Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2234611 C 2006/08/01

(11)(21) 2 234 611

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1996/12/11
(87) Date publication PCT/PCT Publication Date: 1997/06/19
(45) Date de délivrance/Issue Date: 2006/08/01
(85) Entrée phase nationale/National Entry: 1998/04/14
(86) N° demande PCT/PCT Application No.: EP 1996/005529
(87) N° publication PCT/PCT Publication No.: 1997/021670
(30) Priorité/Priority: 1995/12/13 (DE195 46 452.4)

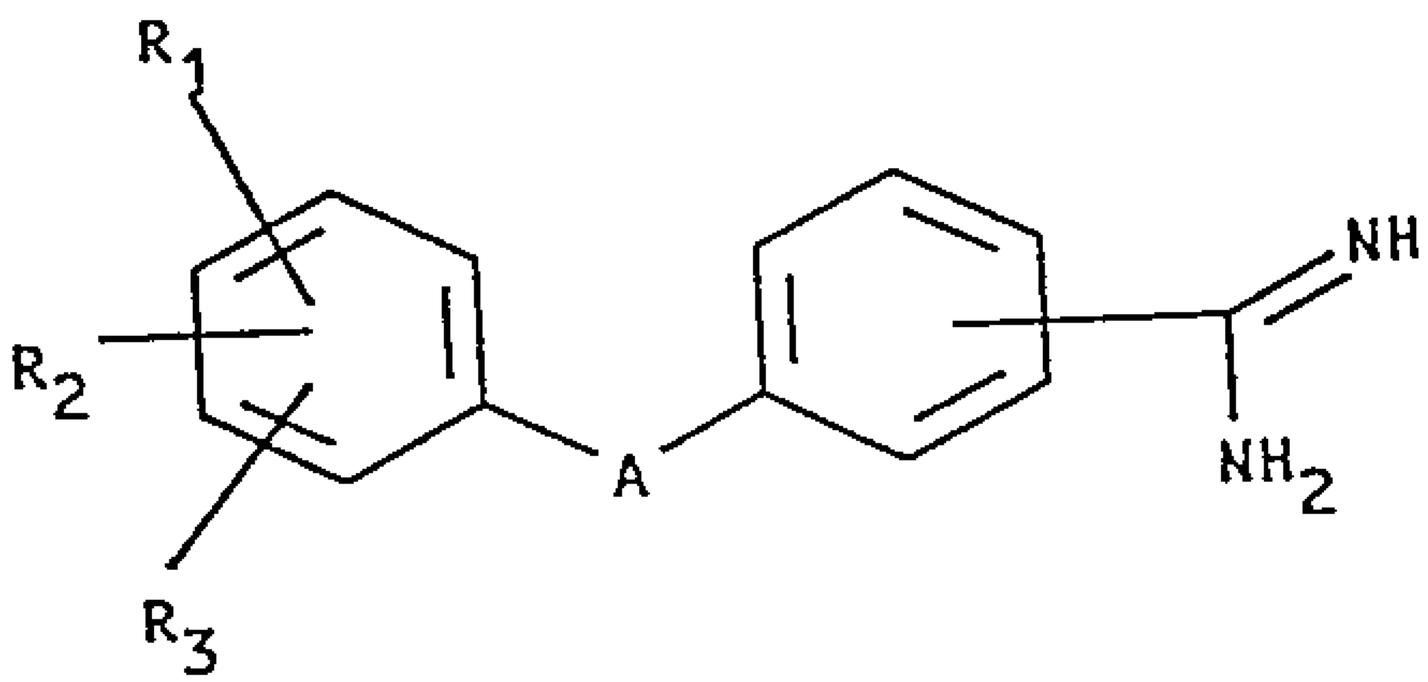
(51) Cl.Int./Int.Cl. *C07C 257/18* (2006.01), *A61K 31/155* (2006.01), *A61K 31/13* (2006.01), *A61K 31/16* (2006.01), *A61K 31/17* (2006.01), *A61K 31/395* (2006.01), *C07C 275/24* (2006.01), *C07C 311/08* (2006.01), *C07C 311/21* (2006.01), *C07D 295/185* (2006.01)

(72) Inventeurs/Inventors:
ANDERSKEWITZ, RALF, DE;
SCHROMM, KURT, DE;
RENTH, ERNST-OTTO, DE;
BIRKE, FRANZ, DE;
JENNEWEIN, HANS, DE;
...

(73) Propriétaire/Owner:

(54) Titre : NOUVEAUX DERIVES DE PHENYLAMIDINE, LEUR PROCEDE DE PREPARATION ET LEUR UTILISATION COMME COMPOSITIONS PHARMACEUTIQUES

(54) Title: NEW PHENYLAMIDINE DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USE AS PHARMACEUTICAL COMPOSITIONS



(I)

(57) Abrégé/Abstract:
The invention relates to new phenylamidine derivatives, processes for preparing them and their use as pharmaceutical compositions. The phenylamidines according to the invention correspond to the general formula I (see formula I).

CA 2234611 C 2006/08/01

(11)(21) 2 234 611

(13) C

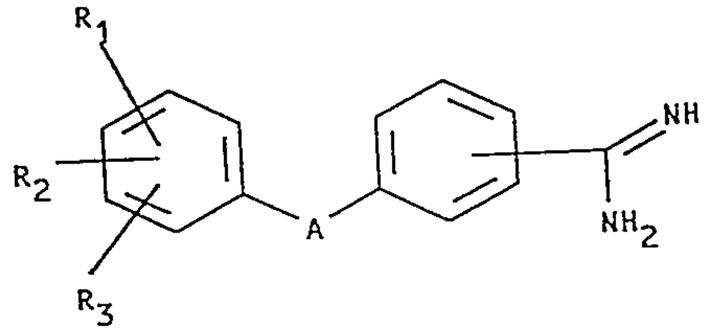
(72) **Inventeurs(suite)/Inventors(continued)**: MEADE, CHRISTOPHER JOHN MONTAGUE, DE; DING, ANDREAS, DE

(73) **Propriétaires(suite)/Owners(continued)**:BOEHRINGER INGELHEIM KG, DE

(74) **Agent**: FETHERSTONHAUGH & CO.

Abstract

The invention relates to new phenylamidine derivatives, processes for preparing them and their use as pharmaceutical compositions. The phenylamidines according to the invention correspond to the general formula I



CA 02234611 1998-04-14

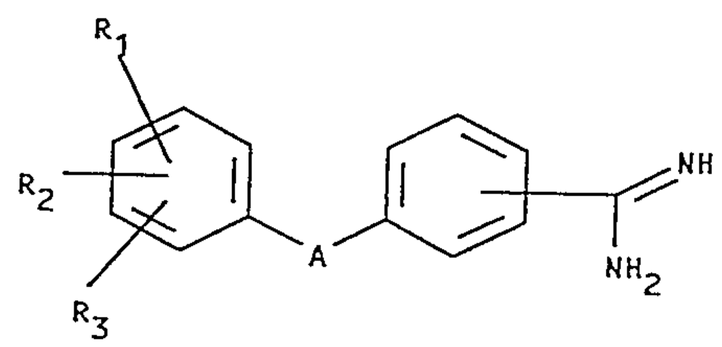
FILE, ~~PIN IN~~ THIS ~~AMENDED TEXT~~ TRANSLATION

S016645J.64

1/1012 - Foreign

New phenylamidine derivatives, processes for preparing them and their use as pharmaceutical compositions

The invention relates to new phenylamidine derivatives, processes for preparing them and their use as pharmaceutical compositions. The phenylamidines according to the invention correspond to the general formula I

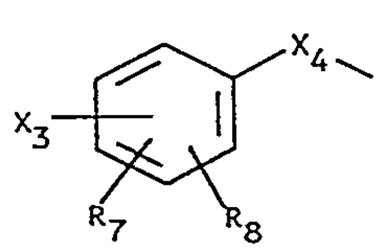


(I)

wherein

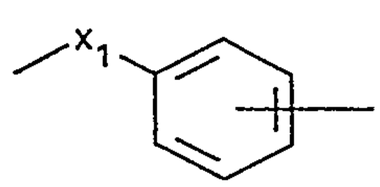
A denotes X_1-C_mH_{2m}-X_2-, in which m is an integer 2, 3, 4, 5 or 6

or



and

X_1 denotes O, NH or NCH_3;

X_2 denotes O, NH, NCH_3 or 

X_3 denotes X_1-C_nH_{2n} in which n is the integer 1 or 2;

X_4 denotes C_n-H_{2n}-X_1, wherein n is the integer 1 or 2;

R_1 denotes C_{5-7}-cycloalkyl, Ar_1, OAr_1, CH_2-Ar_2; $CR_4R_5Ar_3$, $C(CH_3)_2R_6$;

R_2 denotes H, C_{1-6}-alkyl, OH, halogen, O-(C_{1-6})-alkyl;

R_3 denotes H, C_{1-6}-alkyl;

R_4 denotes C_{1-4}-alkyl, CF_3, CH_2OH, COOH, $COO(C_{1-4})$-alkyl;

R_5 denotes H, C_{1-4}-alkyl, CF_3 and

R_4 and R_5 may also together form a C_{4-6}-alkylene group;

R_6 denotes CH_2OH, COOH, $COO(C_{1-4})$-alkyl, $CONR_9R_{10}$, $CH_2NR_9R_{10}$;

R_7 denotes H, halogen, OH, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R_8 denotes H, halogen, OH, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R_9 denotes H, C_{1-6}-alkyl, phenyl, phenyl-(C_{1-6}-alkyl), COR_{11}, $COOR_{11}$, CHO, $CONH_2$, $CONHR_{11}$, SO_2-(C_{1-6}-alkyl), SO_2-phenyl, wherein the phenyl ring may be mono- or polysubstituted by halogen, CF_3, C_{1-4}-alkyl, OH, C_{1-4}-alkoxy;

R_{10} denotes H or C_{1-6}-alkyl and

R_9 and R_{10} together may represent a C_{4-6}-alkylene group;

R_{11} denotes C_{1-6}-alkyl, C_{5-7}-cycloalkyl, aryl, heteroaryl, aralkyl or heteroaryl-(C_{1-6}-alkyl), wherein the aryl or heteroaryl groups may be mono-

or polysubstituted by Cl, F, CF_3, C_{1-4}-alkyl, OH or C_{1-4}-alkoxy;

Ar_1 denotes an optionally mono- or polysubstituted aryl group, with the exception of the unsubstituted phenyl group and the phenyl group which is monosubstituted by halogen, C_{1-4}-alkyl or monosubstituted by C_{1-4}-alkoxy;

Ar_2 denotes an optionally mono- or polysubstituted aryl group, with the exception of the unsubstituted phenyl group;

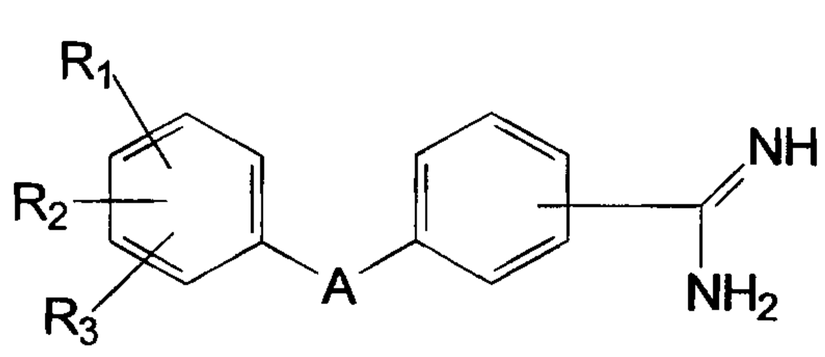
Ar_3 denotes an optionally mono- or polysubstituted aryl group

with the proviso that

R_1 cannot represent an unsubstituted phenyl group bound via a C_{1-4}-alkylene unit;

optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates and in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

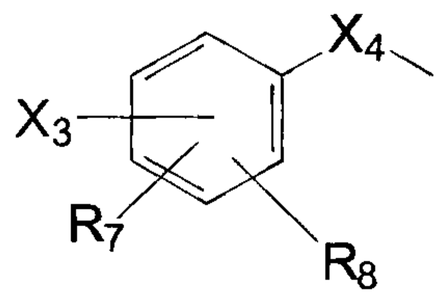
According to one aspect of the present invention, there is provided a compound of formula I



(I)

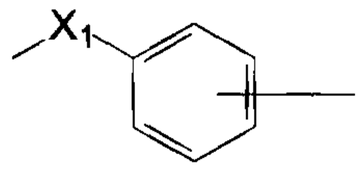
wherein

A is $-X_1-C_mH_{2m}-X_2-$, wherein m is 2, 3, 4, 5 or 6 or



wherein

X_1 is O;

X_2 is O or  ;

X_3 is $-X_1-C_yH_{2y}$, wherein y is 1 or 2;

X_4 is $-C_n-H_{2n}-X_1-$, wherein n is 1 or 2;

R_1 is C_{5-7}-cycloalkyl, $CR_4R_5Ar_3$, or $C(CH_3)_2R_6$;

R_2 is H, C_{1-6}-alkyl, OH, or O-(C_{1-6})-alkyl;

R_3 is H, or C_{1-6}-alkyl;

R_4 is C_{1-4}-alkyl, or CF_3;

R_5 is C_{1-4}-alkyl, or CF_3; or

R_4 and R_5 together form a C_{4-6}-alkylene group;

R_6 is CH_2OH, COOH, $COO(C_{1-4})$-alkyl, $CONR_9R_{10}$, or $CH_2NR_9R_{10}$;

R_7 is H;

R_8 is H;

R_9 is H, C_{1-6}-alkyl, phenyl, phenyl-(C_{1-6}-alkyl), COR_{11}, $COOR_{11}$, CHO, $CONH_2$, $CONHR_{11}$, SO_2-(C_{1-6}-alkyl), SO_2-phenyl, wherein the phenyl ring is optionally mono- or polysubstituted by one or more substituents wherein the

substituents are selected from halogen, CF_3, C_{1-4}-alkyl, OH, and C_{1-4}-alkoxy;

R_{10} is H or C_{1-6}-alkyl; or

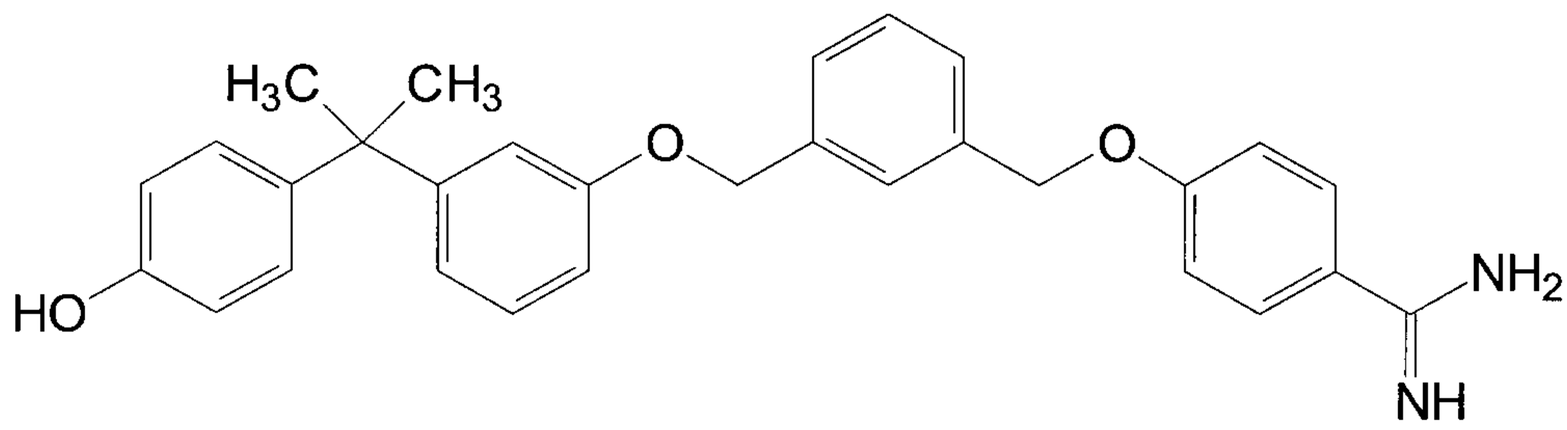
R_9 and R_{10} together form a C_{4-6}-alkylene group;

R_{11} is C_{1-6}-alkyl;

Ar_3 is an optionally mono- or polysubstituted phenyl group

optionally in the form of the single optical isomers, a mixture of individual enantiomers or a racemate thereof, a free base or a corresponding acid addition salt with a pharmacologically acceptable acid.

