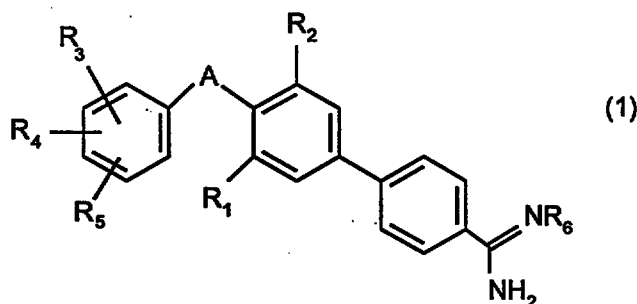


Benzamidine derivatives and their use as medicaments with an LTB₄-antagonistic activity

The present invention relates to new benzamidine derivatives, processes for preparing them and their use in pharmaceutical compositions. The new benzamidine derivatives correspond to general formula 1



wherein

- A denotes -O-C₂₋₄-alkylene-O- or -C₁₋₃-alkylene-O-
- R₁ denotes branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, or F, Cl, Br, I;
- R₂ denotes hydrogen, branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, or F, Cl, Br, I;
- R₃ and R₄, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, C₁₋₆-alkoxy, (C₁₋₄alkyl)OC(O)O, OH or CF₃ or together denote a fused-on mono- or dinuclear ring system which may be wholly or partially conjugated and may optionally contain one or more heteroatoms selected from the group comprising oxygen, sulphur or nitrogen, which may be identical or different, which may optionally be substituted by OH, C₁₋₄-alkoxy or C_{1-C4}-alkyl;
- R₅ denotes hydrogen, aryl, preferably phenyl, -O-phenyl, -CR₇R₈-phenyl, -C(O)phenyl, -SO₂phenyl, -CH(OH)phenyl, wherein the phenyl ring may be substituted by OH, -C₁₋₄-alkoxy, or -C(O)NR₉R₁₀;



R₆ denotes hydrogen, C₁₋₆-alkoxycarbonyl or (C₁₋₅alkyl)carbonyl or -C(O)-O-(C₁₋₆alkylene)-NR₁₁R₁₂;

R₇ and R₈, which may be identical or different, denote hydrogen or branched or unbranched C₁₋₈-alkyl;

R₉ and R₁₀, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₈-alkyl;

R₁₁ and R₁₂, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₈-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.

Preferred compounds of general formula 1 are those wherein

A denotes -OCH₂CH₂O-, -CH₂O-, -CH₂CH₂CH₂O-;

R₁ denotes branched or unbranched C₁₋₅-alkyl or allyl;

R₂ denotes hydrogen;

R₃ denotes hydrogen, C₁₋₆-alkyl, OCH₃, C₂H₅OC(O)O, OH, Cl, F, CF₃;

R₄ denotes hydrogen, -OCH₃, OH;

R₃ and R₄ together denote a fused-on benzene ring, a 3,4-dihydrocumarin system or a 1,3-dioxolane system which may be substituted by OH, C₁₋₃-alkyl or OCH₃;

R₅ denotes hydrogen, phenyl, O-phenyl, -CR₇R₈-phenyl, wherein the phenyl ring may be substituted by OH or OCH₃, or it denotes -C(O)NR₉R₁₀;

R₆ denotes hydrogen or C₁₋₄-alkoxycarbonyl or -C(O)-O-(CH₂)₂-N(C₂H₅)₂;

R₇ and R₈, which may be identical or different, independently of one another denote hydrogen, CH₃ or CF₃;

R₉ and R₁₀, which may be identical or different, denote hydrogen or branched or unbranched C₁-C₈-alkyl.

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

C₁-8-alkyl, C₁-5-alkyl and C₁-4-alkyl generally denote a branched or unbranched hydrocarbon group having 1 to 4 or 5 or 8 carbon atoms, which may optionally be substituted with one or more halogen atoms - preferably fluorine - which may be the same as or different from each other. 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-methylpentyl, 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, *iso*-propyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl are preferred.

Accordingly, alkylene denotes a branched or unbranched double-bonded hydrocarbon bridge having 1 to 8 carbon atoms which may optionally be substituted with one or more halogen atoms - preferably fluorine - which may be the same as or different from each other.

Aryl generally denotes an aromatic group having 6 to 10 carbon atoms - as well as in compositions, where 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 to or different from one another; the preferred aryl group is an optionally substituted phenyl group, whilst the preferred substituents are halogen - such as fluorine, chlorine or bromine - and hydroxyl.

