously represent phenyl or benzyl);

R⁴ denotes

- (a) branched or unbranched C₃₋₆-alkenyl which may be substituted by phenyl, or
- (b) branched or unbranched C₃₋₆-alkynyl which may be substituted by phenyl, or
- (c) branched or unbranched C₁₋₁₃-alkyl, wherein the alkyl may be substituted by



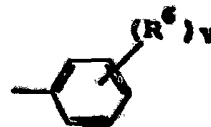
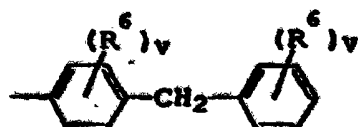
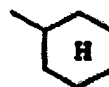
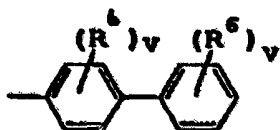
hydroxy,
 (C₁₋₄)alkoxy,
 di(C₁₋₄)alkylamino,
 furyl,
 pyridyl,
 pyrrolidinyl, N-methylpyrrolidinyl,
 morpholino,
 indolyl,
 nitrilo,
 thienyl,
 adamantyl,
 cyclohexyl,
 phenoxy,
 benzyloxy,
 naphthyloxy or
 phenyl,

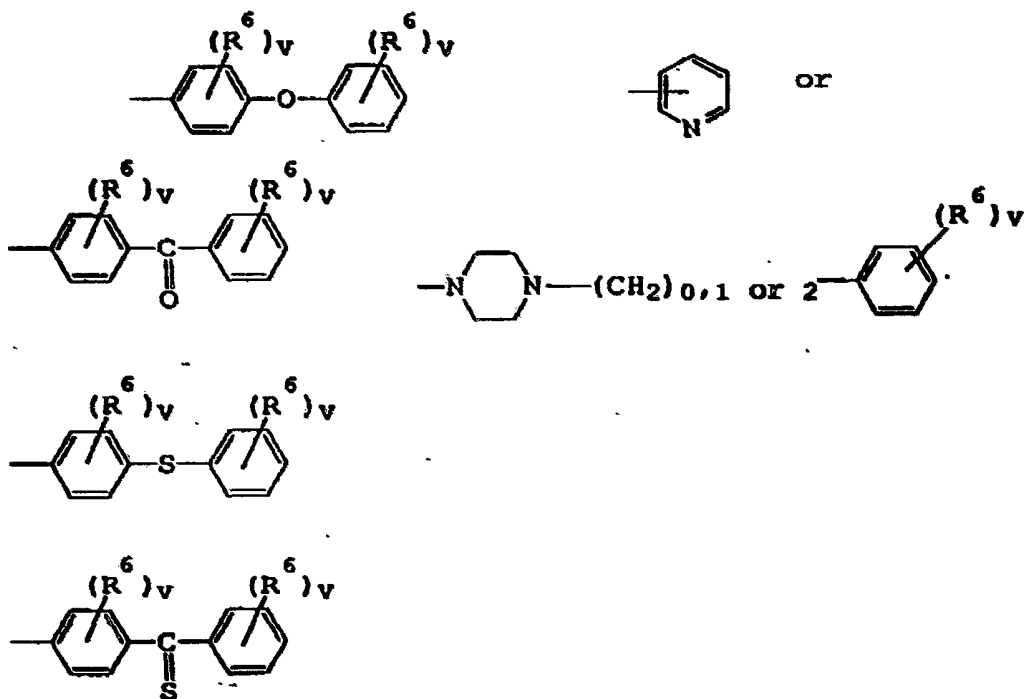
(whilst this phenyl or the phenyl contained in the phenoxy group or benzyloxy group may be mono-, di- or trisubstituted by hydroxy, (C₁₋₄)alkoxy, benzyloxy, halogen (F, Cl, Br, I), CF₃, N₃, NO₂, (C₁₋₄)alkyl, adamantyl, -SO₂NH₂, NHCOCH₃, -NHSO₂CH₃ or -C(O)O-R₁₄, [wherein R₁₄ is (C₃₋₇)cycloalkyl or branched or unbranched (C₁₋₄)alkyl, whilst the alkyl may be substituted by phenyl, and this phenyl may be mono- to trisubstituted by halogen (F, Cl, Br, I), CF₃, C₁- or C₂-alkyl, C₁- or C₂-alkoxy]

or may be substituted by the bridge -O-CH₂-O-),
 or

by 2 unsubstituted phenyl groups;

(d)





wherein R⁶ is (C₁₋₄)alkyl, hydroxy, -N₃, halogen (F, Cl, Br, I), CF₃, NO₂ or (C₁₋₄)alkoxy and v is 0, 1, 2 or 3,

to said subject.