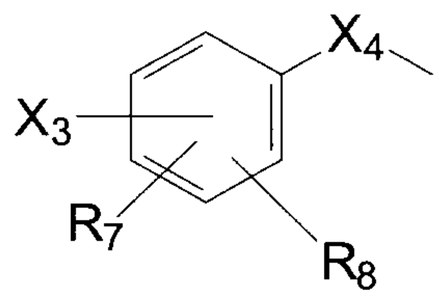
According to another aspect of the present invention, there is provided a compound which is represented by the following formula



optionally in the form a free base or an acid addition salt with a pharmacologically acceptable acid.

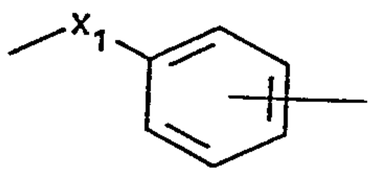
Preferred compounds according to general formula I are those wherein

A denotes X_1-C_m-H_{2m}-X_2 in which m is the integer 2



and

X_1 is O;

X_2 is 

X_3 denotes $-X_1-C_nH_{2n}-$ wherein n is the integer 1 or 2;

X_4 denotes $-C_nH_{2n}-X_1-$ wherein n is the integer 1 or 2;

R_1 denotes C_{5-7}-cycloalkyl, Ar_1, OAr_1, CH_2-Ar_2; $CR_4R_5Ar_3$, $C(CH_3)_2R_6$;

R_2 denotes H, C_{1-6}-alkyl, OH, Cl, O-(C_{1-6})-alkyl;

R_3 denotes H, C_{1-6}-alkyl;

R_4 denotes C_{1-4}-alkyl, CF_3, CH_2OH;

R_5 denotes H, C_{1-4}-alkyl, CF_3, CH_2OH and

R_4 and R_5 together may also form a C_{4-6}-alkylene group;

R_6 denotes CH_2OH, COOH, $COO(C_{1-4})$alkyl, $CONR_9R_{10}$, $CH_2NR_9R_{10}$;

R_7 denotes H, F, Cl, Br, OH, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R_8 denotes H, F, Cl, Br, OH, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R_9 denotes H, C_{1-6}-alkyl;

R_{10} denotes H or C_{1-6}-alkyl and

R_9 and R_{10} together may also represent a C_{4-6}-alkylene group;

Ar_1 denotes an optionally mono- or polysubstituted aryl group, with the exception of the unsubstituted phenyl group and the phenyl group which is monosubstituted by halogen, C_{1-4}-alkyl and monosubstituted by C_{1-4}-alkoxy;

Ar_2 denotes an optionally mono- or polysubstituted aryl group, with the exception of the unsubstituted phenyl group;

Ar_3 denotes an optionally mono- or polysubstituted aryl group

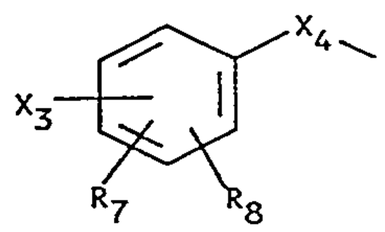
with the proviso that

R_1 cannot represent an unsubstituted phenyl group bound via a C_{1-4}-alkylene unit;

optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates and in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

Particularly preferred compounds of general formula I are those wherein

A denotes



and

X_1 is O;

X_3 denotes X_1-CH_2;

X_4 denotes CH_2-X_1;

R_1 denotes C_{5-7}-cycloalkyl, Ar_1, OAr_1, CH_2-Ar_2; $CR_4R_5Ar_3$, $C(CH_3)_2R_6$;

R_2 denotes H, OH, O-(C_{1-6})-alkyl;

R_3 denotes H;

R_4 denotes CH_3, CH_2OH;

R_5 denotes H, CH_3, CH_2OH and

R_4 and R_5 together may also denote a C_{4-6}-alkylene group;

R_6 denotes CH_2OH, COOH, $COO(C_{1-4})$-alkyl, $CONR_9R_{10}$, $CH_2NR_9R_{10}$;

R_7 denotes H;

R_8 denotes H;

R_9 denotes H, C_{1-6}-alkyl;

R_{10} denotes H or C_{1-6}-alkyl and

R_9 and R_{10} together may also denote a C_{4-6}-alkylene group;

Ar_1 denotes an aryl group optionally mono- or polysubstituted by hydroxy or by hydroxy and C_{1-6}-alkyl;

Ar_2 denotes an aryl group optionally mono- or polysubstituted by hydroxy or by hydroxy and C_{1-6}-alkyl;

Ar_3 denotes an aryl group optionally mono- or

polysubstituted by hydroxy or by hydroxy and C_{1-6}-alkyl

optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates and in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

Unless specifically stated otherwise, the general definitions are used as follows:

C_{1-4}-alkyl, C_{1-6}-alkyl and C_{1-8}-alkyl, respectively, generally denote a branched or unbranched hydrocarbon group having 1 to 4 or 6 or 8 carbon atoms, which may optionally be substituted by one or more halogen atoms, preferably fluorine, which may be the same or different from one another. The following hydrocarbon groups are mentioned by way of example:

methyl, ethyl, propyl, 1-methylethyl(isopropyl), n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylphenyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl. Unless otherwise specified, lower alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl are preferred.

Aryl generally denotes an aromatic group having 6 to 10

carbon atoms, also in compositions in which the aromatic group may be substituted by one or more lower alkyl groups, trifluoromethyl groups, cyano groups, alkoxy groups, nitro groups, amino groups and/or one or more halogen atoms - which may be identical or different; the preferred aryl group is an optionally substituted phenyl group, the preferred substituents being halogen (such as fluorine, chlorine or bromine) and hydroxyl.

Aralkyl generally denotes a C_{7-14}-aryl group bound via an alkylene chain, in which the aromatic group may be substituted by one or more lower alkyl groups, alkoxy groups, nitro groups, amino groups and/or one or more halogen atoms, which may be identical or different. Aralkyl groups having 1 to 6 carbon atoms in the aliphatic part and 6 carbon atoms in the aromatic part are preferred.

Unless otherwise stated, the preferred aralkyl groups are benzyl, phenethyl and phenylpropyl or 2-phenyl-isopropyl.

Alkoxy generally represents a straight-chained or branched C_{1-8}-hydrocarbon group bound via an oxygen atom. A lower alkoxy group having 1 to 3 carbon atoms is preferred. The methoxy group is particularly preferred.

Unless otherwise stated, amino denotes an NH_2 function which may optionally be substituted by one or two C_{1-8}-alkyl, aryl or aralkyl groups, which may be identical or different.

Alkylamino represents, by way of example, methylamino, ethylamino, propylamino, 1-methylene-ethylamino, butylamino, 1-methylpropylamino, 2-methylpropylamino or 1,1-dimethylethylamino.

Dialkylamino denotes, for example, dimethylamino, diethylamino, dipropylamino, dibutylamino, di-(1-methylethyl)amino, di-(1-methylpropyl)amino, di-2-methylpropylamino, ethylmethylamino or methylpropylamino.

Cycloalkyl generally denotes a saturated or unsaturated cyclic hydrocarbon group having 5 to 9 carbon atoms which may optionally be substituted by a halogen atom or a number of halogen atoms, preferably fluorine, which may be the same or different. Cyclic hydrocarbon groups having 3 to 6 carbon atoms are preferred. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cycloheptadienyl, cyclooctyl, cyclooctenyl, cyclooctadienyl and cyclononinyl.

Heteroaryl, within the scope of the above definition, generally represents a 5- to 6-membered ring which may contain oxygen, sulphur and/or nitrogen as heteroatoms and onto which another aromatic ring may be fused. 5- and 6-membered aromatic rings which contain an oxygen, a sulphur and/or up to two nitrogen atoms and which are optionally benzocondensed are preferred.

Examples of particular heterocyclic systems include: acridinyl, acridonyl, alkylpyridinyl, anthraquinonyl, ascorbyl, azaazulenyl, azabenzanthracenyl, azabenzanthrenyl, azachrysenyl, azacyclazinyl, azaindolyl, azanaphthacenyl, azanaphthalenyl, azaprenyl, azatriphenylenyl, azepinyl, azinoindolyl, azinopyrrolyl, benzacridinyl, benzazapinyl, benzofuryl, benzonaphthyridinyl, benzopyranonyl, benzopyranyl, benzopyronyl, benzoquinolinyl, benzoquinolizinyl, benzothiepinyl, benzothiophenyl, benzylisoquinolinyl, bipyridinyl, butyrolactonyl, caprolactamyl, carbazolyl, carbolinyl, catechinyl, chromenopyronyl,

chromonopyranyl, cumarinyl, cumaronyl,
decahydroquinolinyl, decahydroquinolonyl,
diazaanthracenyl, diazaphenanthrenyl, dibenzazapinyl,
dibenzofuranyl, dibenzothiphenyl, dichromylenyl,
dihydrofuranyl, dihydroisocumarinyl,
dihydroisoquinolinyl, dihydropyranyl, dihydropyridinyl,
dihydropyridonyl, dihydropyronyl, dihydrothiopyranyl,
diprylenyl, dioxanthylenyl, oenantholactamyl, flavanyl,
flavonyl, fluoranyl, fluoresceinyl, furandionyl,
furanochromanyl, furanonyl, furanoquinolinyl, furanyl,
furopyranyl, furopyronyl, heteroazulenyl,
hexahydropyrazinoisoquinolinyl, hydrofuranyl,
hydrofuranonyl, hydroindolyl, hydropyranyl,
hydropyridinyl, hydropyrrolyl, hydroquinolinyl,
hydrothiochromenyl, hydrothiophenyl, indolizidinyl,
indolizinyl, indolonyl, isatinyl, isatogenyl,
isobenzofurandionyl, isobenzfuranyl, isochromanyl,
isoflavonyl, isoindolinyl, isoindolobenzazapinyl,
isoindolyl, isoquinolinyl, isoquinuclidinyl, lactamyl,
lactonyl, maleimidyl, monoazabenzonaphthenyl,
naphthalenyl, naphthimidazopyridindionyl,
naphthindolizinedionyl, naphthodihydropyranyl,
naphthofuranyl, naphthyridinyl, oxepinyl, oxindolyl,
oxolenyl, perhydroazolopyridinyl, perhydroindolyl,
phenanthracquinonyl, phthalideisoquinolinyl,
phthalimidyl, phthalonyl, piperidinyl, piperidonyl,
prolinyl, parazinyl, pyranoazinyl, pyranoazolyl,
pyranopyrandionyl, pyranopyridinyl, pyranoquinolinyl,
pyranopyrazinyl, pyranyl, pyrazolopyridinyl,
pyridinethionyl, pyridinonaphthalenyl,
pyridinopyridinyl, pyridinyl, pyridocolinyl,
pyridoindolyl, pyridopyridinyl, pyridopyrimidinyl,
pyridopyrrolyl, pyridoquinolinyl, pyronyl, pyrrocolinyl,
pyrrolidinyl, pyrrolizidinyl, pyrrolizinyl,
pyrrolodioazinyl, pyrrolonyl, pyrrolopyrimidyl,
pyrroloquinolonyl, pyrrolyl, quinacridonyl, quinolinyl,
quinolizidinyl, quinolizinyl, quinolonyl, quinuclidinyl,

rhodaminyl, spirocumaranyl, succinimidyl, sulpholanyl, sulpholenyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothiapyranyl, tetrahydrothiophenyl, tetrahydrothipyranonyl, tetrahydrothipyranyl, tetronyl, thiaphenyl, thiachromanyl, thiadecalinyl, thianaphthenyl, thiapyranyl, thiapyronyl, thiazolopyridinyl, thienopyridinyl, thienopyrrolyl, thienothiophenyl, thiepinyl, thiochromenyl, thiocumarinyl, thiopyranyl, triazaanthracenyl, triazinoindolyl, triazolopyridinyl, tropanyl, xanthenyl, xanthonyl, xanthydrolyl, adeninyl, alloxanyl, alloxazinyl, anthranilyl, azabenzanthrenyl, azabenzonaphthenyl, azanaphthacenyl, azaphenoxazinyl, azapurinyl, azinyl, azoloazinyl, azolyl, barbituric acid, benzazinyl, benzimidazolethionyl, benzimidazolonyl, benzisothiazolyl, benzisoxazolyl, benzocinnolinyl, benzodiazocinyl, benzodioxolanyl, benzodioxolyl, benzopyridazinyl, benzothiazepinyl, benzothiazinyl, benzothiazolyl, benzoxazinyl, benzoxazolinonyl, benzoxazolyl, cinnolinyl, depsidinyl, diazaphenanthrenyl, diazepinyl, diazinyl, dibenzoxazepinyl, dihydrobenzimidazolyl, dihydrobenzothiazinyl, dihydrooxazolyl, dihydropyridazinyl, dihydropyrimidinyl, dihydrothiazinyl, dioxanyl, dioxenyl, dioxepinyl, dioxinonyl, dioxolanyl, dioxolonyl, dioxopiperazinyl, dipyrimidopyrazinyl, dithiolanyl, dithiolenyl, dithiolyl, flavinyl, furopyrimidinyl, glycocyamidinyl, guaninyl, hexahydropyrazinoisoquinolinyl, hexahydropyridazinyl, hydantoinyl, hydroimidazolyl, hydroparazinyl, hydropyrazolyl, hydropyridazinyl, hydropyrimidinyl, imidazolinyl, imidazolyl, imidazoquinazolinyl, imidazothiazolyl, indazolebenzopyrazolyl, indoxazenyl, inosinyl, isoalloxazinyl, isothiazolyl, isoxazolidinyl, isoxazolinonyl, isoxazolinyl, isoxazolonyl, isoxazolyl,

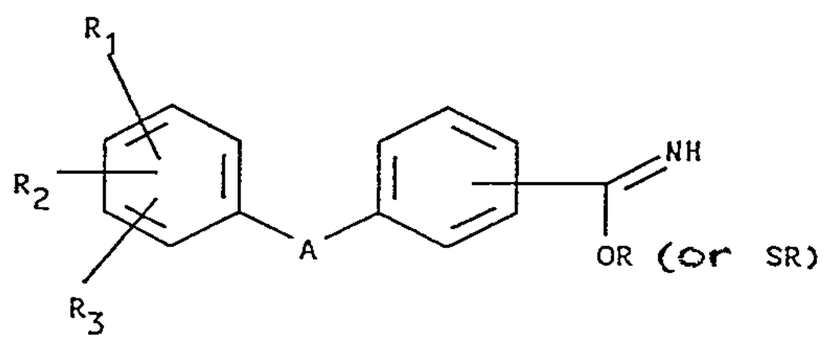
lumazinyl, methylthyminyl, methyluracilyl, morpholinyl, naphthimidazolyl, oroticyl, oxathianyl, oxathiolanyl, oxazinonyl, oxazolidinonyl, oxazolidinyl, oxazolidonyl, oxazolinonyl, oxazolinyl, oxazolonyl, oxazolopyrimidinyl, oxazolyl, perhydrocinnolinyl, perhydropyrroloazinyl, perhydropyrrolothiazinyl, perhydrothiazinonyl, perimidinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phenoxazonyl, phthalazinyl, piperazindionyl, piperazinodionyl, polyquinoxalinyl, pteridinyl, pterinyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolidonyl, pyrazolinonyl, parazolinyl, pyrazolobenzodiazepinyl, pyrazolonyl, pyrazolopyrimidinyl, pyrazolotriazinyl, pyrazolyl, pyridazinyl, pyridazonyl, pyridopyrazinyl, pyridopyrimidinyl, pyrimidinethionyl, pyrimidinyl, pyrimidionyl, pyrimidoazepinyl, pyrimidopteridinyl, pyrrolobenzodiazepinyl, pyrrolodiazinyl, pyrrolopyrimidinyl, quinazolidinyl, quinazolinonyl, quinazolinyl, quinoxalinyl, sultamyl, sultinyl, sultonyl, tetrahydrooxazolyl, tetrahydropyrazinyl, tetrahydropyridazinyl, tetrahydroquinoxalinyl, tetrahydrothiazolyl, thiazepinyl, thiazinyl, thiazolidinonyl, thiazolidinyl, thiazolinonyl, thiazolinyl, thiazolobenzimidazolyl, thiazolyl, thienopyrimidinyl, thiazolidinonyl, thyminyl, triazolopyrimidinyl, uracilyl, xanthinyl, xylitolyl, azabenzonaphththenyl, benzofuroxanyl, benzothiadiazinyl, benzotriazepinonyl, benzotriazolyl, benzoxadiazinyl, dioxadiazinyl, dithiadazolyl, dithiazolyl, furazanyl, furoxanyl, hydrotriazolyl, hydroxytrizinyl, oxadiazinyl, oxadiazolyl, oxathiazinonyl, oxatriazolyl, pentazinyl, pentazolyl, petrazinyl, polyoxadiazolyl, sydonyl, tetraoxanyl, tetrazepinyl, tetrazinyl, tetrazolyl, thiadiazinyl, thiadiazolinyl, thiadiazolyl, thiadioxazinyl, thiatriazinyl, thiatriazolyl, thiatriazolyl, triazepinyl, triazinoindolyl, triazinyl,

triazolinedionyl, triazolinyl, triazolyl, trioxanyl, triphenodioxazinyl, triphenodithiazinyl, trithiadiazepinyl, trithianyl or trioxolanyl.

