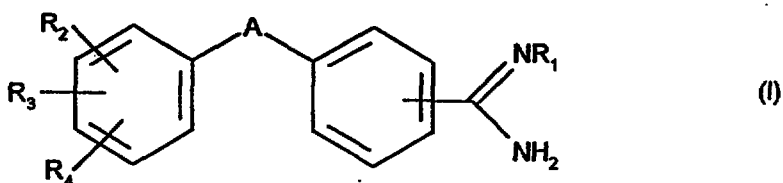


Substituted benzamidines, the preparation thereof
and their use as pharmaceuticals

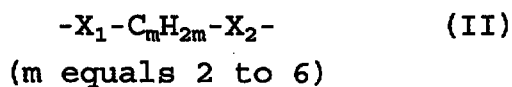
The invention relates to new substituted benzamidines, the preparation thereof using conventional methods and their use, as pharmaceuticals with in particular, an LTB₄-receptor-antagonist activity.

The new substituted benzamidines correspond to the formula

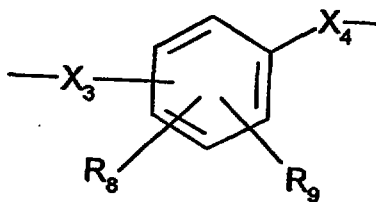


wherein the

A denotes the group

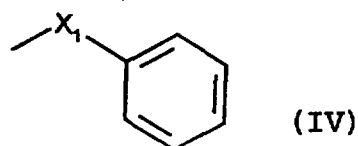


or



X₁ denotes O, NH or NCH₃

X₂ denotes O, NH, NCH₃ or



- X_3 denotes $-X-C_nH_{2n}-$;
- X_4 denotes $-C_nH_{2n}-X-$ ($n = 1$ or 2 , $X = O, NH$ or NCH_3);
- R_1 denotes $OH, CN, COR_{12}, COOR_{12}$ or CHO ;
- R_2 denotes $Br, Cl, F, CF_3, OH, C_1-C_6$ -alkyl, C_5-C_7 -cycloalkyl, aryl, O -aryl, CH_2 -aryl, CR_5R_6 -aryl, $C(CH_3)_2-R_7$;
and also H , when A is a group of Formula III or when X_2 is a group of Formula IV;
and also C_1-C_6 -alkoxy, when A is the group II, X_1 is as hereinbefore defined and X_2 denotes NH, NCH_3 or the group IV,
or when A denotes the group III, X_3 is as hereinbefore defined and in X_4 X denotes NH or NCH_3 ;
- R_3 denotes H, C_1-C_6 -alkyl, OH, Cl, F , and also C_1-C_6 alkoxy when R_2 denotes aryl, O -aryl, CH_2 -aryl, CR_5R_6 -aryl or $C(CH_3)_2-R_7$ or when X_2 denotes the group IV;
- R_2 and R_3 may also together denote a fused aromatic or heteroaromatic ring;
- R_4 denotes H or C_1-C_6 -alkyl;
- R_5 denotes C_1-C_4 -alkyl, $CF_3, CH_2OH, COOH$ or $COO(C_1-C_4$ -alkyl);
- R_6 denotes H, C_1-C_4 -alkyl, or CF_3 ;
- R_5 and R_6 together may also form a C_4-C_6 -alkylene group;
- R_7 denotes $CH_2OH, COOH, COO(C_1-C_4$ -alkyl), $CONR_{10}R_{11}$ or $CH_2NR_{10}R_{11}$;
- R_8, R_9 denote $H, Br, Cl, F, OH, C_1-C_6$ -alkyl or C_1-C_6 -alkoxy;
- R_{10} denotes H, C_1-C_6 -alkyl, phenyl, phenyl- $(C_1-C_6$ -alkyl), $COR_{12}, COOR_{12}, CHO, CONH_2, CONHR_{12}, SO_2-(C_1-C_6$ -alkyl), SO_2 -phenyl, wherein the phenyl group may be mono- or polysubstituted by Cl, F, CF_3, C_1-C_4 alkyl, OH, C_1-C_4 -alkoxy;

R₁₁ denotes H or C₁-C₆-alkyl;

R₁₀ and R₁₁ together may also denote a C₄-C₆-alkylene group;

R₁₂ denotes C₁-C₆-alkyl, C₅-C₇-cycloalkyl, aryl, heteroaryl, aralkyl or heteroaryl-(C₁-C₆-alkyl), wherein the aryl or heteroaryl group may be mono or polysubstituted by Cl, F, CF₃, C₁-C₄-alkyl, OH or C₁-C₄-alkoxy.

The new compounds may occur as free bases or as salts with acids, preferably physiological acceptable acids; if they contain one or more chiral centres, they may be in the form of racemates, in enantiomerically pure or concentrated form, optionally as pairs of diastereomers. Any tautomers (with -C(NH)-NHR₁) are also included.

The preferred compounds of Formula I are those wherein

A, m, n, X₃, X₄ and R₁ are as hereinbefore defined;

X₁ denotes O;

X₂ denotes O or a group IV (wherein X₁ equals O);

R₂ denotes Cl, F, CF₃, OH, C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl or CR₅R₆-aryl, and,

if R₂ is the group IV, R₂ may also represent C₁-C₆-alkoxy;

R₃ denotes H, C₁-C₆-alkyl or OH, and,

if R₂ CR₅R₆-aryl, R₃ also denotes C₁-C₆-alkoxy;

R₄ denotes H;

R₅ denotes C₁-C₃-alkyl, CF₃ or CH₂OH;

R₆ denotes H, C₁-C₃-alkyl or CF₃,

R₅ and R₆ together may also denote C₄-C₅-alkylene;

R₈ and R₉ denote H, F or OH.

Particular mention should be made of the compounds wherein, within the scope of the above definitions

X₁ denotes O;

X₂ represents the group IV (wherein X₁ equals O);

X denotes O;

R₁ denotes COOR₁₂;

R₂ denotes C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl or CR₅R₆-aryl;

R₃ denotes H, OH or C₁-C₆-alkyl and, if R₂ is CR₅R₆-aryl, R₃ may also denote C₁-C₆ alkoxy;

R₄ denotes H;

R₅ and R₆ denote C₁-C₃-alkyl or CF₃;

R₈ and R₉ denote H;

R₁₂ denotes C₁-C₆-alkyl, aralkyl or C₇-C₅-cycloalkyl.

Where the symbols according to the above definitions may have the same or different meanings, both possibilities should be included. Aliphatic chains which have a sufficient number of carbon atoms may be straight chained or branched.

"Aryl" denotes an optionally (mono- or poly-) substituted aryl group, such as naphthyl, but preferably an optionally (mono- or poly-) substituted phenyl group. The preferred substituents are: Cl, F, Br, OH, C₁-C₆-alkyl, C₁-C₆-alkoxy, and CF₃; other possibilities are groups which are generally present only once, such as NH₂, NH(C₁-C₆-alkyl), N(C₁-C₆-alkyl)₂, NH(SO₂-(C₁-C₆-alkyl), NH(SO₂-phenyl), wherein the phenyl group may in turn be substituted, in particular by F, Cl, CF₃, C₁-C₄-alkyl, C₁-C₄ alkoxy or OH. The term "aralkyl" denotes a C₁-C₆-alkyl group which is substituted by an aryl (as hereinbefore defined).

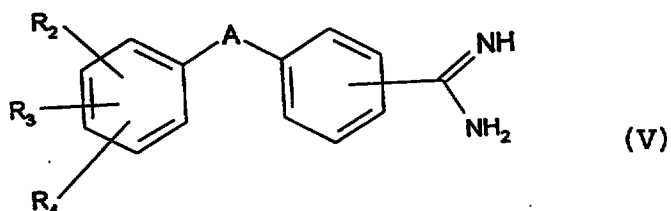
The term "heteroaryl" here preferably refers to pyridyl, pyrimidyl, pyridazinyl and pyrazinyl, thienyl and furyl, which may be mono or polysubstituted, in particular, by Cl, F, Br, OH, C₁-C₆-alkyl, C₁-C₆-alkoxy, CF₃. The cycloalkyl groups may be substituted by C₁-C₆-alkyl groups, e.g. as in the menthyl group. If R₂ and R₃ together denote a fused ring, this refers to a ring which forms a basis for aryl and heteroaryl groups as hereinbefore defined.

In the alkyl and alkoxy groups the number of carbon atoms is

preferably between 1 and 4. The preferred substituents in aromatic or heteroaromatic groups are alkyl and alkoxy groups having up to 3, preferably up to 2, carbon atoms. The amidino group $C(NH_2)NR_1$ is preferably in the para-position relative to Group A.

The new compounds may be obtained by methods known per se, for example as follows:

1. Reacting an amidine as formula



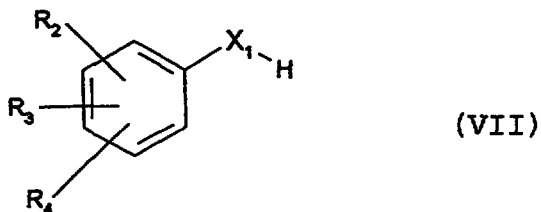
with a compound of formula



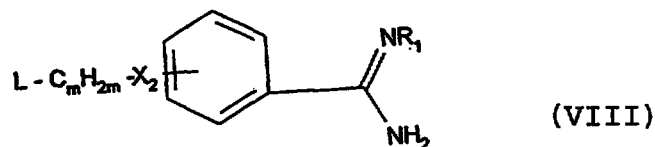
wherein in compound (V) A, R_2 , R_3 and R_4 are as hereinbefore defined, R'_1 has the same meaning as R_1 , with the exception of OH, and L denotes a nucleophilically exchangeable group such as a halogen atom (such as Cl, Br) or acyloxy.