12. The use of a compound of general formula I, as defined in claim 11 in the manufacture of a medicament, for the treatment of ulcerative colitis, Crohn's disease or inflammatory processes, or which provides an antiproliferative or cerebroprotective effect.

13. Compound according to any one of claims 1 to 8 substantially as hereinbefore described with reference to the examples.

14. Process according to claim 9 substantially as hereinbefore described with reference to the preparative examples.



15. Pharmaceutical preparation according to claim 10 substantially as hereinbefore described with reference to the pharmaceutical preparation examples.

DATED this FOURTEENTH day of OCTOBER 1998

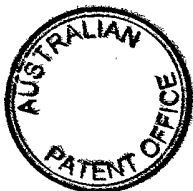
Boehringer Ingelheim International GmbH

By its Patent Attorneys

DAVIES COLLISON CAVE

1998 OCT 14

1998 OCT 14



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 94/04150

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D217/14 C07D217/16 C07D217/18 C07D409/06 C07D409/12
A61K31/47

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IND. J. CHEM., SECT. B, vol. 20B, no.10, 1981 pages 885-890, V.M. KANSAL, A.P. BHADURI 'Possible Antihypertensive Agents: Syntheses of N-Alkyl-beta-substituted Phenylethylamines & N-Alkyl/acyl-6,7-dimethoxy-1-(alpha-phenyl- beta-substituted phenyl)ethyl)-1,2,3,4-tetrahydroisoquinoli- nes' * Compounds 39-42 *	1-7
Y	DE,A,30 23 717 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 29 January 1981 see page 13, line 9 - line 14; claims 1-45 -/-	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *Z* document member of the same patent family

Date of the actual completion of the international search

6 April 1995

Date of mailing of the international search report

09.05.95

Name and mailing address of the ISA

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Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/04150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 037 934 (C.H. BOEHRINGER SOHN) 21 October 1981 cited in the application see page 5, line 26 - line 30; claims 1-9 ---	1-8
Y	EP,A,0 251 194 (BOEHRINGER INGELHEIM KG) 7 January 1988 cited in the application see page 19, line 54 - line 57; claims 1-10 ---	1-8
Y	EP,A,0 288 048 (BOEHRINGER INGELHEIM KG) 26 October 1988 cited in the application see page 14, line 19 - line 22; claims 1-14 ---	1-8
Y	EP,A,0 358 957 (BOEHRINGER INGELHEIM KG) 21 March 1990 see page 14, line 34 - line 35; claims 1-12 -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/04150

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-3023717	29-01-81	AT-B- 384216	12-10-87
		AT-B- 376664	27-12-84
		AU-B- 534697	09-02-84
		AU-A- 6000180	05-02-81
		BE-A- 884101	03-11-80
		CH-A- 651554	30-09-85
		FR-A, B 2460934	30-01-81
		GB-A, B 2053914	11-02-81
		JP-B- 1031502	26-06-89
		JP-C- 1548009	09-03-90
		JP-A- 56049365	02-05-81
		NL-A, B, C 8003803	06-01-81
		SE-A- 8004869	03-01-81
		SU-A- 936809	15-06-82
		SU-A- 1047389	07-10-83
		US-A- 4373104	08-02-83
		US-A- 4425349	10-01-84
		US-E- RE32519	13-10-87
EP-A-37934	21-10-81	DE-A- 3013906	15-10-81
		AU-A- 6938481	29-10-81
		GB-A- 2074159	28-10-81
		JP-A- 56158765	07-12-81
		US-A- 4322418	30-03-82
EP-A-251194	07-01-88	DE-A- 3621413	07-01-88
		AU-B- 598558	28-06-90
		AU-A- 7477587	07-01-88
		DE-A- 3785093	06-05-93
		ES-T- 2053471	01-08-94
		IE-B- 59546	09-03-94
EP-A-288048	26-10-88	JP-A- 63258458	25-10-88
		DE-A- 3713743	17-11-88
		DE-A- 3718570	15-12-88
		AT-T- 107921	15-07-94
		AU-B- 609121	26-04-91
		AU-A- 1509088	27-10-88
		CA-A- 1330798	19-07-94
		DE-D- 3850437	04-08-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/04150

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-288048		ES-T- 2055717	01-09-94
		FI-B- 91750	29-04-94
		HU-B- 208673	28-12-93
		JP-A- 63280069	17-11-88
		NO-B- 174548	14-02-94
		SU-A- 1681724	30-09-91