Particularly preferred heteroaryl groups include, for example, thienyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, thiazolyl, benzothiazolyl, isothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, pyrazolyl and indolyl.

The new compounds may be prepared using the following conventional methods:

1. Reaction of imidoesters of formula II



(II)

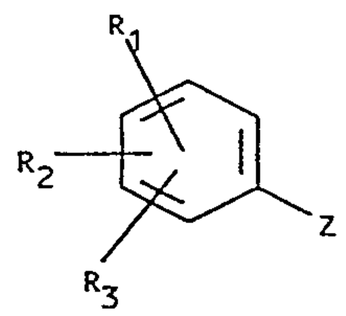
wherein R_1 to R_4, A and B are as hereinbefore defined and R preferably denotes a C_{1-6}-alkyl group or benzyl (however, the person skilled in the art may also, if desired, use derivatives of other alcohols), and ammonia. The reaction is conveniently carried out in an organic solvent at temperatures between about 0°C and the boiling temperature of the reaction mixture, preferably between ambient temperature and about 100°C or boiling temperature, if this is lower. Suitable solvents are polar solvents such as methanol, ethanol and propanol.

If the starting materials are sufficiently acid-stable, the reaction may be carried out via the corresponding acid imide chlorides instead of the imido esters.

2. In order to prepare compounds of formula I wherein A is linked via O or S to at least one of the ring systems:

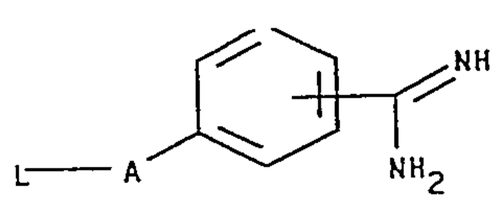
reacting

(a) a phenol or thiophenol of formula III



(III)

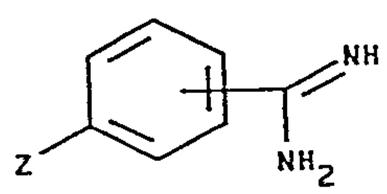
wherein Z denotes OH or SH and R_1, R_2 and R_3 are as hereinbefore defined, with a compound of general formula IV



(IV)

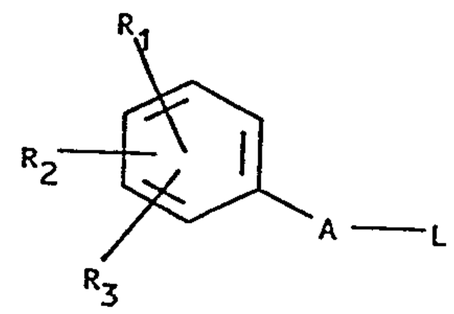
wherein A is as hereinbefore defined and L denotes a nucleofugic leaving group, or

(b) a phenol or thiophenol of formula V



(V)

wherein Z is as hereinbefore defined, with a compound of formula VI:



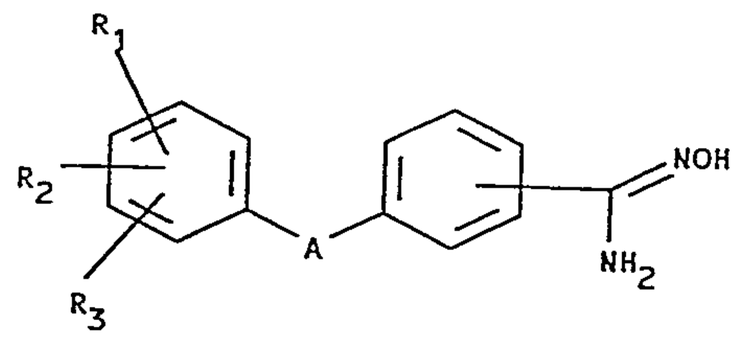
(VI)

wherein A, R_1, R_2, R_3 and L are as hereinbefore defined.

The reaction is carried out in aprotic solvents such as dimethylsulphoxide, dimethylformamide, acetonitrile or alcohols such as methanol, ethanol or propanol using a base (metal carbonate, metal hydroxide, metal hydride) at temperatures between about 0 and 140°C or the boiling temperature of the reaction mixture.

The phenols or thiophenols may also be used in the form of salts, e.g. the alkali metal salts. The nucleofugic leaving group may be, for example, a halogen such as Br or Cl.

3. Reduction of an amidoxime of formula VII



(VII)

wherein A and R_1 to R_3 are as hereinbefore defined.

Catalytic hydrogenation, particularly with Raney nickel in a lower alcohol such as methanol, is suitable for the step of reducing the amidoxime.

Appropriately, the amidoxime of the formula is dissolved in methanol with the addition of the calculated quantity of the particular acid the salt of which is desired as an end product, and hydrogenated at ambient temperature under slight pressure, e.g. 5 bar, until the uptake of hydrogen has ceased.

The starting materials may be obtained from known compounds by conventional methods.

Thus, the starting materials for process 1 may be obtained from the corresponding nitriles by reacting with HCl via the step of the imide chlorides or directly by reacting with C_{1-6}-alcohols or benzyl alcohol, for example, in the presence of an acid such as HCl. Reacting the nitriles with H_2S in solvents such as pyridine or dimethylformamide in the presence of a base such as triethylamine with subsequent alkylation or benzylation also results in compounds of formula II.

Starting from carboxylic acid amides, which moreover correspond to the compounds of formula II by reacting with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures of between 0 and 50°C, preferably at ambient temperature, compounds of formula II are obtained.

In order to prepare the starting materials of general formula VII, the corresponding amidoximes may be reacted instead of amidines analogously to process 1 or 2, or by analogous reaction of corresponding nitriles, from which the starting materials of general formula VII are

finally obtained by the addition of hydroxylamine.

It has been found that the compounds of formula I are characterised by their versatility in therapeutic applications. Particular mention should be made of those applications in which the LTB_4-receptor-antagonistic properties play a part. These include, in particular, arthritis, asthma, chronic obstructive lung diseases, e.g. chronic bronchitis, psoriasis, ulcerative colitis, gastro- or enteropathy induced by non-steroidal antiphlogistics, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage/ischaemia, atherosclerosis and multiple sclerosis.

The new compounds may also be used to treat illnesses or conditions in which the passage of cells from the blood through the vascular endothelium into the tissue is of importance (e.g. metastasis) or diseases and conditions in which the combination of LTB_4 or another molecule (such as 12-HETE) with the LTB_4-receptor affects cell proliferation (such as chronic myeloid leukaemia).

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

The activities may be investigated pharmacologically and biochemically using tests such as those described in WO 93/16036, pages 15 to 17.

The therapeutic or prophylactic dose is dependent not only on the potency of the individual compounds and the

body weight of the patient but also on the nature and gravity of the condition being treated. For oral use the dose is between 10 and 500 mg, preferably between 20 and 250 mg. For administration by inhalation, the dose given to the patient is between about 0.5 and 25, preferably between about 2 and 20 mg of active substance.

Solutions for inhalation generally contain between about 0.5 and 5% of active substance. The new compounds may be administered in conventional preparations, e.g. as tablets, coated tablets, capsules, lozenges, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments and suppositories.

The Examples which follow show some possible formulations for the preparations:

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 may be increased or reduced and the quantity of glucose reduced or increased accordingly.

2. Suppositories

Composition:

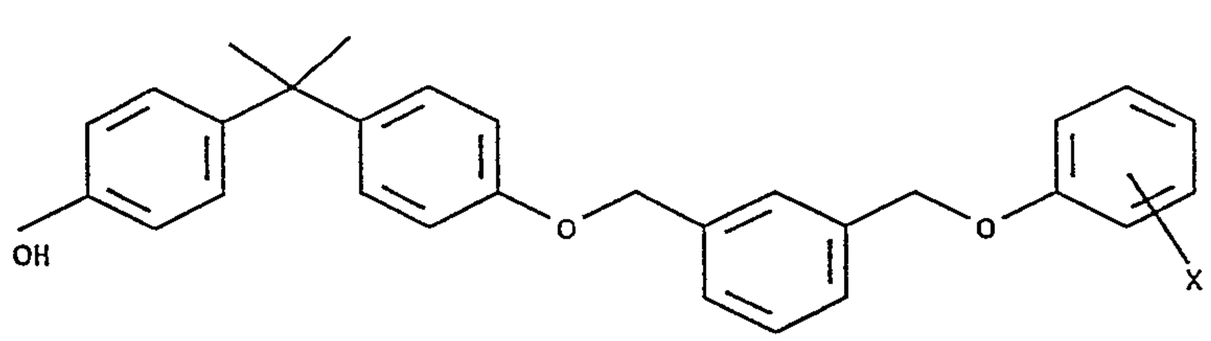
Active substance according to the invention	1000 parts by weight
Powdered lactose	45 parts by weight
Cocoa butter	1555 parts by weight

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

3. Powders for inhalation

Micronised powdered active substance (compound of formula I; particle size approximately 0.5 to 7 μm) are 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, to which reference is hereby made.

Example of synthesis



Amidoxime: X = *para*-C(=NOH)NH_2

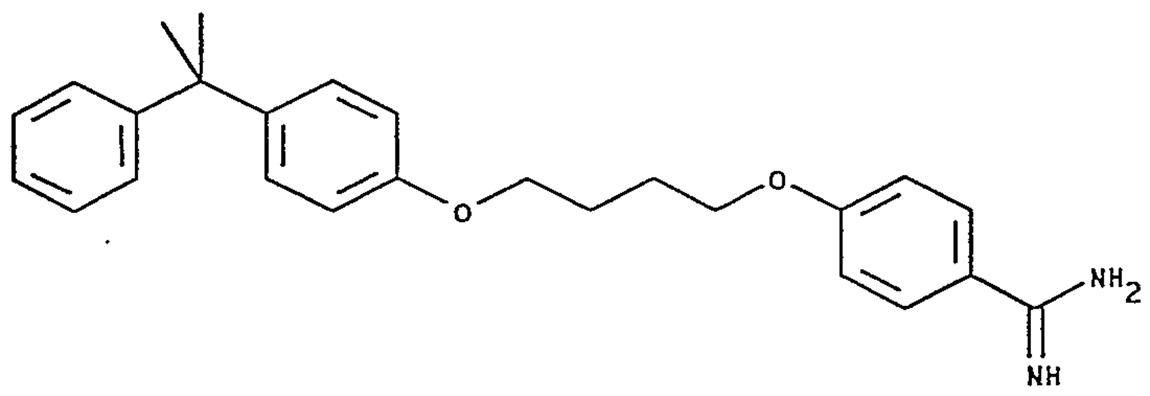
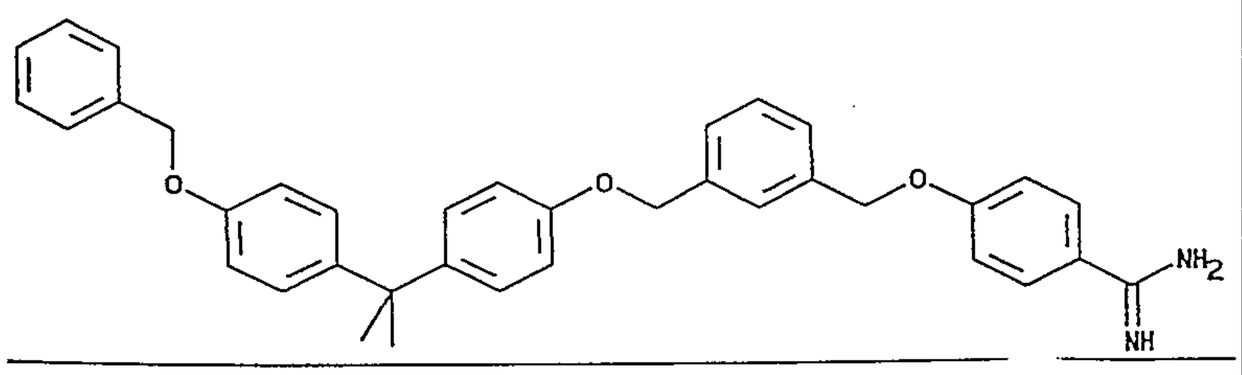
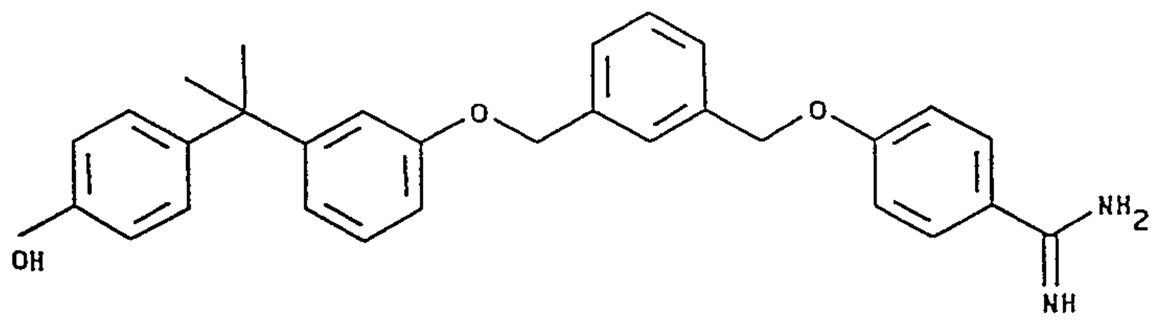
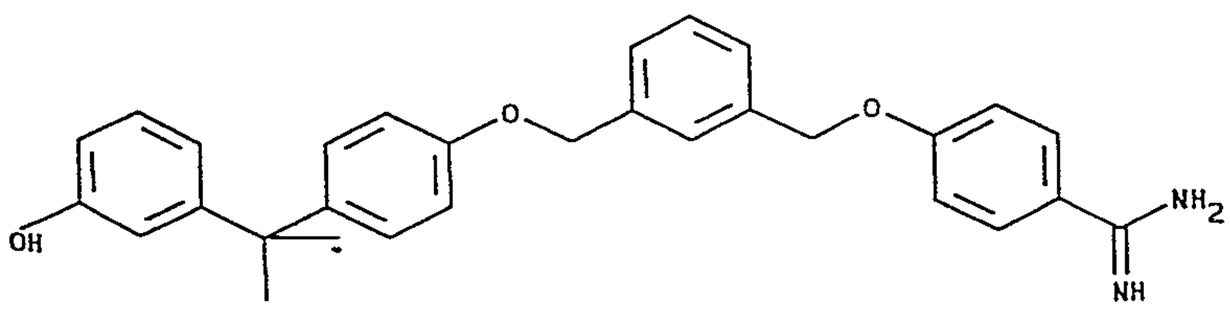
2.0 g of the nitrile of the above formula (X = *para*-CN) are placed in 40 ml of ethanol, refluxed and a mixture of 1 g of Na_2CO_3 in 5 ml of water and 1.24 g of hydroxylamine x HCl is added dropwise. After 5 hours' refluxing the solvent is distilled off, the residue is