The reaction is appropriately carried out in a solvent such as tetrahydrofuran, methylene chloride, chloroform or dimethylformamide, preferably in the presence of a base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine which may simultaneously serve as solvents, at temperatures between -30 and 100°C , but preferably at temperatures between -10 and 80°C .

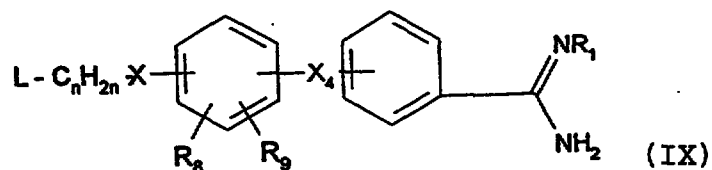
2. Reacting compounds of Formula



(wherein R_2 , R_3 , R_4 and X_1 are as hereinbefore defined),
with a benzamidine derivative of Formula

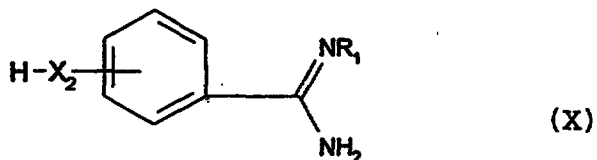


or

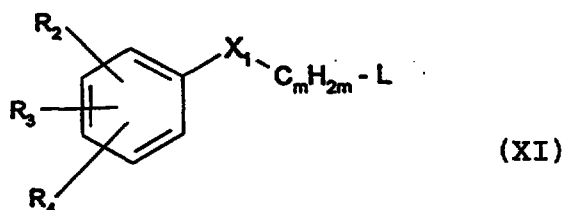


(wherein L , m , n , X , X_2 , X_4 , R_1 , R_8 and R_9 are as
hereinbefore defined).

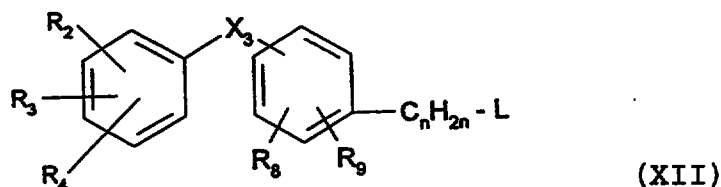
3. Reacting compounds of Formula



(wherein R_1 and X_2 are as hereinbefore defined)
with a compound of Formula



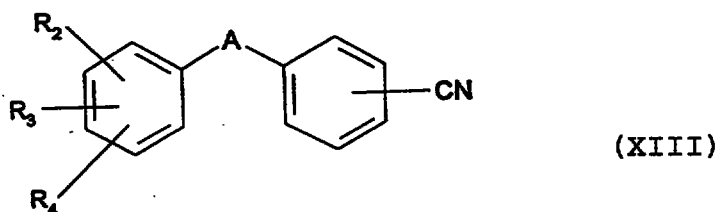
or



(wherein L, m, n, R₂, R₃, R₄, R₈, R₉, X₁ and X₃ are as hereinbefore defined).

Methods 2 and 3 are preferably carried out in aprotic solvents such as dimethylsulfoxide, dimethylformamide, acetonitrile or alcohols (e.g. methanol, ethanol, isopropanol) with the addition of basic substances (e.g. metal carbonates, metal hydroxides, metal hydrides) at temperatures between about 0 and 140°C or at the boiling temperature of the reaction mixture.

4. In order to prepare compounds of Formula I wherein R₁ denotes OH;
a nitrile of formula



wherein A, R₂, R₃ and R₄ are as hereinbefore defined, is reacted with hydroxylamine.

Method 4 is preferably carried out in an alcohol (methanol, ethanol, propanol) or an aprotic solvent such as dimethylsulfoxide, dimethylformamide, or acetonitrile, or optionally in admixture with water, in warm conditions. The hydroxylamine is used, for example, in the form of the hydrochloride or methane sulfonate, and a suitable base such as sodium carbonate is added.

The starting materials may be synthesised using conventional methods.

It has been found that the compounds of Formula 1 are characterised by their versatility in the therapeutic field. Particular mention should be made of those possible applications for which the LTB₄-receptor-antagonistic properties come into play. Example include, in particular: arthritis, asthma, chronic obstructive lung diseases, such as chronic bronchitis, psoriasis, ulcerative colitis, gastro or enteropathy induced by non-steroidal antiphlogistics, Alzheimers disease, shock, reperfusion damage/ischaemia, atherosclerosis and multiple sclerosis.

The new compounds may also be used to treat diseases or conditions in which the passage of cells from the blood through the vascular endothelium into tissue is of importance (such as metastasis) or diseases and conditions in which the combination of LTB₄ or another molecule (for example 12-HETE) with the LTB₄-receptor influences cell proliferation (such as chronic myelocytic leukaemia).

The new compounds may also be used in conjunction with other active substances, e.g. those which are used for the same indications or, for example, with antiallergics, secretolytics, β_2 -adrenergics, steroids administered by inhalation, antihistamines and/or PAF-antagonists. The substances may be administered topically, orally, transdermally, nasally, parenterally or by inhalation.

The new compounds are characterised by being well tolerated and having good bioavailability.

The therapeutic or prophylactic dose depends not only on the potency on the individual compounds and the body weight of the patient, but also on the nature and gravity of the condition. For oral use the dose is between 10 and 500 mg, preferably

between 20 and 250 mg. For inhalation a dosage of between 0.5 and 25, preferably between 2 and 20 mg of active substance is delivered to the patient. Inhalation solutions generally contain between about 0.5 and 5% of active substance. The new compounds may be administered, e.g. as plain or coated tablets, capsules, lozenges, powders, granules, solutions, emulsions, syrups, inhalation aerosols, ointments or suppositories.

Pharmacological and biochemical investigation of the activity may be carried out using tests as described for example in WO 93/16036, Pages 15 to 17.

Examples of formulations

1. Tablets

Composition:

Active substance according

to the invention 20 parts by weight

Stearic acid 6 parts by weight

Glucose 474 parts by weight

The ingredients are processed in the usual way to form tablets weighing 500 mg. If desired, the content of active substance increased or reduced and the quantity of glucose increased or reduced accordingly.

2. Suppositories

Compositions:

Active substance according

to the invention 100 parts by weight

Powdered lactose 45 parts by weight

Cocoa butter 1555 parts by weight

The ingredients are processed in the usual way to form suppositories weighing 1.7 g.

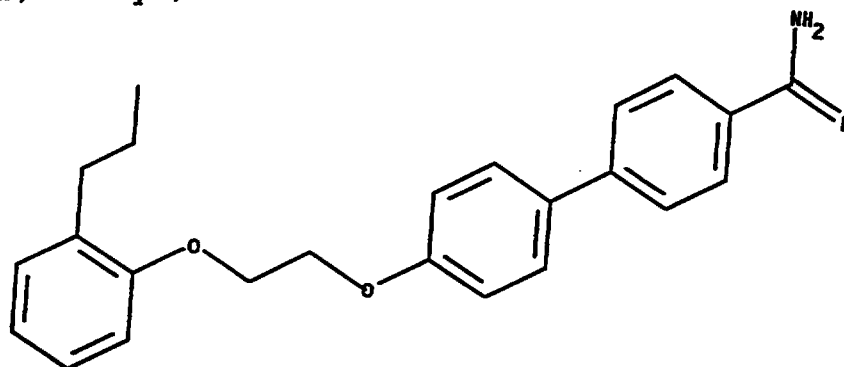
3. Inhalation powder

Micronised powdered active substance (Compound of formula 1; particle size of about 0.5 to 7 μm) is packed into hard gelatine capsules in a quantity of 5 mg, optionally with the addition of micronised lactose. The powder is inhaled from conventional inhalers, e.g. according to DE-A 33 45 722.

The following Examples provide a guide to the preparation of the new compounds.

Example 1

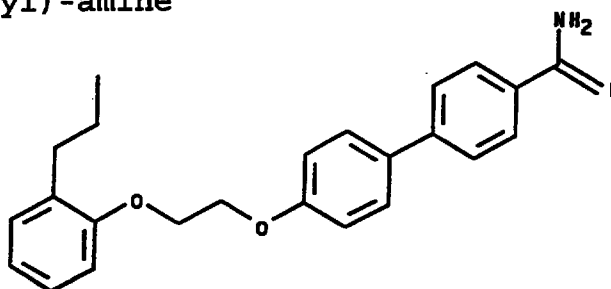
(Methoxycarbonyl-imino-(4'-[2-(2-propylphenoxy)-ethoxy]-biphenyl-4-yl)-methyl)-amine



3.8 g of the amidine compound of the above formula (R equals NH), which may be obtained by conventional methods, e.g. using the method according to WO 93/16036, are suspended in 200 ml of chloroform. 1.6 ml of triethylamine are added and 0.8 ml of methyl chloroformate are added dropwise at ambient temperature. After the components have dissolved the mixture is stirred for 3 hours, then extracted three times with water, evaporated down and the residue is stirred with ether and suction filtered. Yield of compound of the above formula wherein R equals NCOOCH₃ : 3.7 g, melting point 170-176°C

Example 2

(Benzyloxycarbonyl-imino-{4'-[2-(2-propylphenoxy)-ethoxy]-biphenyl-4-yl}methyl)-amine



2.6 g of the amidine compound of the above formula (R = NH) are placed in 200 ml of chloroform. 1.3 ml of triethylamine

are added and 1 ml of benzylchloroformate is added dropwise at ambient temperature. After the components have dissolved, the mixture is stirred for 3 hours, then extracted three times with water, evaporated down and the residue is stirred with ether and suction filtered. The substance is recrystallised from ethanol. Yield of the compound of the above formula wherein $R = \text{NCOOCH}_2\text{Ph}$: 2.2 g, Mp. 128-131°C.