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

As has been found, the compounds of formula 1 are characterised by their wide range of possible applications in the therapeutic field. Particular mention should be made of those

applications in which the LTB₄-receptor-antagonistic properties play a part. Examples include, in particular:

arthritis, asthma, chronic obstructive lung diseases, such as chronic bronchitis, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by nonsteroidal antiinflammatories, cystic fibrosis, Alzheimer's 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 the tissues is of importance (such as metastasis) or diseases and conditions in which the combination of LTB₄ or another molecule (such as 12-HETE) with the LTB₄-receptor influences cell proliferation (such as chronic myeloid leukaemia).

The new compounds may also be used in combination with other active substances, e.g. those which are used for the same indications, or for example with antiallergics, secretolytics, β_2 -adrenergics, inhaled steroids, antihistamines and/or PAF-antagonists. They may be administered by topical, oral, transdermal, nasal or parenteral route or by inhalation.

The activity ratios may be investigated pharmacologically and biochemically using tests such as those described in WO 93/16036, pp. 15 to 17 - the contents of which are referred to herein.

The therapeutic or prophylactic dose depends 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 illness. For oral administration the dose is between 10 and 500 mg, preferably between 20 and 250 mg. For inhalation the patient is given between about 0,5 and 25 mg, preferably between about 2 and 20 mg of active substance.

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

The Examples which follow show some possible ways of formulating the preparations:

Formulation examples

1. Tablets

Composition:

Active substance according to 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 invention	100 parts by weight
Lactose, powdered	45 parts by weight
Cocoa butter	1555 parts by weight

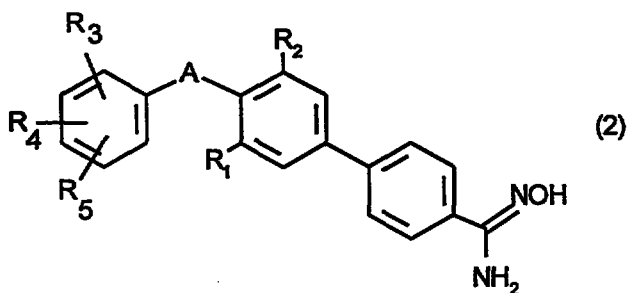
The ingredients are processed in the usual way to form suppositories weighing 1.7 g.

3. Powder for Inhalation

Micronised active substance powder (compound of formula 1; particle size about 0.5 to 7 μm) is packed into hard gelatin 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, which is referred to herein.

The new compounds may be prepared using the following conventional methods, which are known from the prior art:

1. Reduction of an amidoxime of general formula 2

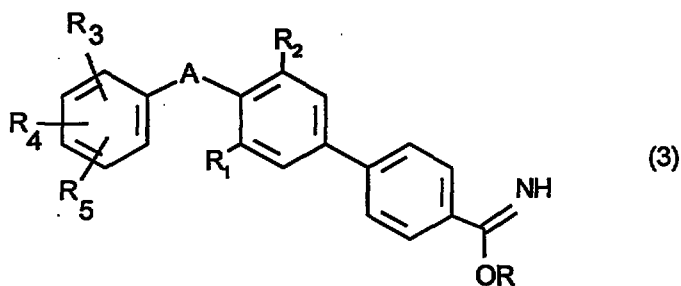


wherein R_1 to R_5 and A are as hereinbefore defined.

The reduction of the amidoxime of general formula 2 may conveniently be carried out by catalytic hydrogenation, especially with Raney nickel in a lower alcohol, e.g. methanol.

The amidoxime of general formula 2 is conveniently dissolved in methanol with the addition of the calculated amount of the particular acid, the salt of which is the desired end product, and hydrogenated at ambient temperature under gentle pressure, e.g. at 5 bar, until the uptake of hydrogen has ceased.

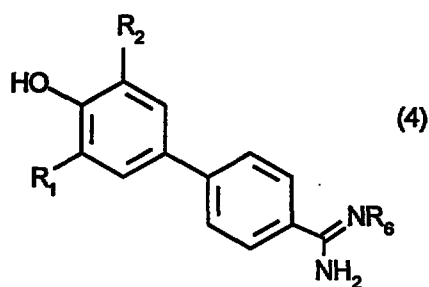
2. Reaction of iminoesters of general formula 3



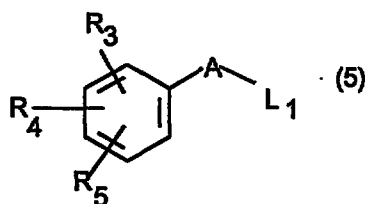
wherein R_1 to R_5 and A are as hereinbefore defined and R preferably denotes a lower alkyl group, with ammonia.

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 propanols.