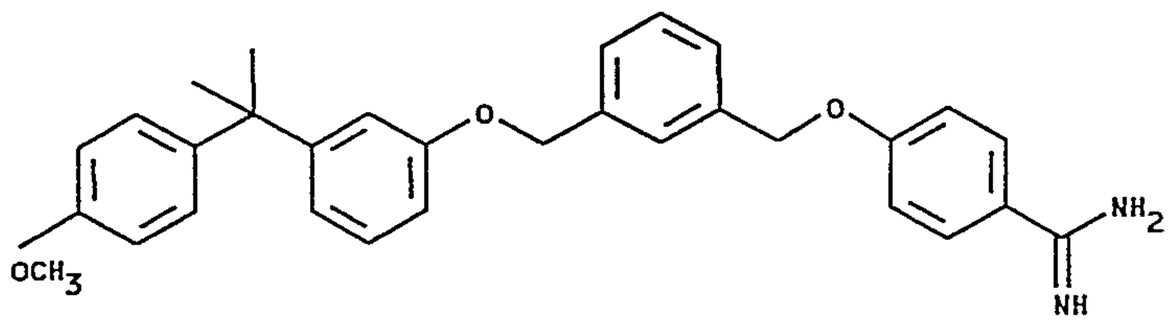
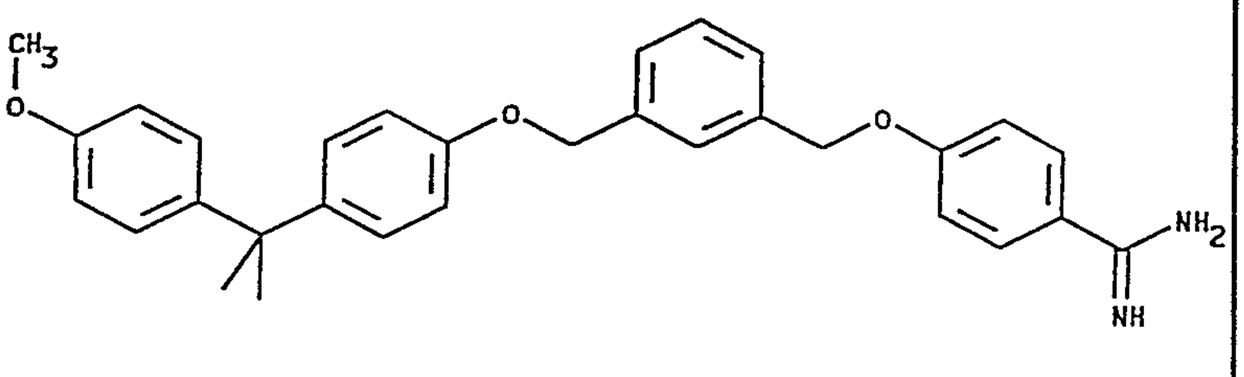
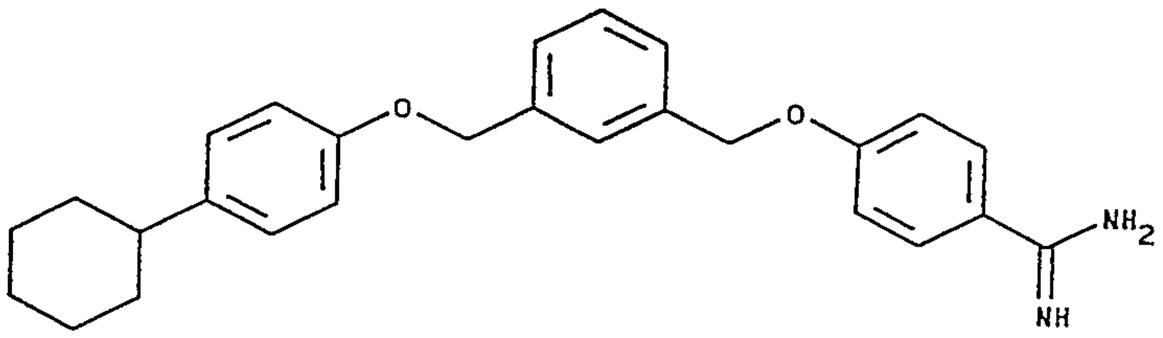
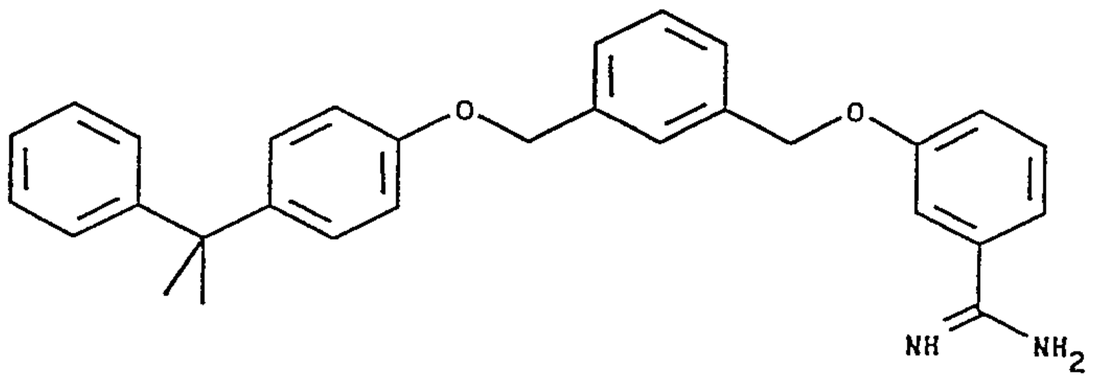
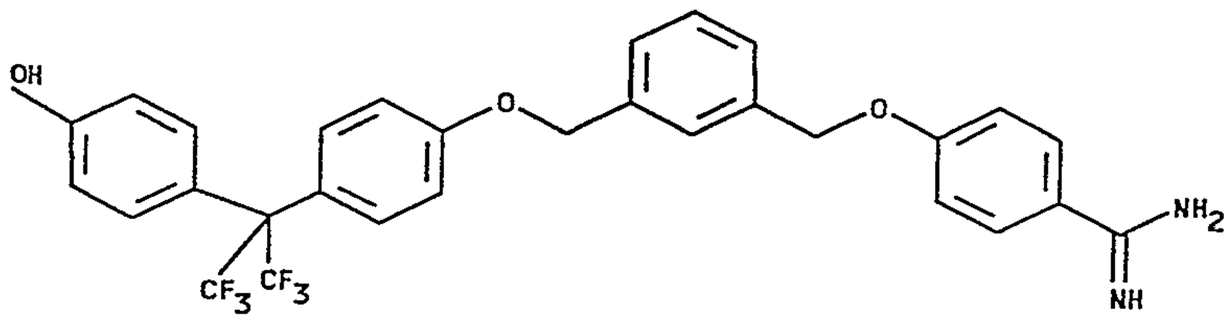
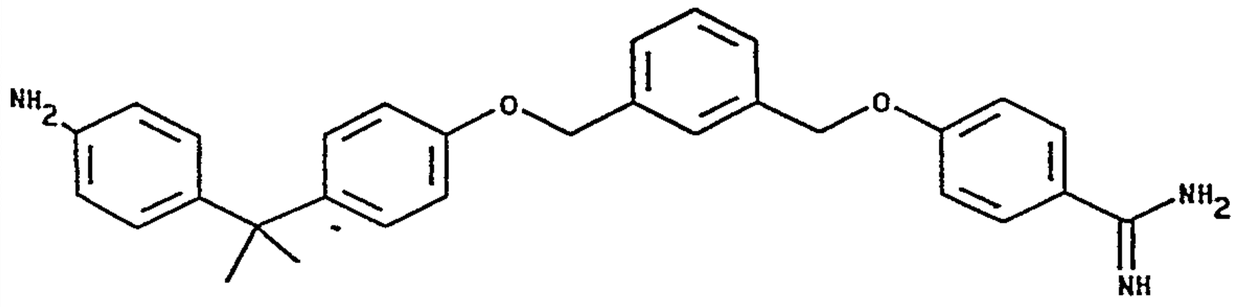
stirred with 50 ml of water, extracted 3 x with 50 ml of ethyl acetate and the combined organic phases are dried. After filtering, the substance is evaporated down *in vacuo* and the residue is purified by flash chromatography (silica gel 60, CH_2Cl_2/methanol 9:1). The product is dissolved in ethanol, acidified with ethanolic HCl and precipitated as the hydrochloride using ether. The oil obtained is crystallised with ethyl acetate. Yield: 2.0 g of white crystals.

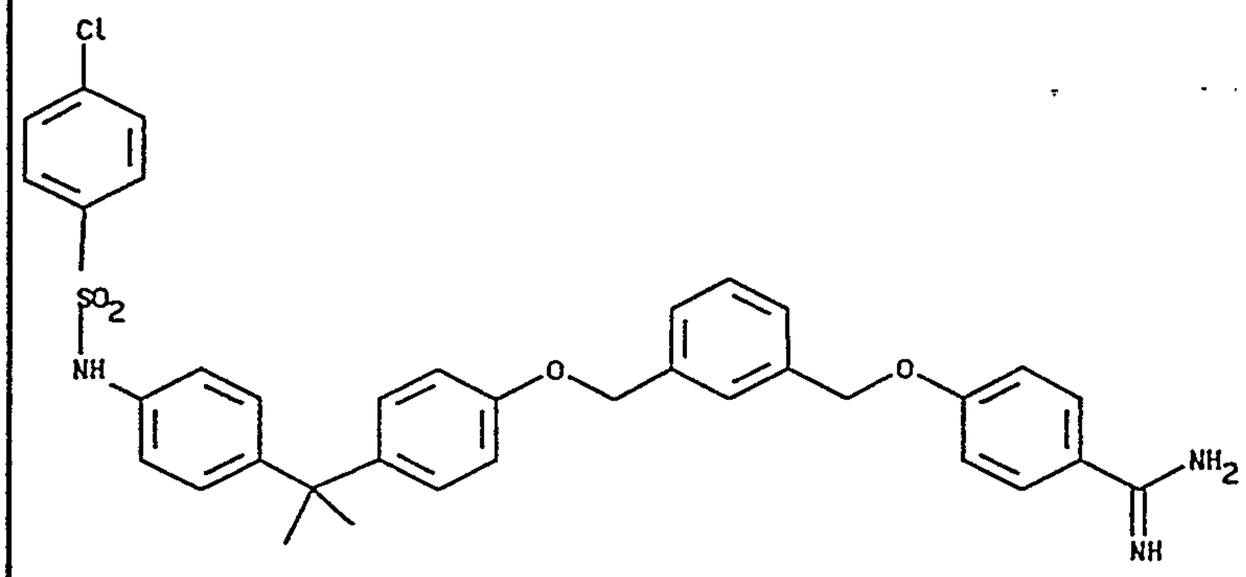
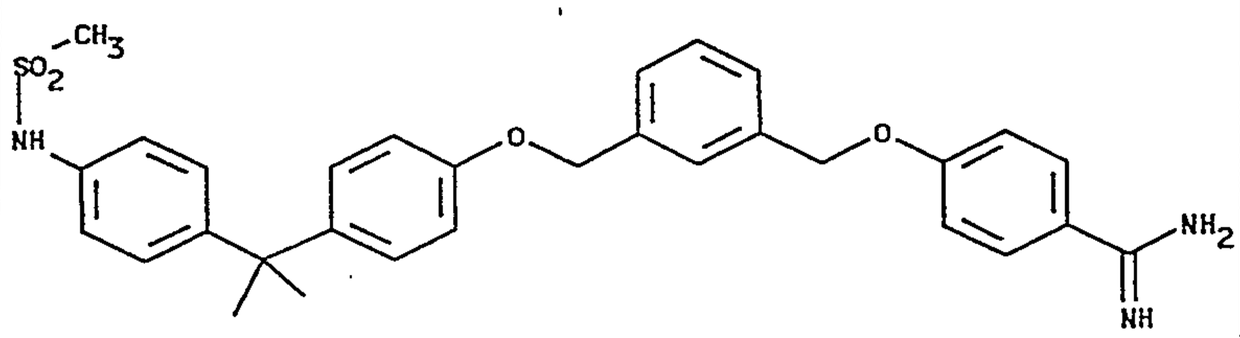
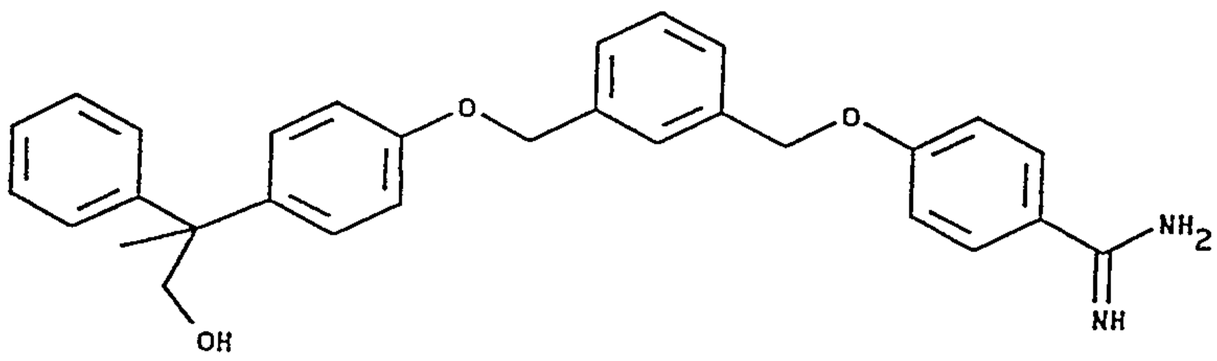
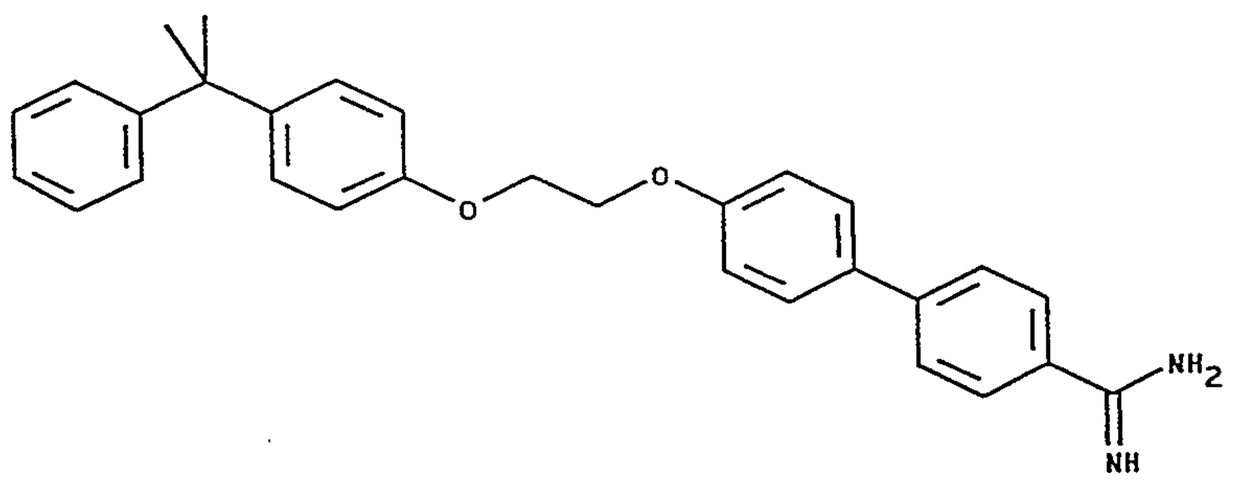
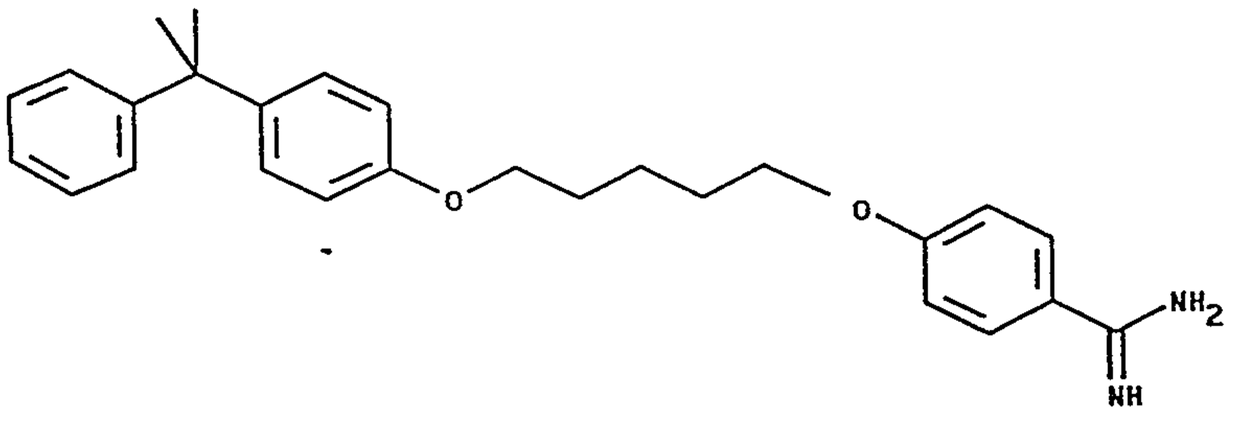
4-[[3-[[4-[1-(4-Hydroxyphenyl)-1-methylethyl]phenoxy]-methyl]phenyl]methoxy]benzolcarboximidamide hydrochloride (X = *para*-C(=NH)-NH_2)