Compounds with other groups R prepared in an analogous way:

$R = \text{NCOOC}_2\text{H}_5$; Mp. 120 - 123°C

$R = \text{NCOO-n-C}_3\text{H}_7$; Mp. 113 - 114°C

$R = \text{NCOO-i-C}_3\text{H}_7$; Mp. 110 - 117°C

$R = \text{NCOO-n-C}_4\text{H}_9$; Mp. 135 - 138°C

$R = \text{NCOO-i-C}_4\text{H}_9$; Mp. 103°C

$R = \text{NCOO-t-C}_4\text{H}_9$; Mp. 129 - 132°C

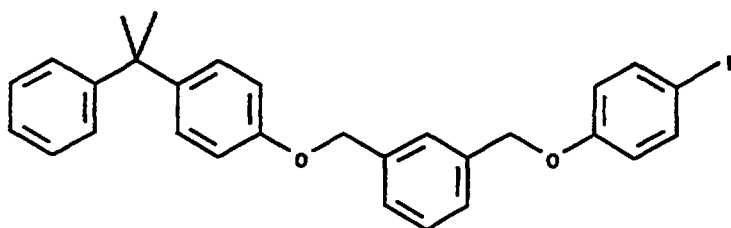
$R = \text{NCOO-n-C}_6\text{H}_{13}$; Mp. 117 - 121°C

Example 3

3.5 g of the amidine compound of the above formula ($R = \text{NH}$) are placed in 150 ml of chloroform. 2 ml of triethylamine are added and 1 ml of di-tert.-butyldicarbonate is added dropwise at ambient temperature. After the components have dissolved, the mixture is stirred for 3 hours, then extracted three times with water, evaporated down and the residue is stirred with ether and suction filtered. The substance is recrystallised from 20 ml of ethanol. Yield of the compound of the above formula wherein $R = \text{N-COO-t-butyl}$: 3 g, Mp. 129-132°C.

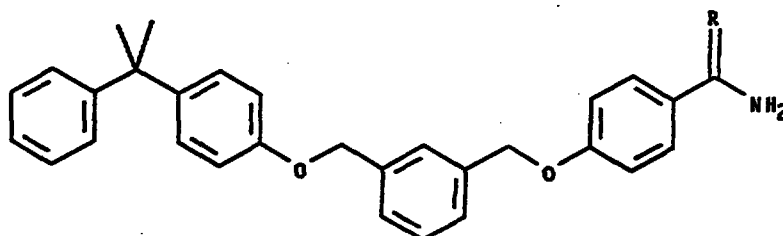
Example 4

(a) [Hydroxy-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]benzyloxy}phenyl)-methyl]-amine



5.25 g of nitrile of the above formula ($R = \text{CN}$, prepared by conventional methods) are placed in 60 ml of ethanol and heated to boiling. In the course of 30 minutes, a solution of 2.7 g of sodium carbonate and 3.4 g of hydroxylamine hydrochloride in 10 ml of water is added dropwise. The mixture is then refluxed for 5 hours. After cooling, the mixture is evaporated down, the residue is taken up in 50 ml of water and extracted three times with 40 ml of ethyl acetate. The organic phases are dried over MgSO_4 , filtered and concentrated by evaporation. The crystals are taken up in 20 ml of acetone and acidified with ethereal hydrochloric acid. After brief dissolution, 5.3 g of the hydrochloride of the amidoxime of the above formula are obtained wherein $R = \text{C}(\text{NOH})-\text{NH}_2$. Mp. $180-181^\circ\text{C}$.

(b) [Imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]methyl}-benzyloxy)phenyl)-methyl]-amine



5.1 g of the amidoxime of the above formula ($R = \text{NOH}$) are dissolved in 120 ml of methanol and hydrogenated in the presence of 10 g of methanol-moistened Raney nickel for 2 hours under normal pressure and at ambient temperature. The

nickel is removed by suction filtration and the solution is filtered over silica gel. The filtrate is acidified with ethanolic hydrochloric acid, the solution is evaporated down and recrystallised from ethanol. The yield is 3.3 g of the amidine compound (in the above formula, R = NH). Mp. 160°C.

(c) [Ethoxycarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]benzyloxy}phenyl)-methyl]-amine

2.44 g of the amidine compound of the above formula (R = NH) obtained according to (b) are placed in 150 ml of dichloromethane, 0.6 g of ethylchloroformate are added, then at ambient temperature 52.5 ml of 0.2 N sodium hydroxide solution are added dropwise over 15 minutes. The solution obtained is stirred for 2 hours at ambient temperature, then the organic phase is separated, extracted with 100 ml of water and dried over sodium sulphate. The solution is evaporated down and the residue is recrystallised from 10 ml of ethanol. 2.1 g of title compound are obtained (R = NCOOC₂H₅), Mp. 99°C.

The following compounds of the formula given in Example 4(b), for example, may be obtained analogously:

R = NCOO-(-)-menthyl; Mp. 113°C

R = NCO-C₆H₅; Mp. 101 - 103°C

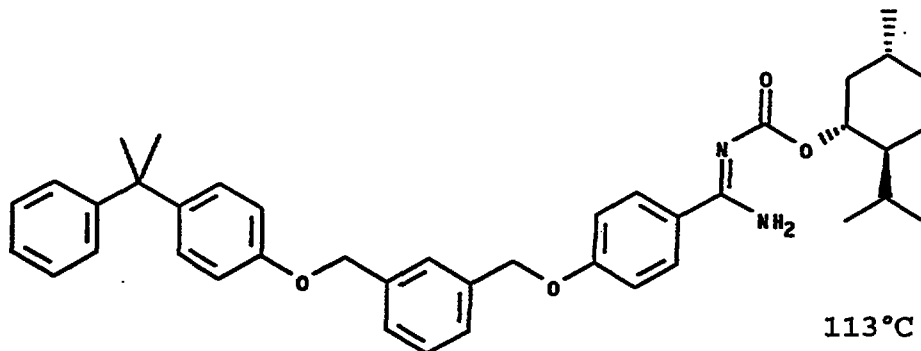
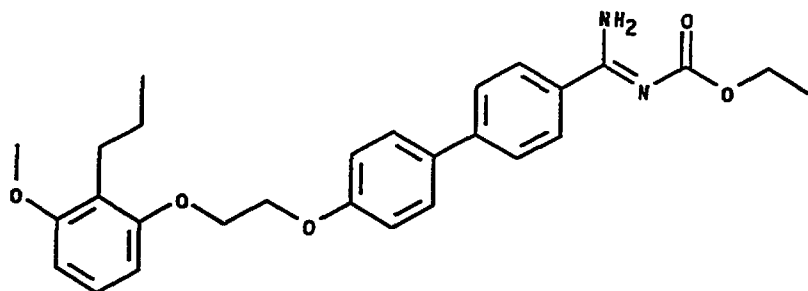
Example 5

[3'-Pyridylcarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]benzyloxy}phenyl)-methyl]-amine

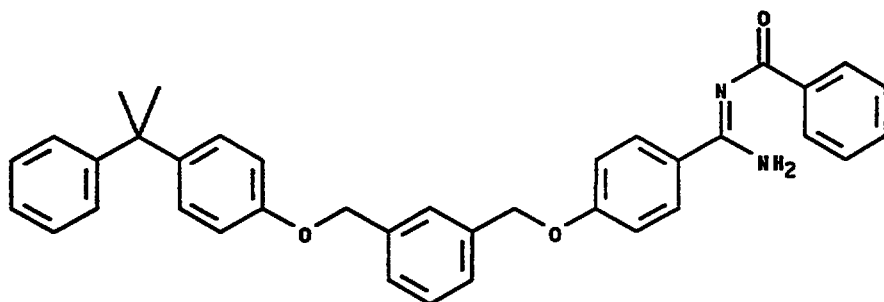
5.0 g of the amidine compound of the above formula (R = NH, cf. Example 4(b)) are placed in 250 ml of dichloromethane. Over 10 minutes, at ambient temperature, a solution of 3.9 g of nicotinic acid chloride hydrochloride and 16.3 ml of triethylamine in 50 ml of dichloromethane is added dropwise. After 15 hours at ambient temperature the mixture is extracted twice with 300 ml of water, the organic phase is dried over

sodium sulphate, filtered and the filtrate is evaporated down. The residue is purified by low-pressure chromatography over silica gel 60 using ethyl acetate, the product is dissolved in 50 ml of acetone, acidified with ethanolic hydrochloric acid and precipitated with ether as its hydrochloride. The yield is 2.0 g of the nicotinoyl derivative of the above formula wherein R = N-CO-3-pyridyl, Mp. 172°C.