EP-A-358957	21-03-90	DE-A- 3827727	22-02-90
		AU-B- 637767	10-06-93
		AU-A- 3992589	22-02-90
		DE-U- 8817109	26-11-92
		JP-A- 2160767	20-06-90

INTERNATIONALER RECHERCHENBERICHT

In nationales Aktenzeichen
PCT/EP 94/04150

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C07D217/14 C07D217/16 C07D217/18 C07D409/06 C07D409/12
A61K31/47

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 C07D A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	IND. J. CHEM., SECT. B, Bd. 20B, no.10, 1981 Seiten 885-890, V.K. KANSAL, A.P. BHADURI 'Possible Antihypertensive Agents: Syntheses of N-Aralkyl-beta-substituted Phenylethylamines & N-Alkyl/acyl-6,7-dimethoxy-1-((alpha-phenyl 1-beta-substituted phenyl)ethyl)-1,2,3,4-tetrahydroisoquinoli nes' * Compounds 39-42 *	1-7
Y	DE,A,30 23 717 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 29.Januar 1981 siehe Seite 13, Zeile 9 - Zeile 14; Ansprüche 1-45 --- -/--	1-8

☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

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"a" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

6. April 1995

Absenddatum des internationalen Recherchenberichts

09.05.95

Name und Postanschrift der Internationalen Recherchenbehörde
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Fax (+31-70) 340-3016

Bevollmächtigter Bediensteter

Herz, C

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 94/04150

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	EP,A,0 037 934 (C.H. BOEHRINGER SOHN) 21.Oktober 1981 in der Anmeldung erwähnt siehe Seite 5, Zeile 26 - Zeile 30; Ansprüche 1-9 ---	1-8
Y	EP,A,0 251 194 (BOEHRINGER INGELHEIM KG) 7.Januar 1988 in der Anmeldung erwähnt siehe Seite 19, Zeile 54 - Zeile 57; Ansprüche 1-10 ---	1-8
Y	EP,A,0 288 048 (BOEHRINGER INGELHEIM KG) 26.Oktober 1988 in der Anmeldung erwähnt siehe Seite 14, Zeile 19 - Zeile 22; Ansprüche 1-14 ---	1-8
Y	EP,A,0 358 957 (BOEHRINGER INGELHEIM KG) 21.März 1990 siehe Seite 14, Zeile 34 - Zeile 35; Ansprüche 1-12 -----	1-8

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

In internationales Aktenzeichen

PCT/EP 94/04150

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE-A-3023717	29-01-81	AT-B- 384216	12-10-87
		AT-B- 376664	27-12-84
		AU-B- 534697	09-02-84
		AU-A- 6000180	05-02-81
		BE-A- 884101	03-11-80
		CH-A- 651554	30-09-85
		FR-A, B 2460934	30-01-81
		GB-A, B 2053914	11-02-81
		JP-B- 1031502	26-06-89
		JP-C- 1548009	09-03-90
		JP-A- 56049365	02-05-81
		NL-A, B, C 8003803	06-01-81
		SE-A- 8004869	03-01-81
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		US-A- 4373104	08-02-83
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		US-E- RE32519	13-10-87
EP-A-37934	21-10-81	DE-A- 3013906	15-10-81
		AU-A- 6938481	29-10-81
		GB-A- 2074159	28-10-81
		JP-A- 56158765	07-12-81
		US-A- 4322418	30-03-82
EP-A-251194	07-01-88	DE-A- 3621413	07-01-88
		AU-B- 598558	28-06-90
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		ES-T- 2053471	01-08-94
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		JP-A- 63258458	25-10-88
EP-A-288048	26-10-88	DE-A- 3713743	17-11-88
		DE-A- 3718570	15-12-88
		AT-T- 107921	15-07-94
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		AU-A- 1509088	27-10-88
		CA-A- 1330798	19-07-94
		DE-D- 3850437	04-08-94

INTERNATIONALER RECHERCHENSERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 94/04150

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP-A-288048		ES-T- 2055717	01-09-94
		FI-B- 91750	29-04-94
		HU-B- 208673	28-12-93
		JP-A- 63280069	17-11-88
		NO-B- 174548	14-02-94
		SU-A- 1681724	30-09-91

EP-A-358957	21-03-90	DE-A- 3827727	22-02-90
		AU-B- 637767	10-06-93
		AU-A- 3992589	22-02-90
		DE-U- 8817109	26-11-92
		JP-A- 2160767	20-06-90