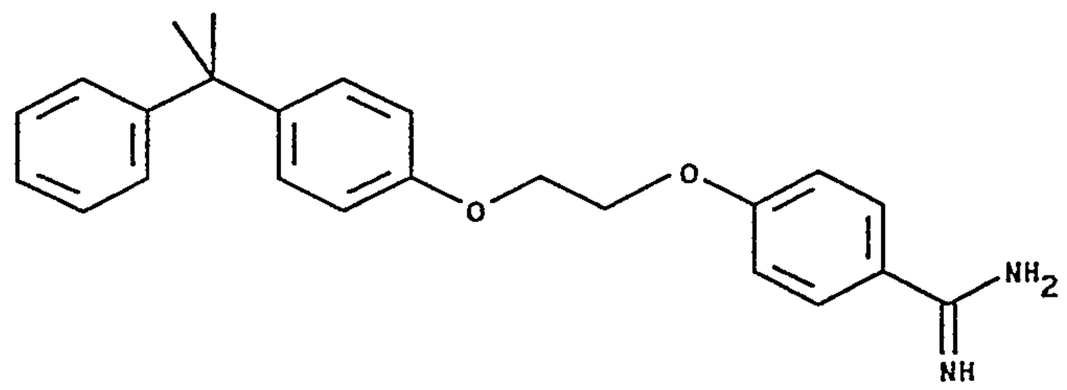
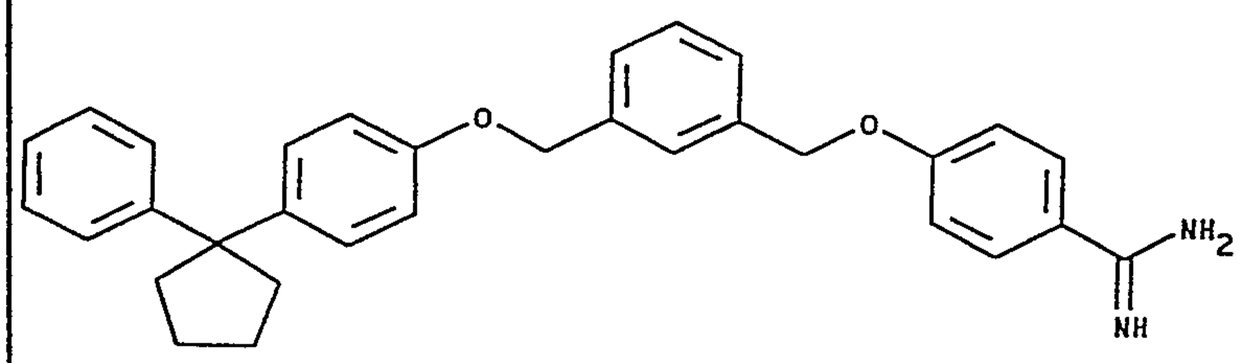
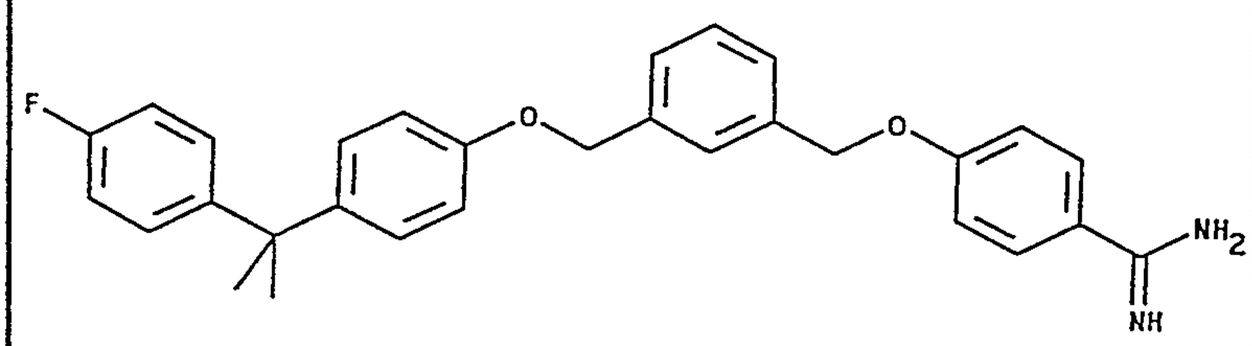
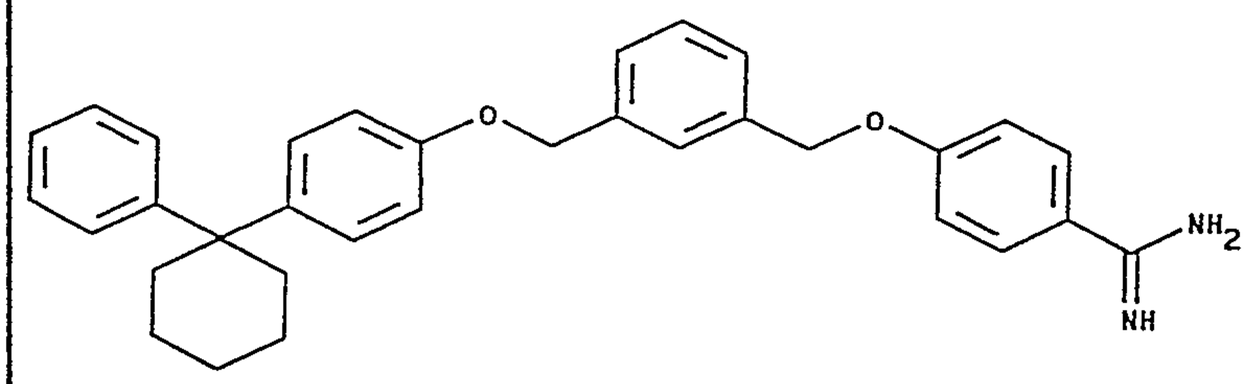
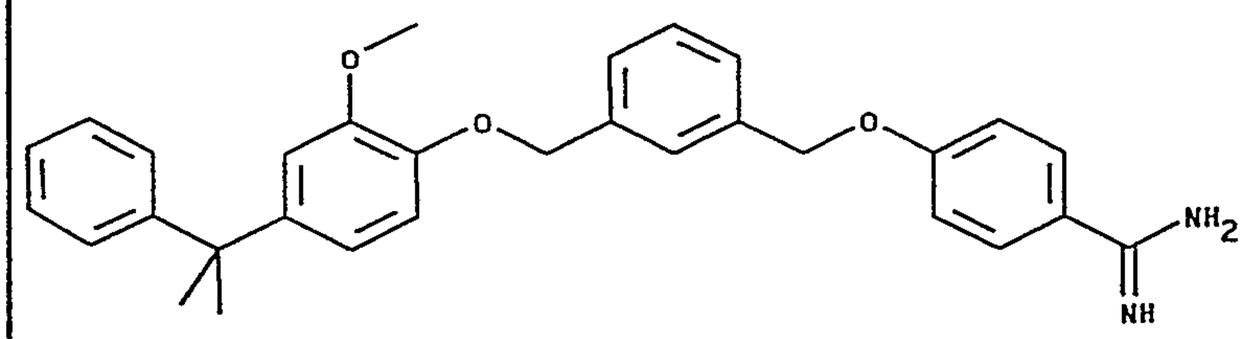
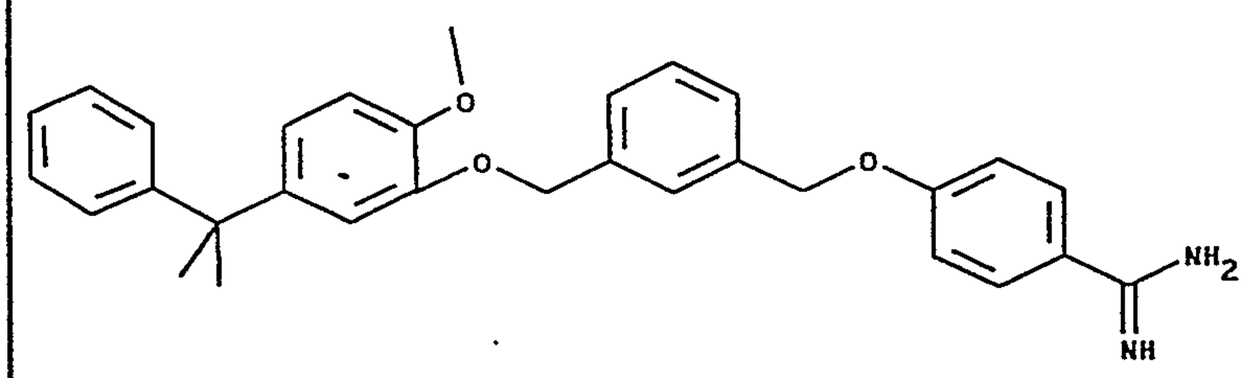
2.0 g of the amidoxime of the above formula (X = *para*-C(=NOH)-NH_2) are dissolved in 50 ml of methanol and hydrogenated with 5 g of methanol-moistened Raney nickel with the addition of 1 ml of 20% ammonium chloride solution for 5 hours under normal pressure and at ambient temperature. The nickel is suction filtered and the solution is filtered through kieselguhr. After concentration by evaporation *in vacuo*, the residue is stirred with 50 ml of water. The crystals are suction filtered and recrystallised twice from ethanol/ether. Yield: 1.0 g of the amidine compound (the above formula, X = *para*-C(=NH)-NH_2 as hydrochloride, m.p. 234-236°C.

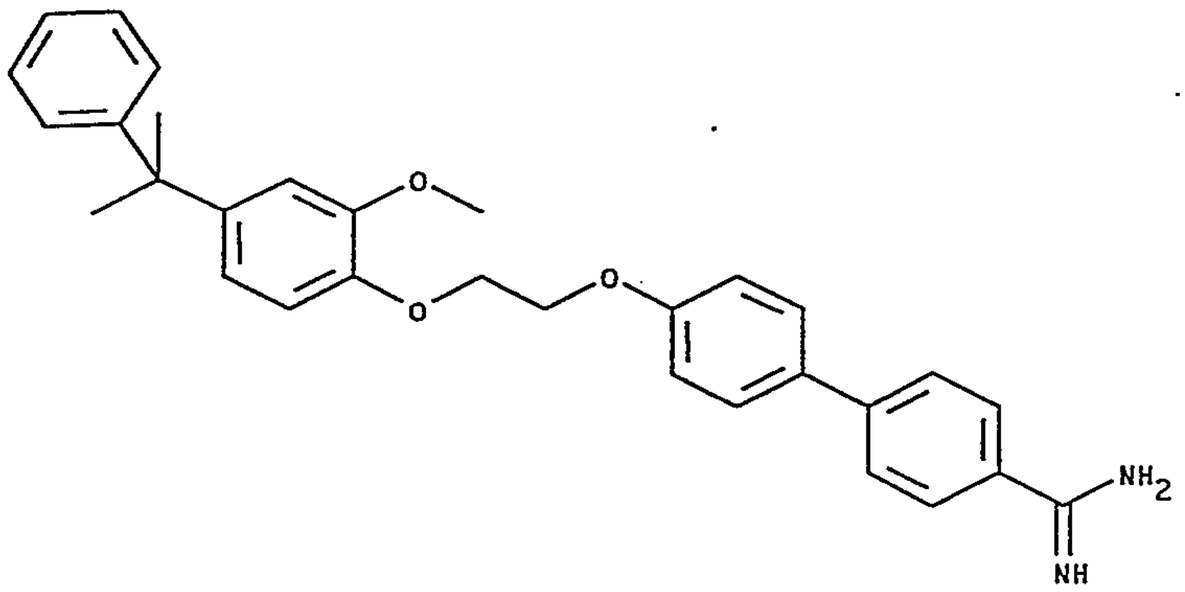
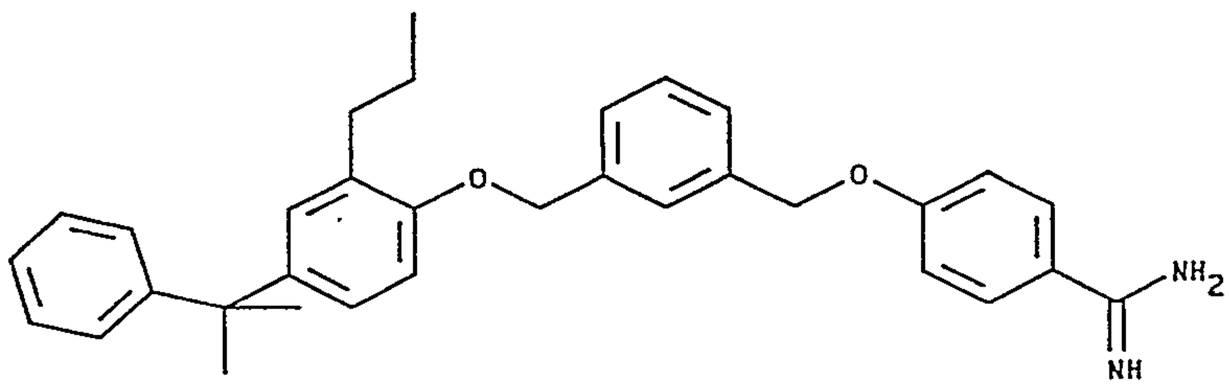
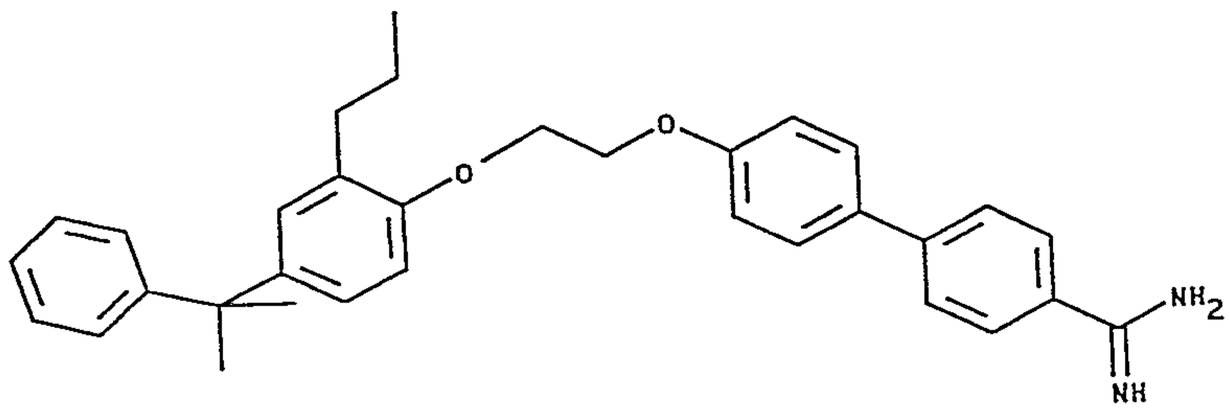
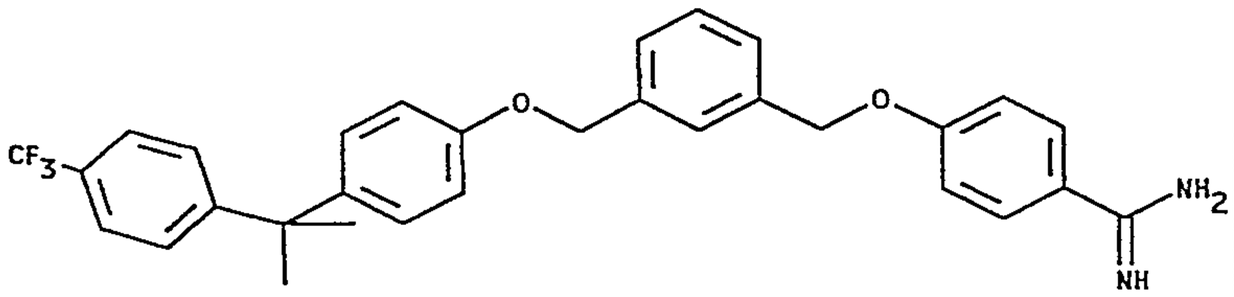
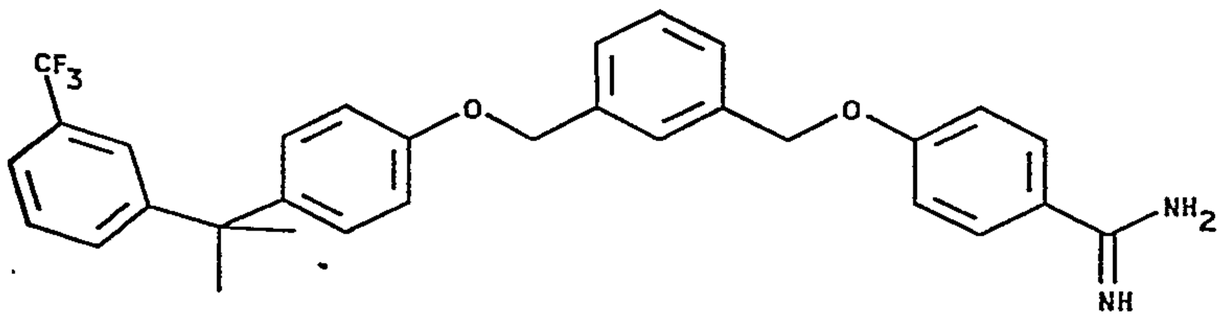
The following compounds are also obtained, *inter alia*, using this procedure:

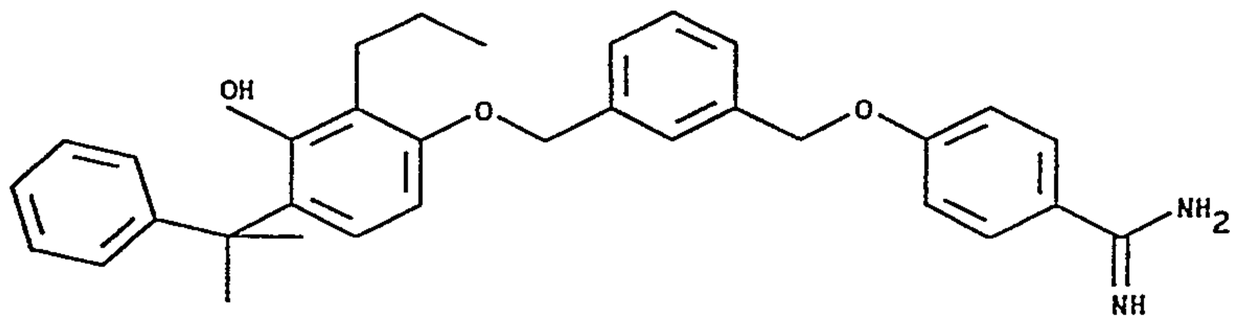
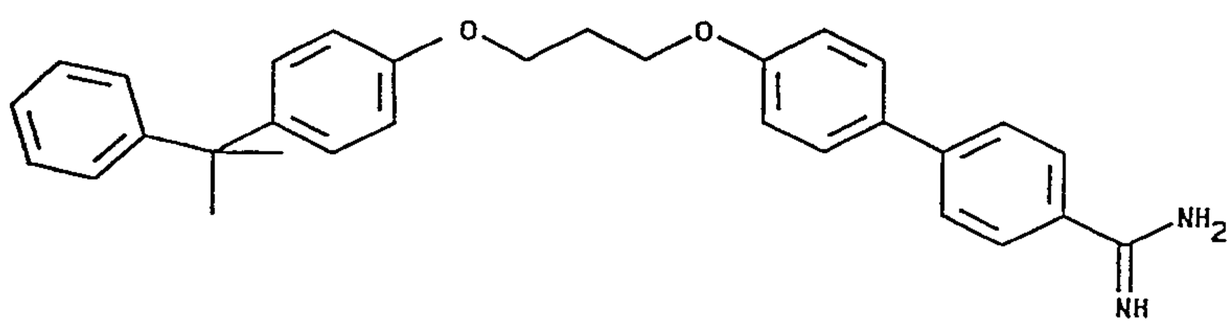
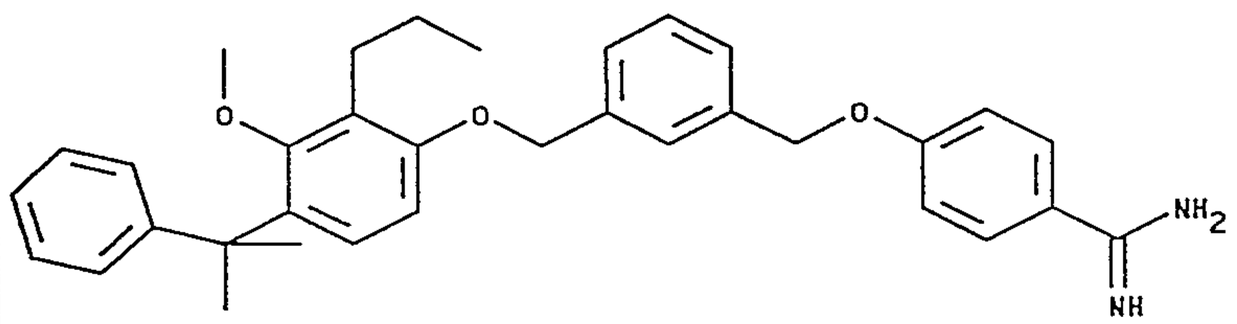
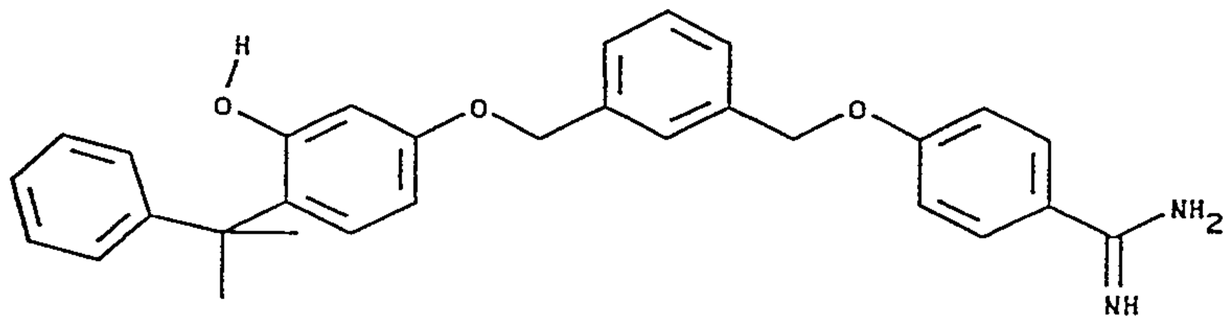
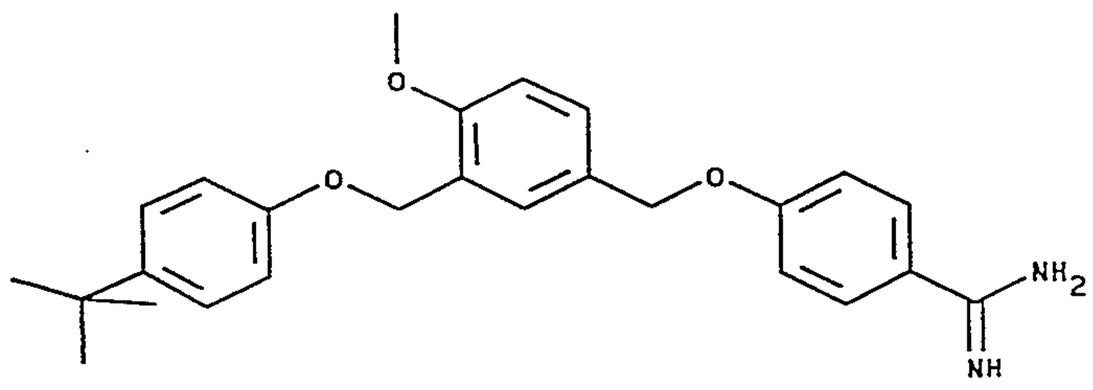
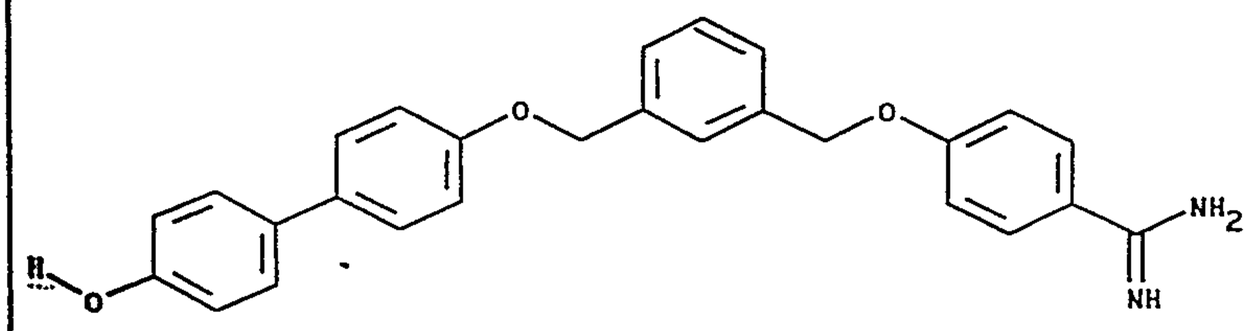
No.	Compound	Salt form	M.p. [°C] min	M.p. [°C] max
2		Chloride	135	140
3		Chloride	136	
4		Fumarate	199	200
5		Methane-sulphonate	193	198

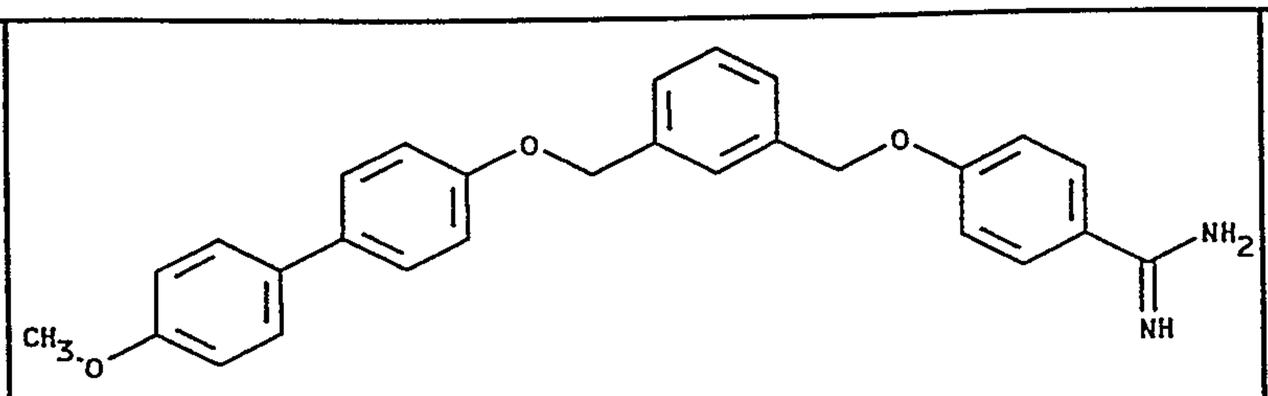
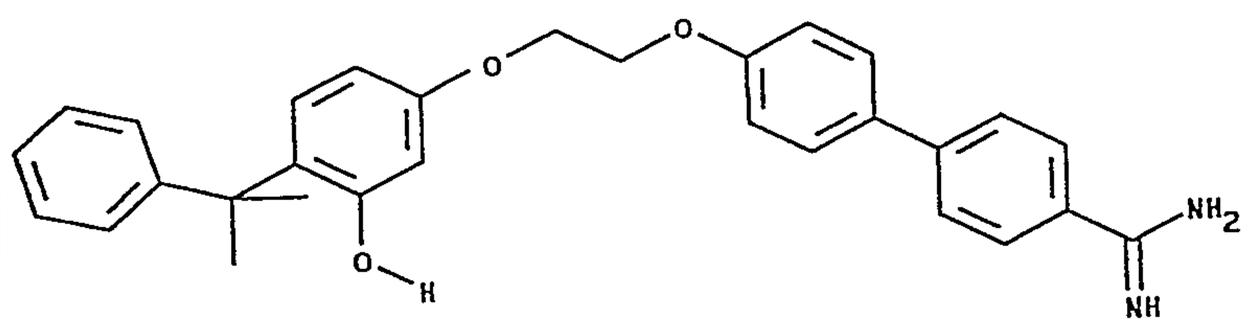
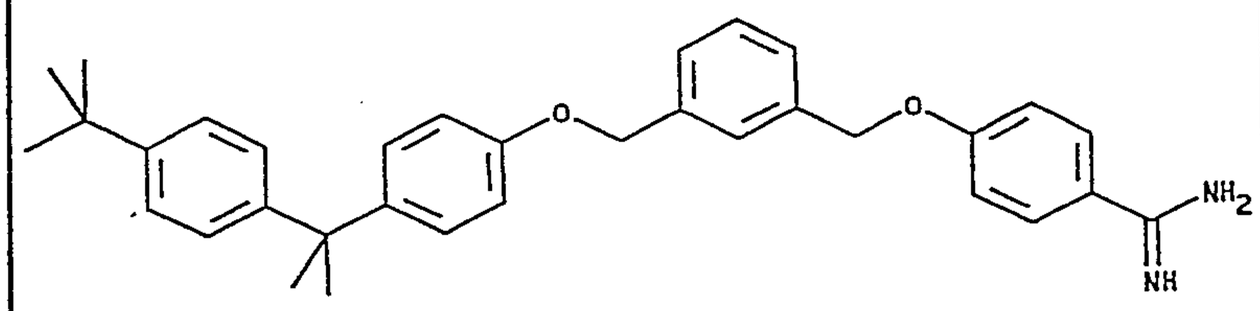
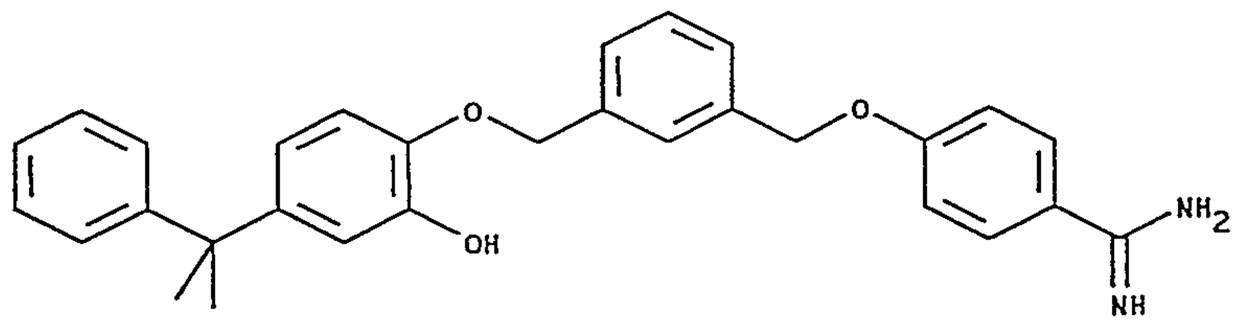
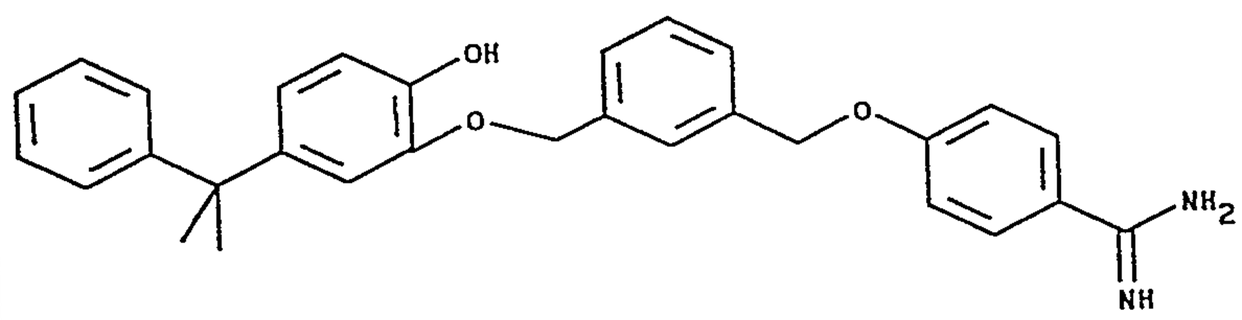
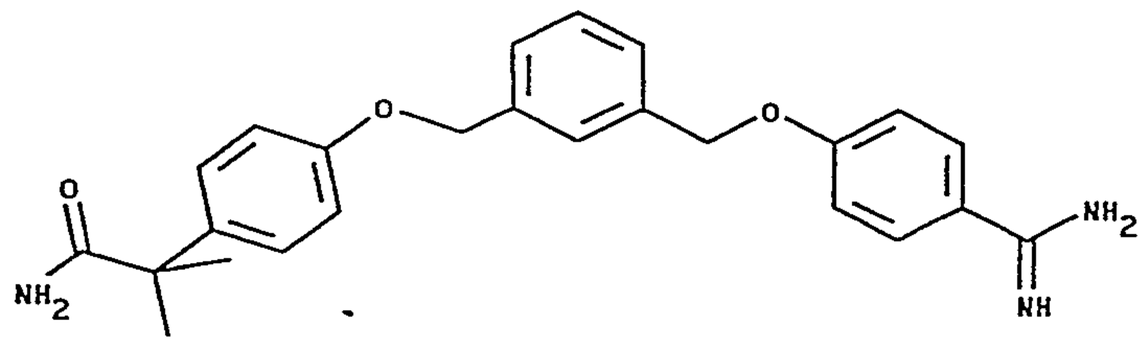
6		Methane-sulphonate	118	125
7		Chloride	156	
8		Chloride	218	220
9		Chloride	130	132
10		Chloride	117	121
11		Dichloride	206	