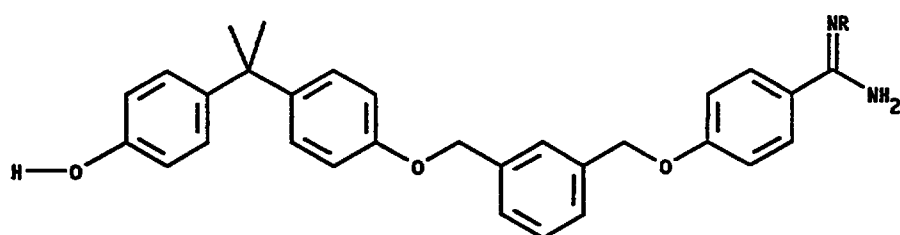
The following compounds may also be prepared, inter alia, analogously with the Examples:



(-)-Menthylester

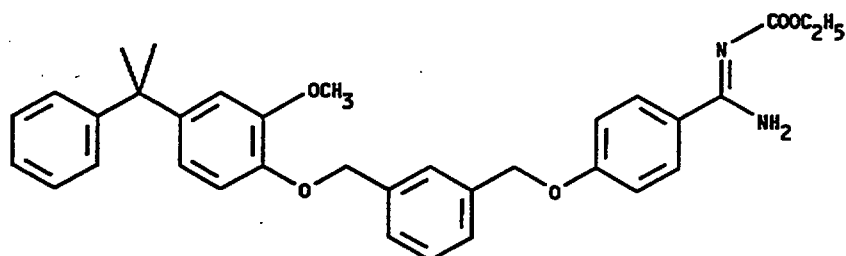


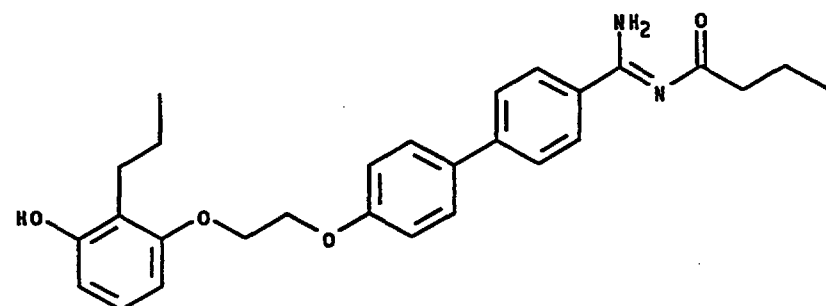
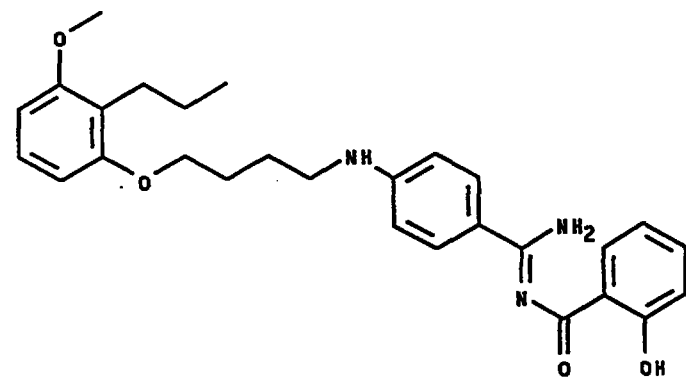
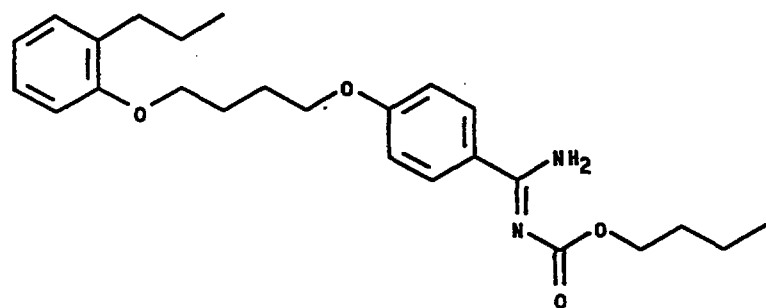
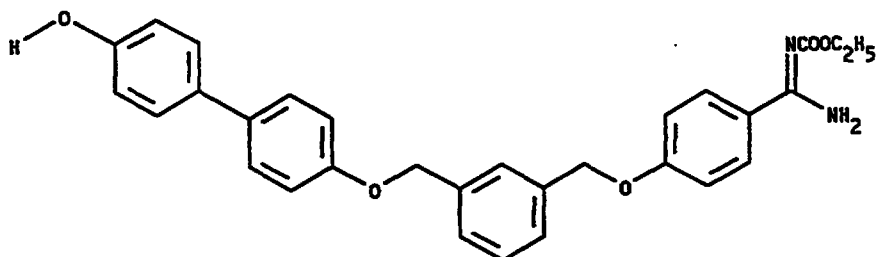
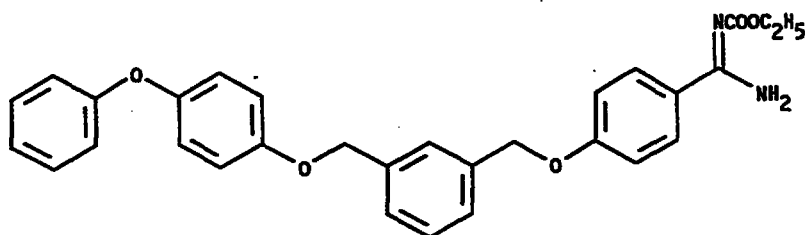
101-103°C

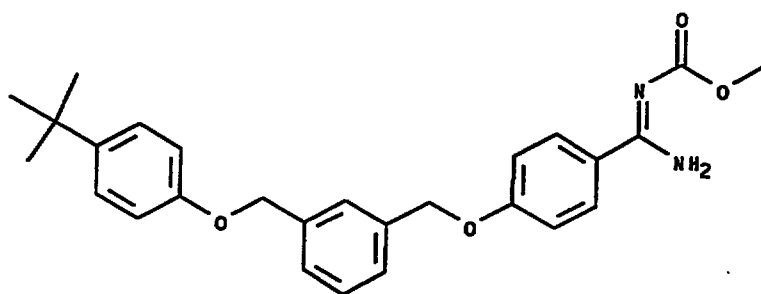
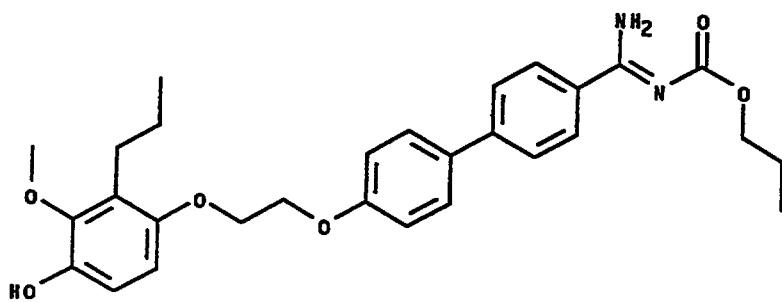
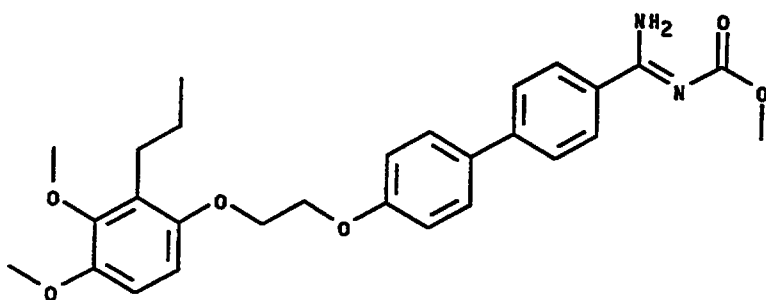
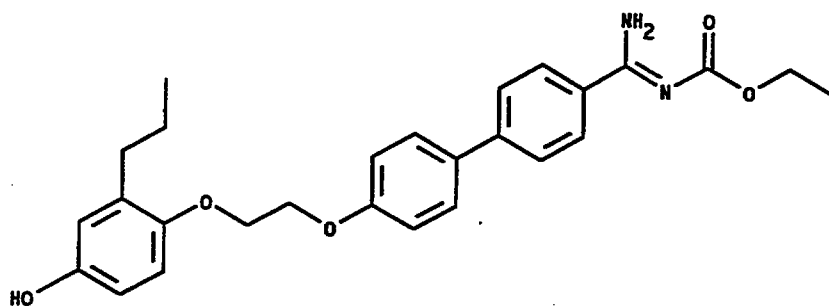
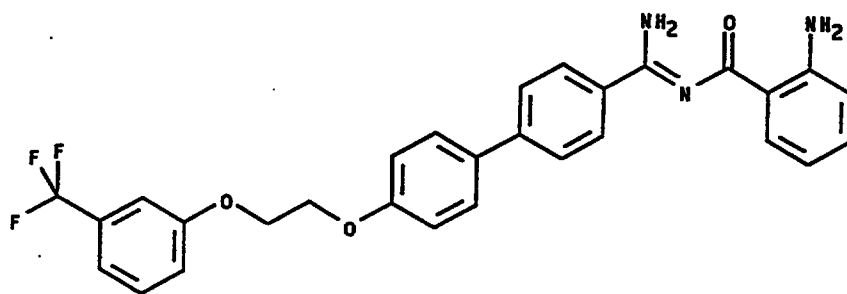