12		Chloride	165	
13		Chloride	220	
14		Chloride	172	175
15		Chloride	199	275
16		Chloride	152	155

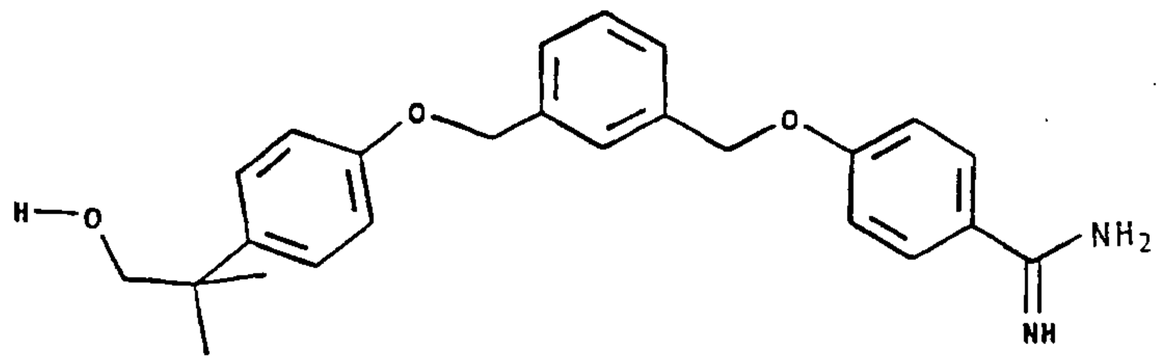
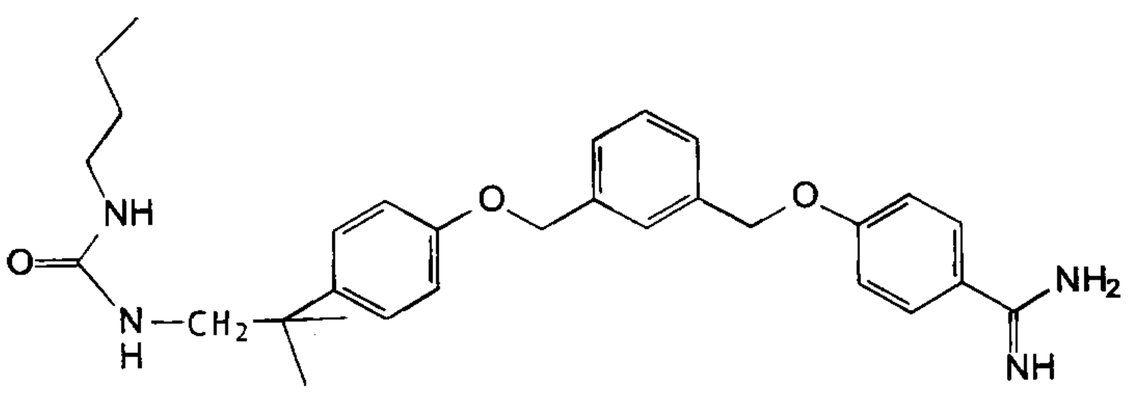
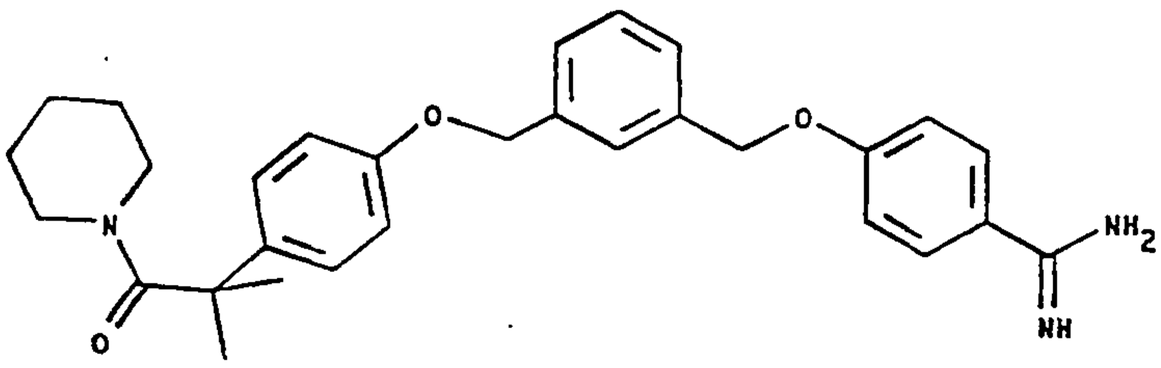
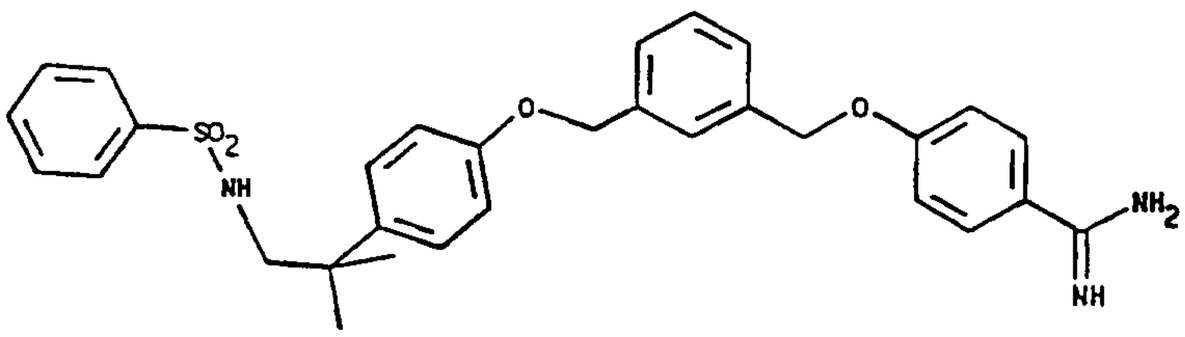
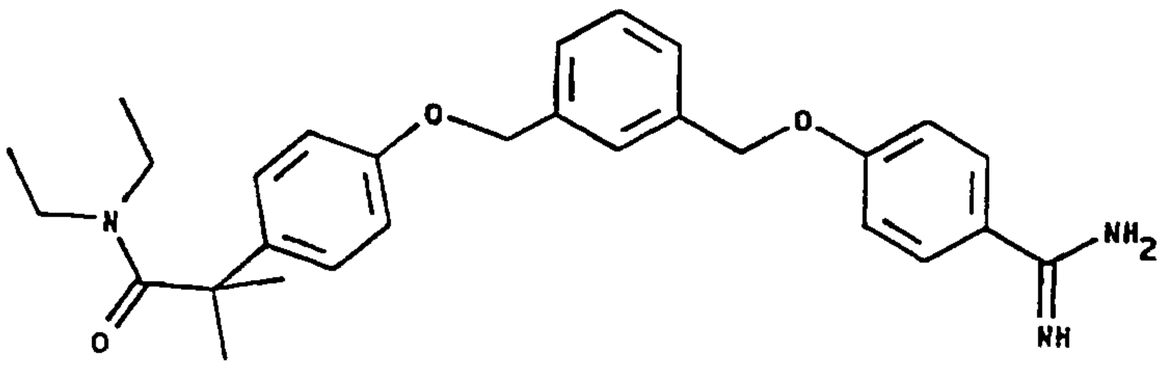
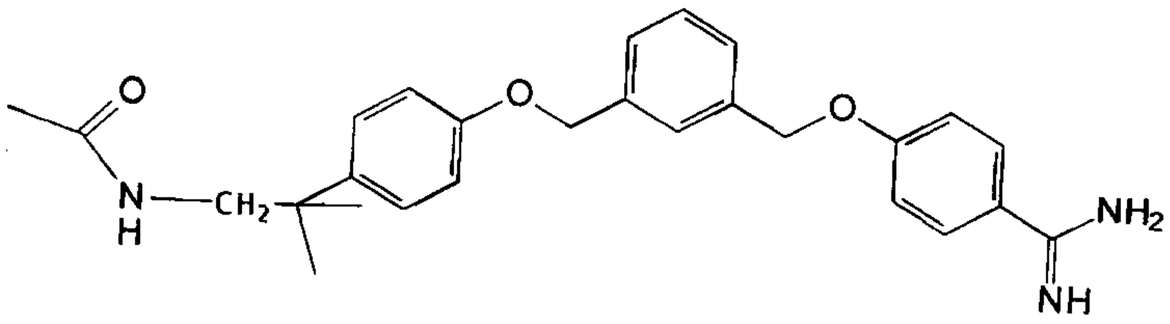
17		Chloride	186	193
18		Chloride	162	165
20		Methane-sulphonate	148	154
21		Sulphate	195	
21		Methane-sulphonate	153	156
22		Fumarate	215	240

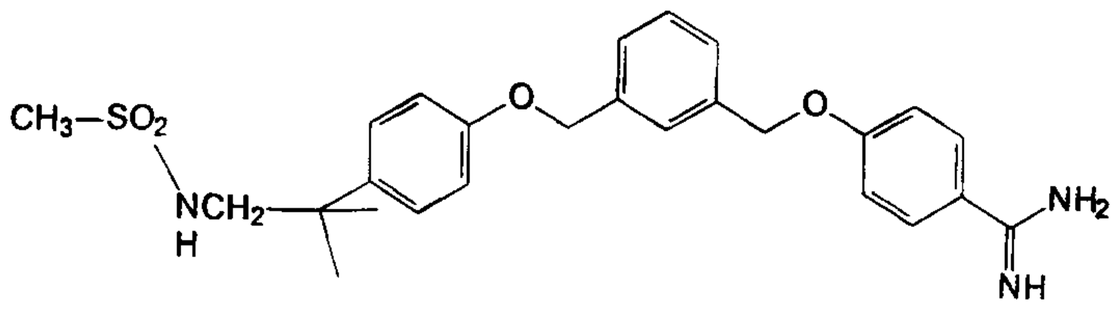
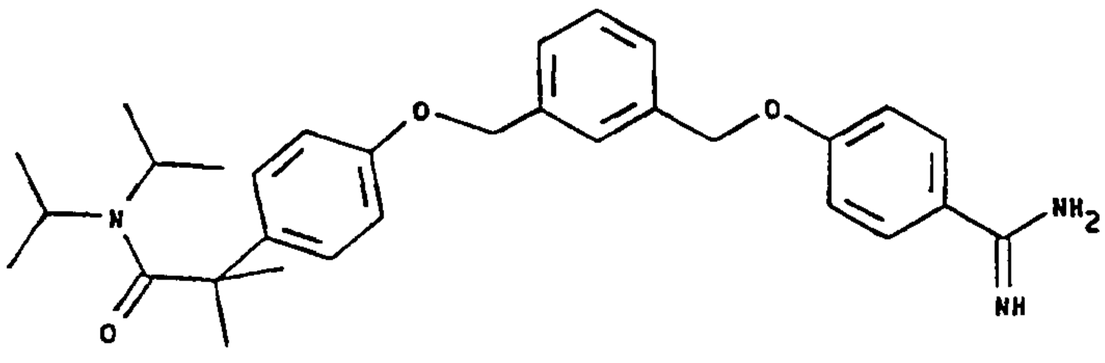
23		Methane-sulphonate	221	224
24		Sulphate	217	
25		Methane-sulphonate	215	218
26		Methane-sulphonate	178	181
27		Methane-sulphonate	138	140

28		Methane-sulphonate	123	126
29		Chloride	193	196
30		Methane-sulphonate	133	137
31		Fumarate	225	
32		Sulphate	230	
33		Methane-sulphonate	230	

34		Methane-sulphonate	230	
35		Methane-sulphonate	230	233
36		Methane-sulphonate	184	187
37		Methane-sulphonate	175	177
38		Methane-sulphonate	160	167
39		Chloride	258	259

27400-185

40		Chloride	212	213
41		Fumarate	219	220
42		Fumarate	257	
43		Fumarate	211	212
44		Fumarate	258	260
45		Fumarate	224	226

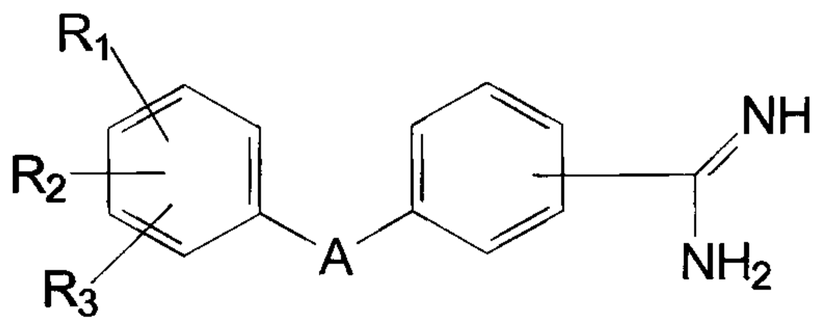
46		Fumarate	224	226
47		Fumarate	216	

Surprisingly, the compounds in the Example and in the Table have outstanding K_i values which are largely within the range from 0.2 to 0.7 nmol/l (RB.LTB4/U937 cells).

27400-185

CLAIMS:

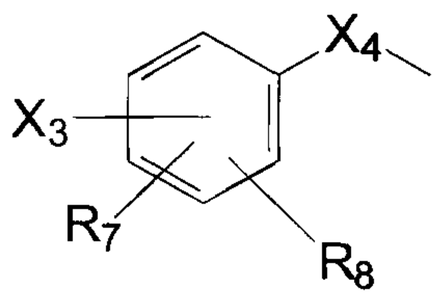
1. A compound of formula I



(I)

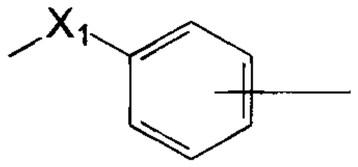
wherein

A is $-X_1-C_mH_{2m}-X_2-$, wherein m is 2, 3, 4, 5 or 6 or



wherein

X_1 is O;

X_2 is O or  ;

X_3 is $-X_1-C_yH_{2y}$, wherein y is 1 or 2;

X_4 is $-C_n-H_{2n}-X_1-$, wherein n is 1 or 2;

R_1 is C_{5-7}-cycloalkyl, $CR_4R_5Ar_3$, or $C(CH_3)_2R_6$;

R_2 is H, C_{1-6}-alkyl, OH, or O-(C_{1-6})-alkyl;

R_3 is H, or C_{1-6}-alkyl;

R_4 is C_{1-4}-alkyl, or CF_3;

R_5 is C_{1-4}-alkyl, or CF_3; or

R_4 and R_5 together form a C_{4-6}-alkylene group;

R_6 is CH_2OH, COOH, $COO(C_{1-4})$-alkyl, $CONR_9R_{10}$, or $CH_2NR_9R_{10}$;

R_7 is H;

R_8 is H;

R_9 is H, C_{1-6}-alkyl, phenyl, phenyl-(C_{1-6}-alkyl), COR_{11}, $COOR_{11}$, CHO, $CONH_2$, $CONHR_{11}$, SO_2-(C_{1-6}-alkyl), SO_2-phenyl, wherein the phenyl ring is optionally mono- or polysubstituted by one or more substituents wherein the substituents are selected from halogen, CF_3, C_{1-4}-alkyl, OH, and C_{1-4}-alkoxy;

R_{10} is H or C_{1-6}-alkyl; or

R_9 and R_{10} together form a C_{4-6}-alkylene group;

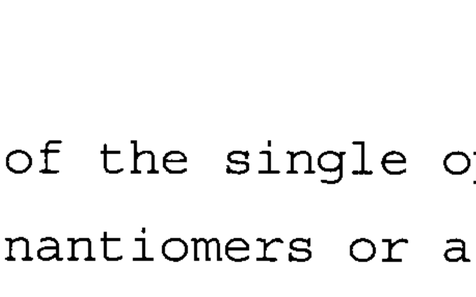
R_{11} is C_{1-6}-alkyl; and

Ar_3 is an optionally mono- or polysubstituted phenyl group

optionally in the form of the single optical isomers, a mixture of individual enantiomers or a racemate thereof, a free base or a corresponding acid addition salt with a pharmacologically acceptable acid.

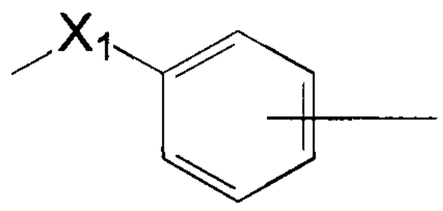
2. A compound isomer, mixture, racemate, free base or salt according to claim 1 wherein

A is $-X_1-C_m-H_{2m}-X_2-$ wherein m is 2 or



wherein

X_2 is



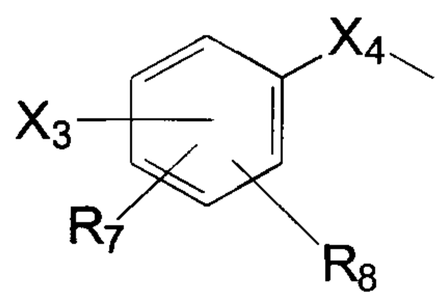
R_9 denotes H, C_{1-6}-alkyl; and

R_{10} denotes H or C_{1-6}-alkyl or

R_9 and R_{10} together form a C_{4-6}-alkylene group.