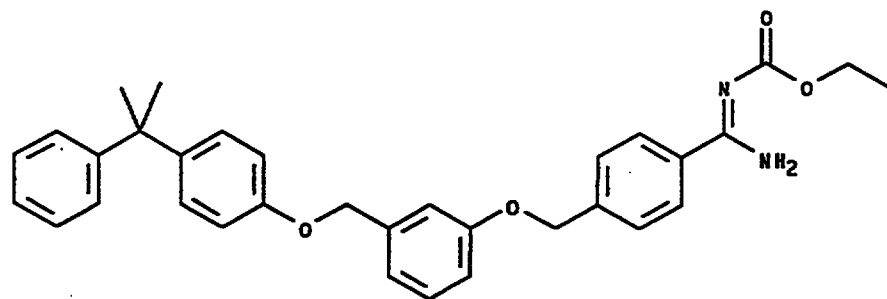
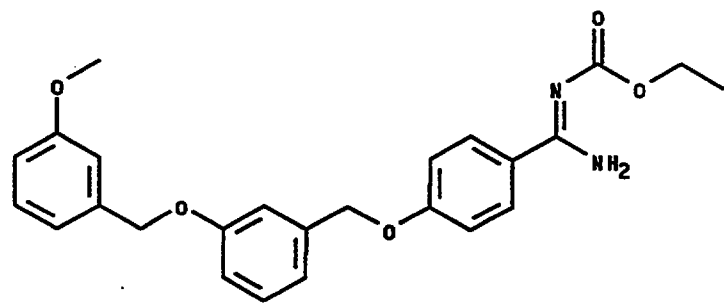
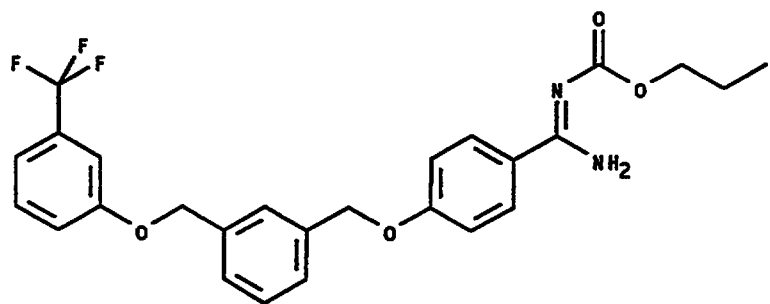
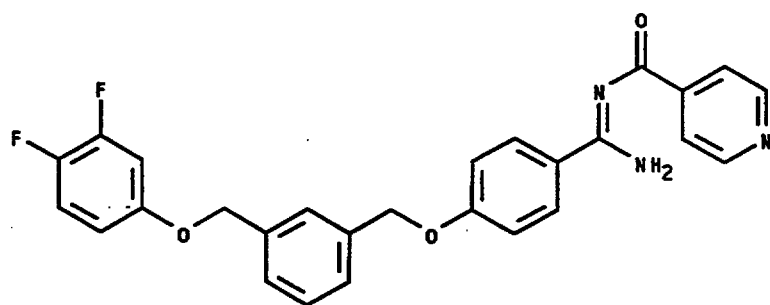
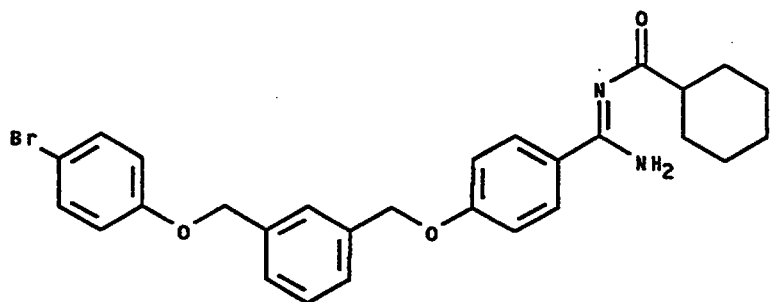
R = OH Mp. 181°C

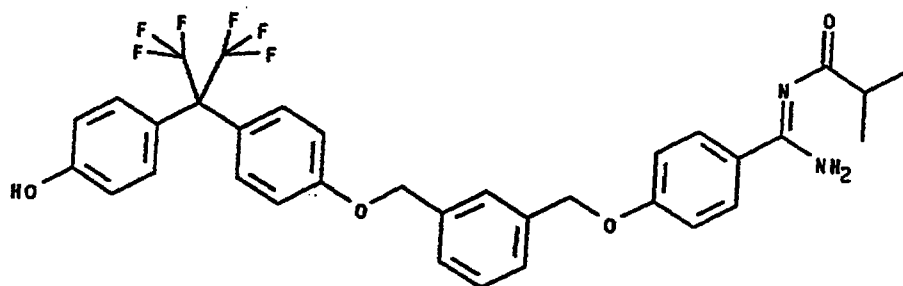
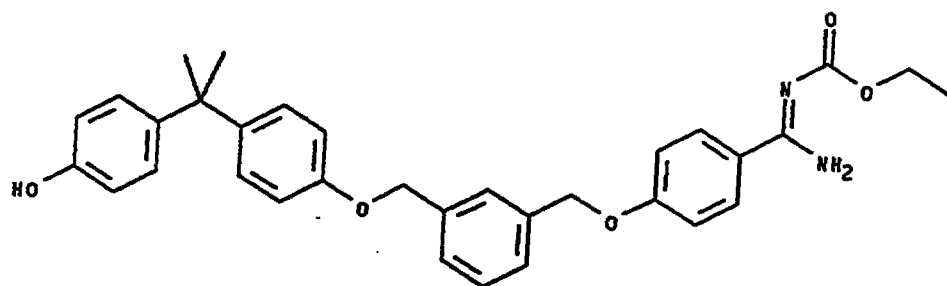
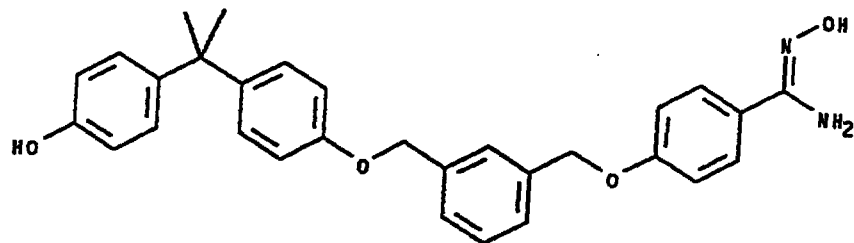
R = COOC₂H₅ Mp. 131°C (with 1 mol of ethanol)













THIS SHEET HAS BEEN
REPLACED

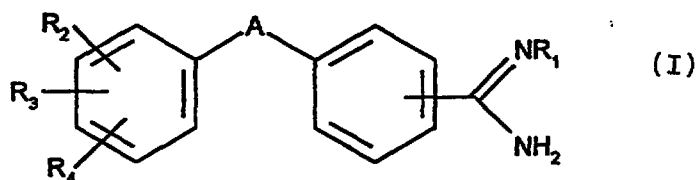
- 21 -

Claims

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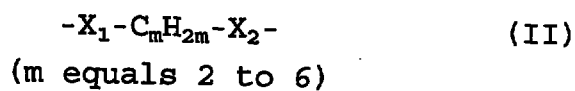


1. Substituted benzamidines of formula

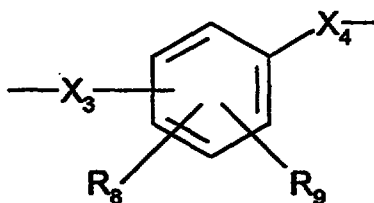


wherein

A denotes the group

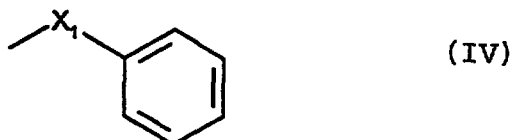


or



X₁ denotes O, NH or NCH₃

X₂ denotes O, NH, NCH₃ or



X₃ denotes -X-C_nH_{2n}-;

X₄ denotes -C_nH_{2n}-X- (n = 1 or 2, X = O, NH or NCH₃);



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- R_1 denotes OH, CN, COR_{12} , $COOR_{12}$ or CHO;
- R_2 denotes Br, Cl, F, CF_3 , OH, C_1 - C_6 -alkyl, C_5 - C_7 -cycloalkyl, aryl, O-aryl, CH_2 -aryl, CR_5R_6 -aryl, $C(CH_3)_2-R_7$; and also H, when A is a group of Formula III or when X_2 is a group of Formula IV; and also C_1 - C_6 -alkoxy, when A is the group II, X_1 is as hereinbefore defined and X_2 denotes NH, NCH_3 or the group IV, or when A denotes the group III, X_3 is as hereinbefore defined and in X_4 X denotes NH or NCH_3 ;
- R_3 denotes H, C_1 - C_6 -alkyl, OH, Cl, F, and also C_1 - C_6 alkoxy when R_2 denotes aryl, O-aryl, CH_2 -aryl, CR_5R_6 -aryl or $C(CH_3)_2-R_7$ or when X_2 denotes the group IV;
- R_2 and R_3 may also together denote a fused aromatic or heteroaromatic ring;
- R_4 denotes H or C_1 - C_6 -alkyl;
- R_5 denotes C_1 - C_4 -alkyl, CF_3 , CH_2OH , COOH or $COO(C_1-C_4\text{-alkyl})$;
- R_6 denotes H, C_1 - C_4 -alkyl, or CF_3 ;
- R_5 and R_6 together may also form a C_4 - C_6 -alkylene group;
- R_7 denotes CH_2OH , COOH, $COO(C_1-C_4\text{-alkyl})$, $CONR_{10}R_{11}$ or $CH_2NR_{10}R_{11}$;
- R_8 , R_9 denote H, Br, Cl, F, OH, C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy;
- R_{10} denotes H, C_1 - C_6 -alkyl, phenyl, phenyl- $(C_1-C_6\text{-alkyl})$, COR_{12} , $COOR_{12}$, CHO, $CONH_2$, $CONHR_{12}$, $SO_2-(C_1-C_6\text{-alkyl})$, SO_2 -phenyl, wherein the phenyl group may be mono- or polysubstituted by Cl, F, CF_3 , C_1 - C_4 -alkyl, OH and/or C_1 - C_4 -alkoxy;
- R_{11} denotes H or C_1 - C_6 -alkyl;



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R₁₀ and R₁₁ together may also denote a C₄-C₆-alkylene group;

R₁₂ denotes C₁-C₆-alkyl, C₅-C₇-cycloalkyl, aryl, heteroaryl, aralkyl or heteroaryl-(C₁-C₆-alkyl), wherein the aryl or heteroaryl group may be mono or polysubstituted by Cl, F, CF₃, C₁-C₄-alkyl, OH or C₁-C₄-alkoxy.

"and enantiomeric forms thereof, diastereomeric forms thereof, tautomeric forms thereof, mixtures thereof including racemic mixtures, and acid addition salts thereof.

2. Compounds as defined in claim 1, wherein aryl denotes phenyl or mono- or polysubstituted phenyl and heteroaryl denotes pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl or furyl.

3. Compounds as defined in claim 1 or 2, wherein

A, m, n, X₃, X₄ and R₁ are as hereinbefore defined;

X₁ denotes O;

X₂ denotes O or a group IV (wherein X₁ equals O);

R₂ denotes Cl, F, CF₃, OH, C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl or CR₅R₆-aryl, and,

if R₂ is the group IV, R₂ may also represent C₁-C₆-alkoxy;

R₃ denotes H, C₁-C₆-alkyl or OH, and,

if R₂ is CR₅R₆-aryl, R₃ may also denote C₁-C₆-alkoxy;

R₄ denotes H;

R₅ denotes C₁-C₃-alkyl, CF₃ or CH₂OH;

R₆ denotes H, C₁-C₃-alkyl or CF₃,

R₅ and R₆ together may also denote C₄-C₅-alkylene;

R₈ and R₉ denote H, F or OH.

4. Compounds as defined in claim 1 or 2 wherein

X₁ denotes O;

X₂ represents the group IV (wherein X₁ equals O);

X denotes O;

R₁ denotes COOR₁₂;

R₂ denotes C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl or CR₅R₆-aryl;



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R_3 denotes H, OH or C_1-C_6 -alkyl and, if R_2 is CR_5R_6 -aryl, R_3 may also denote C_1-C_6 alkoxy;

R_4 denotes H;

R_5 and R_6 denote C_1-C_3 -alkyl or CF_3 ;

R_8 and R_9 denote H;

R_{12} denotes C_1-C_6 -alkyl, aralkyl or C_7-C_5 -cycloalkyl.

5. (Methoxycarbonyl-imino-{4'-[2-(2-propylphenoxy)-ethoxy]-biphenyl-4-yl}-methyl)-amine and the acid addition salts thereof.

6. (Benzyloxycarbonyl-imino-{4'-[2-(2-propylphenoxy)-ethoxy]-biphenyl-4-yl}-methyl)-amine and the acid addition salts thereof.

7. [Hydroxy-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzoyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

8. [Ethoxycarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzoyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

9. [3'-Pyridylcarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

10. Pharmaceutical preparations comprising a compound as defined in any one of claims 1 to 9 in association with pharmacologically acceptable diluents excipients and/or carriers.

11. Use of compounds as defined in any one of claims 1 to 9 in the preparation of pharmaceutical compositions for the treatment of illnesses in which LBT_4 -antagonists can be used therapeutically.

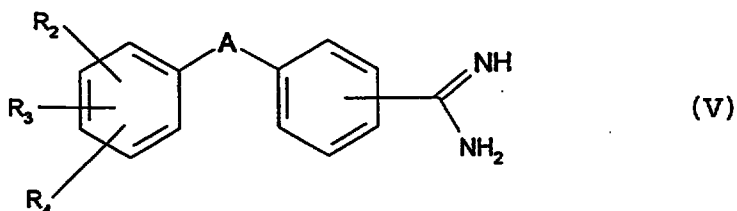


- 25 -

12. Use of compounds as defined in any one of claims 1 to 9 in the treatment of diseases in which inflammatory and/or allergic processes play a part, especially arthritis, asthma, chronic obstructive lung diseases, psoriasis, ulcerative colitis, Alzheimer's disease, shock, atherosclerosis, multiple sclerosis, and for the treatment of gastropathy induced by non-steroidal antiphlogistics and in metastasis and chronic myelocytic leukaemia.

13. A process for preparing the compounds as defined in any one of claims 1 to 9, characterised in that

a.) an amidine of the formula



is reacted with a compound of formula



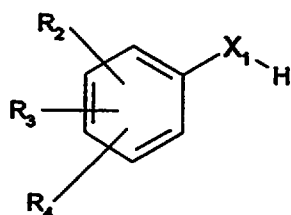
wherein in (V) A, R₂, R₃ and R₄ are as hereinbefore defined, R'₁ has the same meaning as R₁, with the exception of OH, and L denotes a nucleophilically exchangeable group such as a halogen atom (e.g. Cl, Br) or acyloxy,

or

b.) a compound of formula

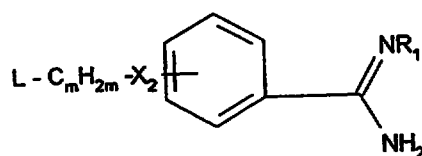


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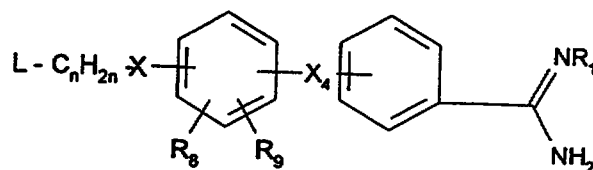
(VII)

(wherein R_2 , R_3 , R_4 and X_1 are as hereinbefore defined) is reacted with a benzamidine derivative of the formula



(VIII)

or

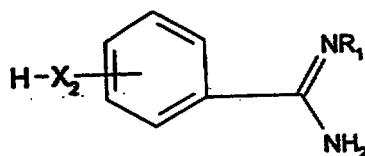


(IX)

(wherein L , m , n , X , X_2 , X_4 , R_1 , R_8 and R_9 are as hereinbefore defined),

or

c.) a compound of formula

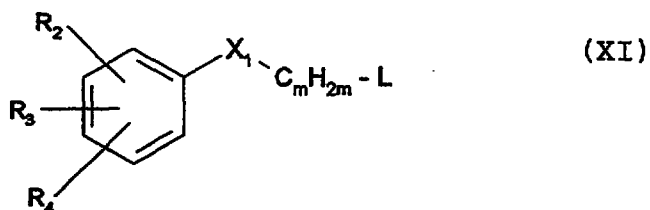


(X)

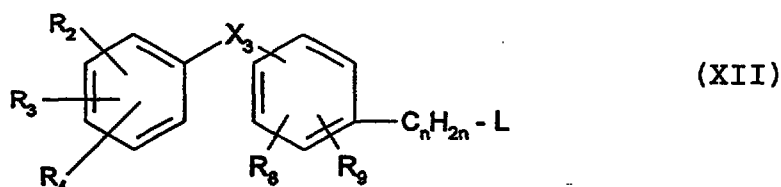


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(wherein R_1 and X_2 are as hereinbefore defined) is reacted with a compound of formula



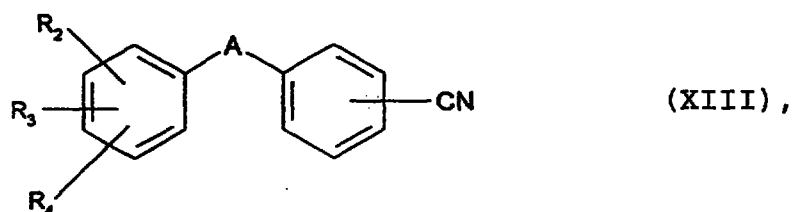
or



(wherein L , m , n , R_2 , R_3 , R_4 , R_8 , R_9 , X_1 and X_3 are as hereinbefore defined),

or

d.) in order to prepare compounds of formula I wherein R_1 denotes OH, a nitrile of formula

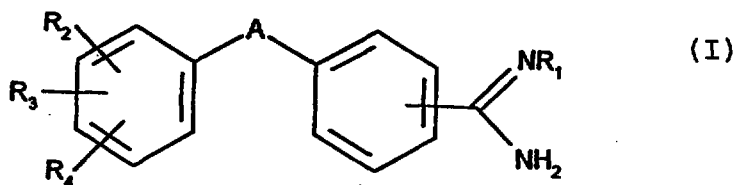


wherein A , R_2 , R_3 and R_4 are as hereinbefore defined, is reacted with hydroxylamine

and from the resulting products, depending on their nature, optical isomers or diastereomeric pairs of isomers or mixtures thereof may be prepared or, if bases are obtained, acid addition salts may be prepared and if acid addition salts are obtained initially, free bases may be obtained or, tautomeric forms may be prepared and/or separated.