3. A compound isomer, mixture, racemate, free base or salt according to claim 1 wherein

A is



and

X_3 denotes X_1-CH_2;

X_4 denotes CH_2-X_1;

R_2 is H, OH, or O-(C_{1-6})-alkyl;

R_3 is H;

R_4 is CH_3;

R_5 is CH_3;

R_9 denotes H, C_{1-6}-alkyl; and

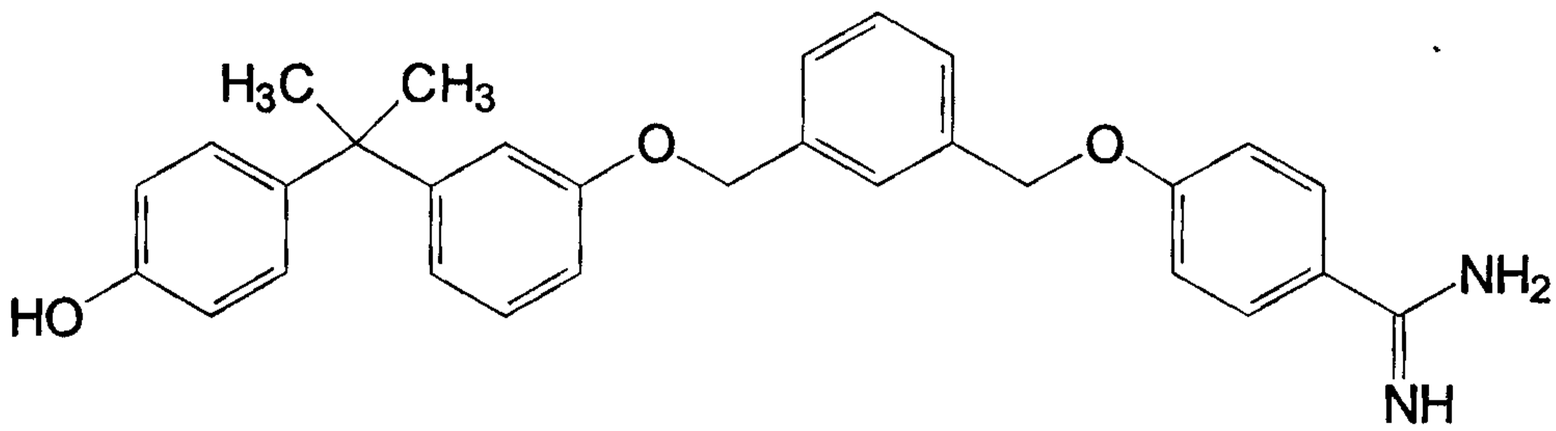
R_{10} denotes H or C_{1-6}-alkyl or

27400-185

R_9 and R_{10} together may also denote a C_{4-6}-alkylene group; and

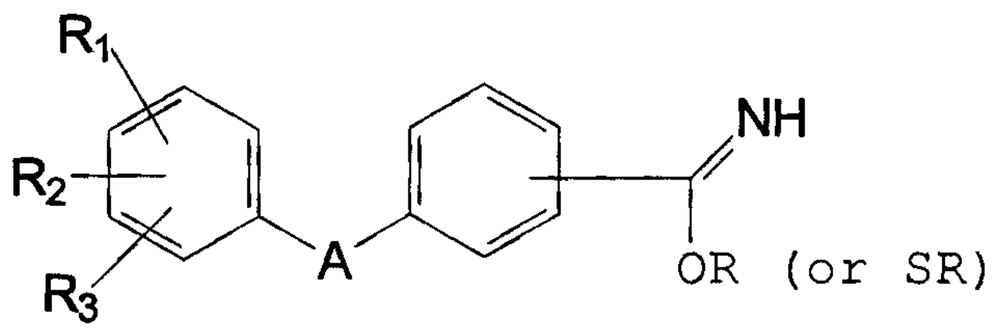
Ar_3 is phenyl optionally mono- or polysubstituted by hydroxy or polysubstituted by hydroxy and C_{1-6}-alkyl.

4. A compound according to claim 1 which is represented by the following formula



optionally in the form a free base or an acid addition salt with a pharmacologically acceptable acid.

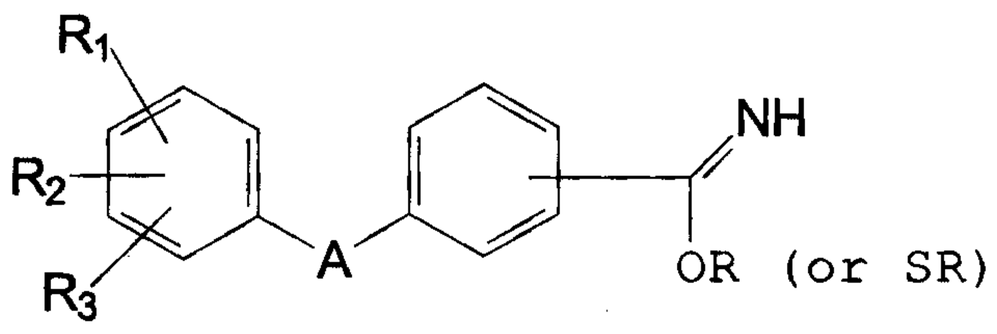
5. A process for preparing a compound according to claim 1, wherein an imido ester of general formula II



(II)

wherein R_1 to R_3 and A are defined as in claim 1 and R is a C_{1-6}-alkyl group or benzyl, is reacted with ammonia, in an organic solvent, at a temperature between about 0°C and boiling temperature of the reaction mixture.

6. A process for preparing a compound according to claim 1, wherein an imido ester of general formula II



(II)

27400-185

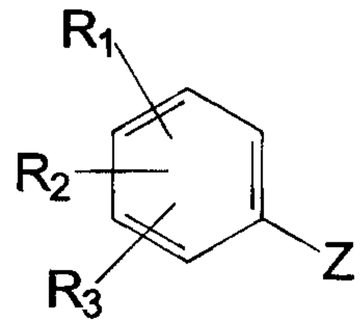
wherein R_1 to R_3 and A are defined as in claim 1 and R is a C_{1-6}-alkyl group or benzyl, is reacted with ammonia in an organic solvent at a temperature between ambient temperature and the boiling point of the solvent if the boiling point of the solvent is greater than 100°C and between ambient temperature and 100°C if the boiling point of the solvent is less than 100°C.

7. A process according to claim 5 or 6 wherein the organic solvent is a polar organic solvent.

8. A process according to claim 5 or 6 wherein the organic solvent is methanol, ethanol or propanol.

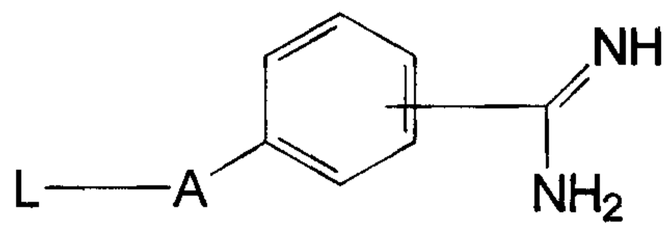
9. A process according to any one of claims 5 to 8, wherein instead of the imido esters of general formula II, the corresponding acid imide chlorides are used as starting material.

10. A process for preparing a compound according to claim 1, wherein A is linked to at least one of the ring systems of the compound of formula I via O, wherein a phenol of formula III



(III)

or a salt thereof, wherein Z denotes OH, and R_1, R_2 and R_3 are as defined in claim 1, is reacted with a compound of general formula IV



(IV)

wherein A is defined as in claim 1 and L denotes a nucleofugic leaving group, in an aprotic solvent or an alcohol with the addition of a base, at a temperature between 0 and 140°C or boiling temperature of the reaction mixture.

11. A process according to claim 10, wherein the aprotic solvent is selected from dimethylsulphoxide, dimethylformamide, and acetonitrile.

12. A process according to claim 10, wherein the alcohol is selected from methanol, ethanol and propanol.

13. A process according to any one of claims 10 to 12, wherein the base is selected from a metal carbonate, a metal hydroxide and a metal hydride.

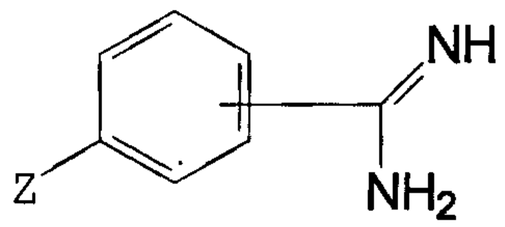
14. A process according to any one of claims 10 to 13, wherein the phenol of formula III is in the form of the salt thereof.

15. A process according to claim 14 wherein the salt is an alkali metal salt.

16. A process according to any one of claims 10 to 15 wherein the nucleofugic leaving group is a halogen.

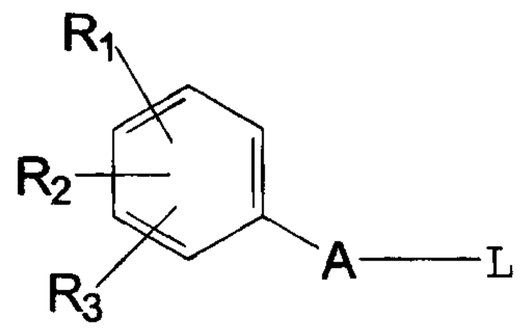
17. A process according to claim 16, wherein the halogen is bromine or chlorine.

18. A process for preparing a compound according to claim 1 wherein A is linked to at least one of the ring systems of the compound of formula I via O, wherein a phenol of general formula V



(V)

wherein Z is OH, is reacted with a compound of formula VI



(VI)

wherein A, R_1, R_2, R_3 and L are defined as in claim 1, in an aprotic solvent or an alcohol with the addition of a base, at a temperature between 0 and 140°C or boiling temperature of the reaction mixture.

19. A process according to claim 18, wherein the aprotic solvent is selected from dimethylsulphoxide, dimethylformamide, and acetonitrile.

20. A process according to claim 18, wherein the alcohol is selected from methanol, ethanol and propanol.

21. A process according to any one of claims 18 to 20, wherein the base is selected from a metal carbonate, a metal hydroxide and a metal hydride.

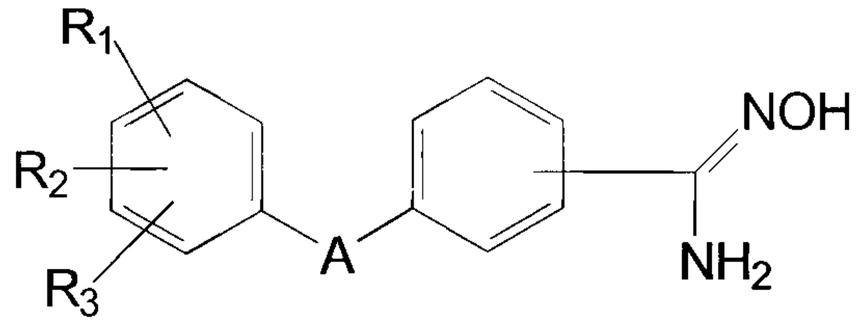
22. A process according to any one of claims 18 to 21, wherein the phenol of formula V is in the form of the salt thereof.

23. A process according to claim 22 wherein the salt is an alkali metal salt.

24. A process according to any one of claims 18 to 23 wherein the nucleofugic leaving group is a halogen.

25. A process according to claim 24, wherein the halogen is bromine or chlorine.

26. A process for preparing a compound according to claim 1, wherein an amidoxime of general formula VII



(VII)

wherein A and R_1 to R_3 are defined as in claim 1, is reduced, in an inert polar solvent, under pressure greater than atmospheric pressure.

27. A process according to claim 26, wherein the reduction is performed by a catalytic method.

28. A process according to claim 27, wherein the catalytic method is performed in the presence of Raney nickel™.

29. A process according to any one of claims 26 to 28, wherein the inert polar solvent is a lower alcohol.

30. A process according to claim 29, wherein the lower alcohol is methanol.

31. A process according to any one of claims 26 to 30, wherein the pressure greater than atmospheric pressure is 5 bar.

32. A pharmaceutical composition comprising a compound or acid addition salt of any one of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.

33. Use of a compound isomer, mixture, racemate, free base or salt according to any one of claims 1 to 3 in preparation of a medicament with LTB_4-antagonistic activity.

27400-185

34. Use of a compound isomer, mixture, racemate, free base or salt of any one of claims 1 to 3 in preparing a medicament for therapeutic treatment of arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by non-steroidal antiphlogistics, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage, ischaemia, atherosclerosis or multiple sclerosis.

35. A use according to claim 34 wherein the chronic obstructive lung disease is chronic bronchitis.

36. A use of a compound, isomer, mixture, racemate, free base, or salt according to any one of claims 1 to 4 for therapeutic treatment of arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by non-steroidal antiphlogistics, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage, ischaemia, atherosclerosis or multiple sclerosis.

37. A use according to claim 36 wherein the chronic obstructive lung disease is chronic bronchitis.

38. A use of a compound or salt according to claim 4 in preparation of a medicament with LTB_4-antagonistic activity.

39. A use of a compound or salt according to claim 4 in preparing a medicament for therapeutic treatment of arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by non-steroidal antiphlogistics, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage, ischaemia, atherosclerosis or multiple sclerosis.

27400-185

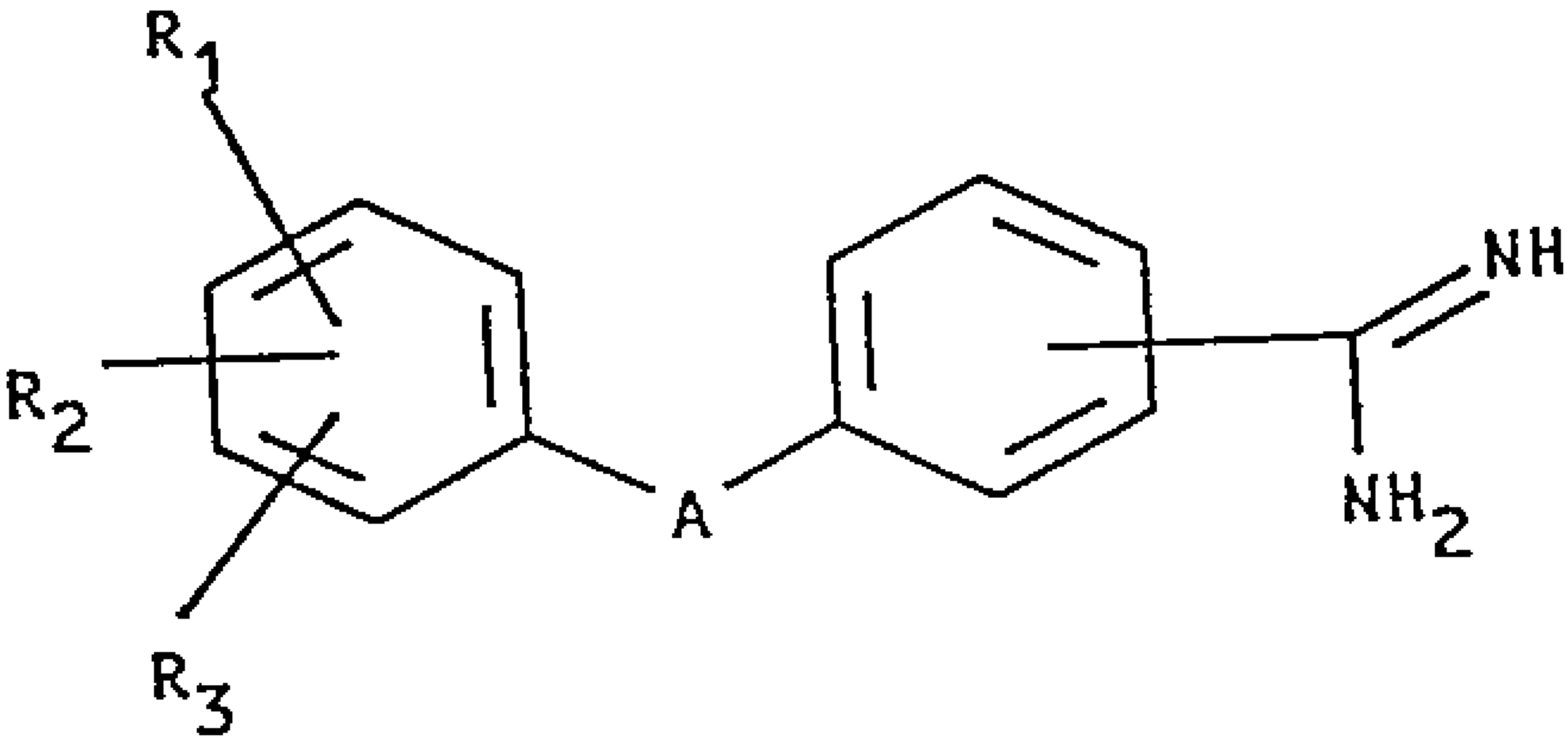
40. A use according to claim 39, wherein the chronic obstructive lung disease is chronic bronchitis.

41. A use of a compound or salt according to claim 4 for therapeutic treatment of arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by non-steroidal antiphlogistics, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage, ischaemia, atherosclerosis or multiple sclerosis.

42. A use according to claim 41, wherein the chronic obstructive lung disease is chronic bronchitis.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS



(I)