Abstract

The new compounds of formula

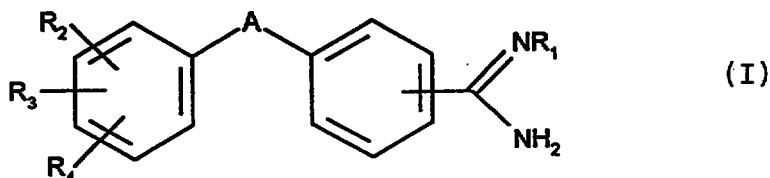


(the definition of A and R_1 to R_4 is given in the specification) may be prepared by conventional methods and may be used therapeutically, inter alia, as LTB_4 -antagonists.



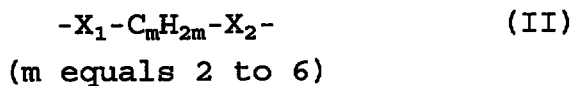
Claims

1. New substituted benzamidines of formula

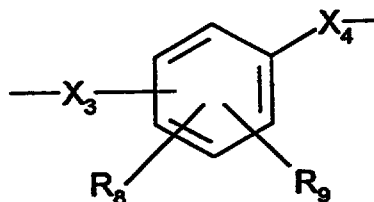


wherein

A denotes the group



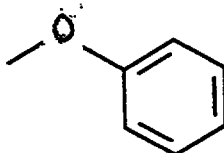
or



(III);

X₁ denotes O, NH or NCH₃

X₂ denotes O, NH, NCH₃ or



(IV)

X₃ denotes -X-C_nH_{2n}-;

X₄ denotes -C_nH_{2n}-X- (n = 1 or 2, X = O, NH or NCH₃);



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- R_1 denotes OH, CN, COR_{12} , $COOR_{12}$ or CHO;
- R_2 denotes Br, Cl, F, CF_3 , OH, C_1 - C_6 -alkyl, C_5 - C_7 -cycloalkyl, aryl, O-aryl, CH_2 -aryl, CR_5R_6 -aryl, $C(CH_3)_2-R_7$; and also H, when A is a group of Formula III or when X_2 is a group of Formula IV; and also C_1 - C_6 -alkoxy, when A is the group II, X_1 and m are as hereinbefore defined and X_2 denotes NH, NCH_3 or the group IV, or when A denotes the group III, X_3 is as hereinbefore defined and in X_4 X denotes NH or NCH_3 ;
- R_3 denotes H, C_1 - C_6 -alkyl, OH, Cl, F, and also C_1 - C_6 alkoxy when R_2 denotes aryl, O-aryl, CH_2 -aryl, CR_5R_6 -aryl or $C(CH_3)_2-R_7$ or when X_2 denotes the group IV;
- R_2 and R_3 may also together denote a fused aromatic or heteroaromatic ring;
- R_4 denotes H or C_1 - C_6 -alkyl;
- R_5 denotes C_1 - C_4 -alkyl, CF_3 , CH_2OH , COOH or $COO(C_1-C_4\text{-alkyl})$;
- R_6 denotes H, C_1 - C_4 -alkyl, or CF_3 ;
- R_5 and R_6 together may also form a C_4 - C_6 -alkylene group;
- R_7 denotes CH_2OH , COOH, $COO(C_1-C_4\text{-alkyl})$, $CONR_{10}R_{11}$ or $CH_2NR_{10}R_{11}$;
- R_8 , R_9 denote H, Br, Cl, F, OH, C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy;
- R_{10} denotes H, C_1 - C_6 -alkyl, phenyl, phenyl- $(C_1-C_6\text{-alkyl})$, COR_{12} , $COOR_{12}$, CHO, $CONH_2$, $CONHR_{12}$, $SO_2-(C_1-C_6\text{-alkyl})$, SO_2 -phenyl, wherein the phenyl group may be mono- or polysubstituted by Cl, F, CF_3 , C_1 - C_4 -alkyl, OH and/or C_1 - C_4 -alkoxy;
- R_{11} denotes H or C_1 - C_6 -alkyl;



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R_{10} and R_{11} together may also denote a C_4 - C_6 -alkylene group;

R_{12} denotes C_1 - C_6 -alkyl, C_5 - C_7 -cycloalkyl, aryl, heteroaryl, aralkyl or heteroaryl- $(C_1$ - C_6 -alkyl), wherein the aryl or heteroaryl group may be mono or polysubstituted by Cl, F, CF_3 , C_1 - C_4 -alkyl, OH or C_1 - C_4 -alkoxy,

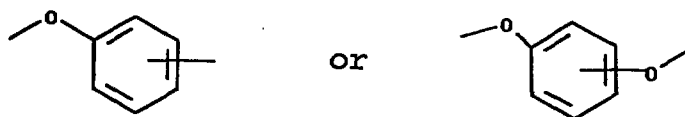
with the proviso that if

A denotes a group $-X_1-C_mH_{2m}-X_2-$

wherein m represents an integer 2, 3, or 4; and

X_1 denotes O, NH;

X_2 denotes O, NH or



and

R_2 denotes hydrogen, Br, Cl, CF_3 , C_1 - C_6 -alkyl, phenyl;

R_3 denotes hydrogen, C_1 - C_6 -alkyl, hydroxy, Cl, F, C_1 - C_6 -alkoxy;

R_4 denotes hydrogen, C_1 - C_6 -alkyl;

R_1 must not denote hydroxy.

2. Compounds as defined in claim 1, wherein aryl denotes phenyl or mono- or polysubstituted phenyl and heteroaryl denotes pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl or furyl.



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3. Compounds as defined in claim 1 or 2, wherein
A, m, n, X₃, X₄ and R₁ are as hereinbefore defined;

X₁ denotes O;

X₂ denotes O or a group IV (wherein X₁ equals O);

R₂ denotes Cl, F, CF₃, OH, C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl
or CR₅R₆-aryl, and,

if R₂ is the group IV, R₂ may also represent C₁-C₆-alkoxy;

R₃ denotes H, C₁-C₆-alkyl or OH, and,

if R₂ is CR₅R₆-aryl, R₃ may also denote C₁-C₆-alkoxy;

R₄ denotes H;

R₅ denotes C₁-C₃-alkyl, CF₃ or CH₂OH;

R₆ denotes H, C₁-C₃-alkyl or CF₃,

R₅ and R₆ together may also denote C₄-C₅-alkylene;

R₈ and R₉ denote H, F or OH.

4. Compounds as defined in claim 1 or 2 wherein

X₁ denotes O;

X₂ represents the group IV (wherein X₁ equals O);

X denotes O;

R₁ denotes COOR₁₂;

R₂ denotes C₁-C₆-alkyl, aryl, O-aryl, CH₂-aryl or CR₅R₆-aryl;

R₃ denotes H, OH or C₁-C₆-alkyl and, if R₂ is CR₅R₆-aryl, R₃
may also denote C₁-C₆ alkoxy;

R₄ denotes H;

R₅ and R₆ denote C₁-C₃-alkyl or CF₃;

R₈ and R₉ denote H;

R₁₂ denotes C₁-C₆-alkyl, aralkyl or C₇-C₅-cycloalkyl.

5. (Methoxycarbonyl-imino-{4'-[2-(2-propylphenoxy)-ethoxy]-
biphenyl-4-yl}-methyl)-amine and the acid addition salts
thereof.

6. (Benzyloxycarbonyl-imino-{4'-[2-(2-propylphenoxy)-ethoxy]-
biphenyl-4-yl}-methyl)-amine and the acid addition salts
thereof.



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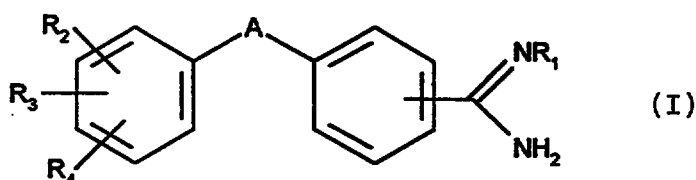
7. [Hydroxy-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzoyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

8. [Ethoxycarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzoyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

9. [3'-Pyridylcarbonyl-imino-(4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy-methyl]-benzyloxy}phenyl)-methyl]-amine and the acid addition salts thereof.

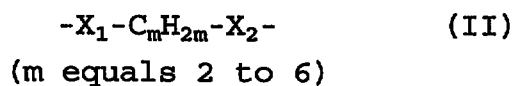
10. Pharmaceutical preparations characterised in that they contain a compound with conventional excipients and/or carriers, according to claims 1 to 9.

11. Use of compounds of formula

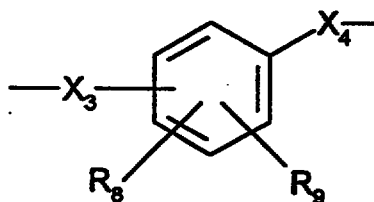


wherein

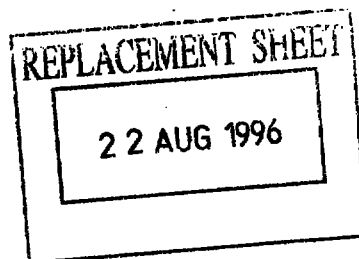
A denotes the group



or

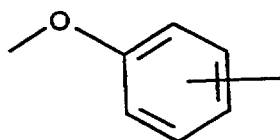


(III);



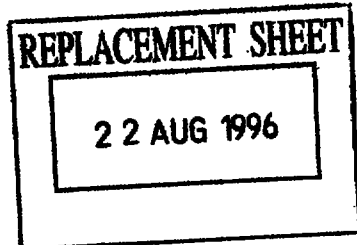
- 26 -

X₁ denotes O, NH or NCH₃
X₂ denotes O, NH, NCH₃ or



(IV)

- X₃ denotes -X-C_nH_{2n}-;
X₄ denotes -C_nH_{2n}-X- (n = 1 or 2, X = O, NH or NCH₃);
R₁ denotes OH, CN, COR₁₂, COOR₁₂ or CHO;
R₂ denotes Br, Cl, F, CF₃, OH, C₁-C₆-alkyl, C₅-C₇-cycloalkyl, aryl, O-aryl, CH₂-aryl, CR₅R₆-aryl, C(CH₃)₂-R₇;
and also H, when A is a group of Formula III or when X₂ is a group of Formula IV;
and also C₁-C₆-alkoxy, when A is the group II, X₁ and m are as hereinbefore defined and X₂ denotes NH, NCH₃ or the group IV,
or when A denotes the group III, X₃ is as hereinbefore defined and in X₄ X denotes NH or NCH₃;
- R₃ denotes H, C₁-C₆-alkyl, OH, Cl, F, and also C₁-C₆ alkoxy when R₂ denotes aryl, O-aryl, CH₂-aryl, CR₅R₆-aryl or C(CH₃)₂-R₇ or when X₂ denotes the group IV;
- R₂ and R₃ may also together denote a fused aromatic or heteroaromatic ring;
- R₄ denotes H or C₁-C₆-alkyl;



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R₅ denotes C₁-C₄-alkyl, CF₃, CH₂OH, COOH or COO(C₁-C₄-alkyl);

R₆ denotes H, C₁-C₄-alkyl, or CF₃;

R₅ and R₆ together may also form a C₄-C₆-alkylene group;

R₇ denotes CH₂OH, COOH, COO(C₁-C₄-alkyl), CONR₁₀R₁₁ or CH₂NR₁₀R₁₁;

R₈, R₉ denote H, Br, Cl, F, OH, C₁-C₆-alkyl or C₁-C₆-alkoxy;

R₁₀ denotes H, C₁-C₆-alkyl, phenyl, phenyl-(C₁-C₆-alkyl), COR₁₂, COOR₁₂, CHO, CONH₂, CONHR₁₂, SO₂-(C₁-C₆-alkyl), SO₂-phenyl, wherein the phenyl group may be mono- or polysubstituted by Cl, F, CF₃, C₁-C₄-alkyl, OH and/or C₁-C₄-alkoxy;

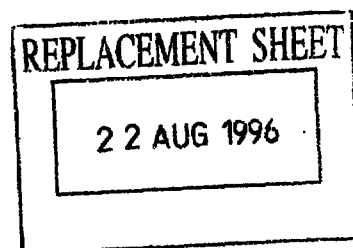
R₁₁ denotes H or C₁-C₆-alkyl;

R₁₀ and R₁₁ together may also denote a C₄-C₆-alkylene group;

R₁₂ denotes C₁-C₆-alkyl, C₅-C₇-cycloalkyl, aryl, heteroaryl, aralkyl or heteroaryl-(C₁-C₆-alkyl), wherein the aryl or heteroaryl group may be mono or polysubstituted by Cl, F, CF₃, C₁-C₄-alkyl, OH or C₁-C₄-alkoxy, in the preparation of pharmaceutical compositions for treating diseases in which LBT₄-antagonists can be used therapeutically.

12. Use of compounds as defined in claim 11 in the treatment of diseases in which inflammatory and/or allergic processes play a part, especially arthritis, asthma, chronic obstructive lung diseases, psoriasis, ulcerative colitis, Alzheimer's disease, shock, atherosclerosis, multiple sclerosis, and for the treatment of gastropathy induced by non-steroidal antiphlogistics and in metastasis and chronic myelocytic leukaemia.

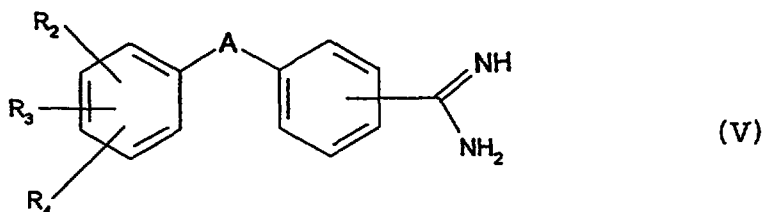
13. A process for preparing the compounds as defined in any



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one of claims 1 to 9, characterised in that

a.) an amidine of the formula



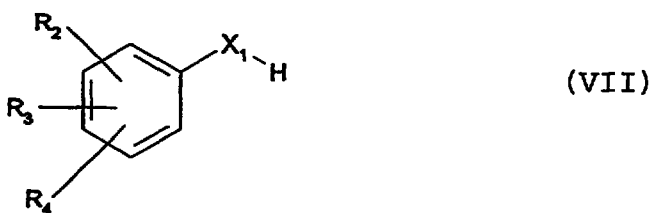
is reacted with a compound of formula



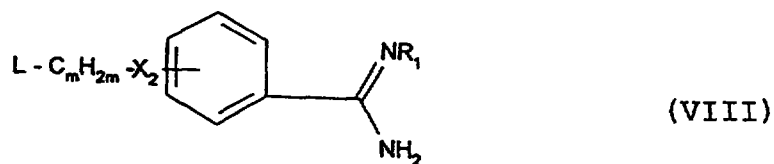
wherein in (V) A, R₂, R₃ and R₄ are as hereinbefore defined, R'₁ has the same meaning as R₁, with the exception of OH, and L denotes a nucleophilically exchangeable group such as a halogen atom (e.g. Cl, Br) or acyloxy,

or

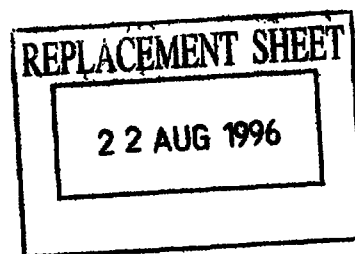
b.) a compound of formula



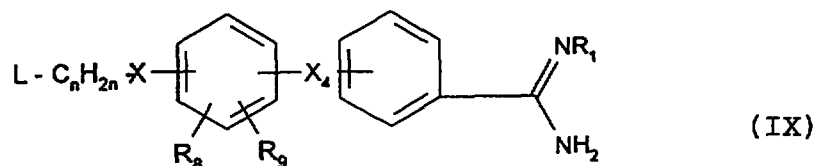
(wherein R₂, R₃, R₄ and X₁ are as hereinbefore defined) is reacted with a benzamidine derivative of the formula



or



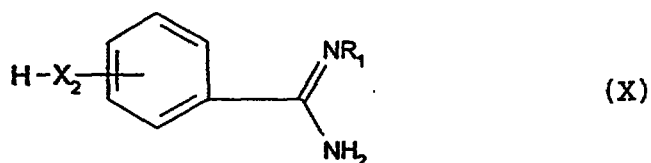
- 29 -



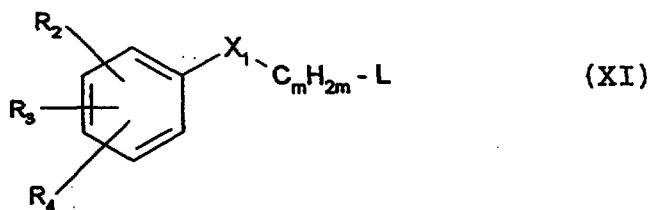
(wherein L, m, n, X, X₂, X₄, R₁, R₈ and R₉ are as hereinbefore defined),

or

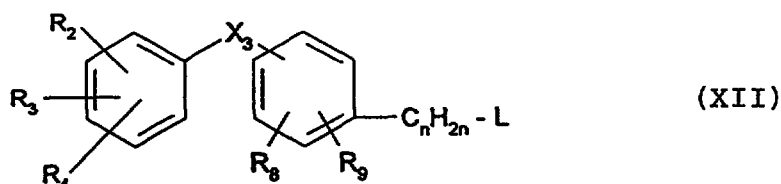
c.) a compound of formula



(wherein R₁ and X₂ are as hereinbefore defined) is reacted with a compound of formula

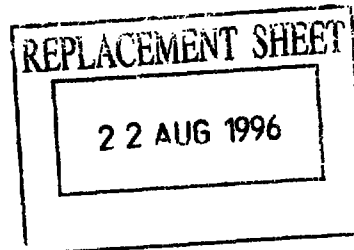


or



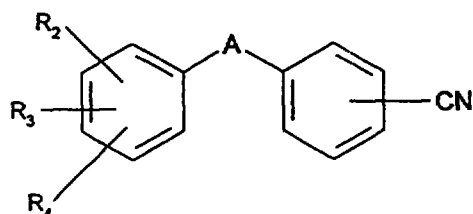
(wherein L, m, n, R₂, R₃, R₄, R₈, R₉, X₁ and X₃ are as hereinbefore defined),

or



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d.) in order to prepare compounds of formula I wherein R_1 denotes OH, a nitrile of formula



(XIII),

wherein A , R_2 , R_3 and R_4 are as hereinbefore defined, is reacted with hydroxylamine

and from the resulting products, depending on their nature, optical isomers or diastereomeric pairs of isomers may be prepared or, if bases are obtained, acid addition salts may be prepared and if acid addition salts are obtained initially, free bases may be obtained.