3. Reaction of a phenol of general formula 4



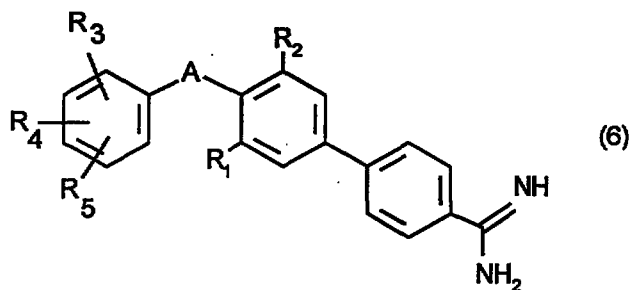
wherein R_1 , R_2 , R_6 are as hereinbefore defined, with a compound of formula 5



wherein A, R_3 , R_4 and R_5 are as hereinbefore defined and L_1 denotes a nucleofugal leaving group such as a halogen atom or a sulphonic acid group.

The reaction is carried out in aprotic solvents such as dimethyl sulphoxide, dimethylformamide, acetonitrile or alcohols such as methanol, ethanol or propanol with the addition of a base (preferably an alkali metal or alkaline earth metal carbonate, hydroxide or hydride) at temperatures of between about 0 and 140°C or the boiling temperature of the reaction mixture.

4. Reaction of an amidine of general formula 6



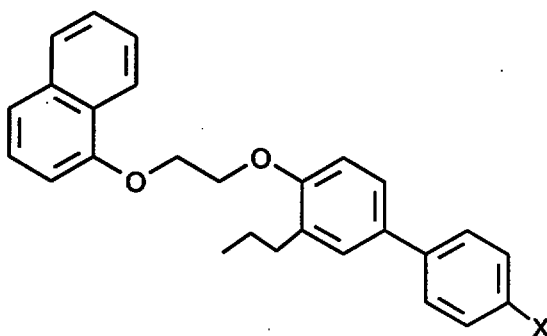
wherein R_1 to R_5 and A are as hereinbefore defined, with a compound of formula 7



wherein R_6' has the same meanings as R_6 , with the exception of H, and L_2 denotes a nucleofugal leaving group such as a halogen atom (such as Cl or Br) or acyloxy.

The reaction is conveniently 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-methylmorpholine or pyridine, which may simultaneously serve as solvents, at temperatures between -30 and 100°C , but preferably at temperatures between -10 and 80°C .

The compounds according to the invention may be prepared from compounds known from the prior art, *inter alia* using the methods described in the following Examples. Various other embodiments of the processes will become apparent to the skilled person from the specification. However, it is expressly pointed out that these Examples and the associated description are intended solely as an illustration and must not be regarded as limiting the invention.



Amidoxime: $X = C(=NOH)NH_2$

5.3 g of the nitrile of the above formula ($X = CN$) is refluxed together with 98 ml of ethanol, 3.65 g of hydroxylamine $\times$ HCl, 2.9 g of Na_2CO_3 and 21 ml of water for 5 hours. Then the mixture is distilled to dryness and the residue is stirred with water and suction filtered. 5.7 g are suspended in 25 ml of acetonitrile and mixed with 0.85 ml of methanesulphonic acid, heated and cooled again.

After suction filtering 6.4 g of the methanesulphonate are obtained in the form of white crystals.

Amidine: $X = C(=NH)-NH_2$

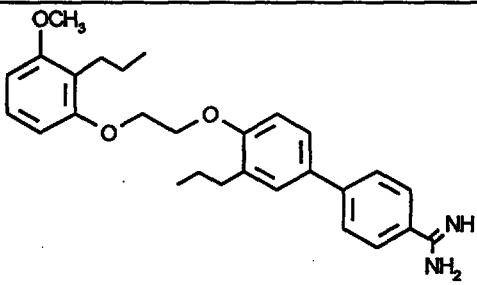
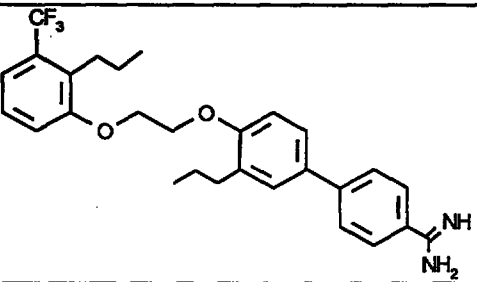
6.4 g of the amidoxime [$X = C(=NOH)-NH_2$] in the form of the methanesulphonate are dissolved in 100 ml of methanol and hydrogenated, using Raney nickel as catalyst, under

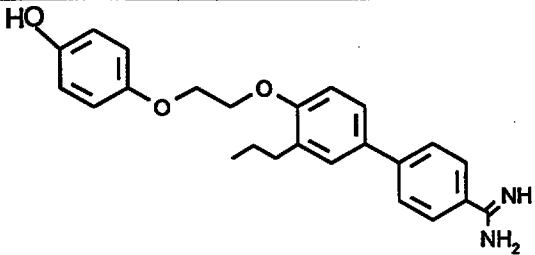
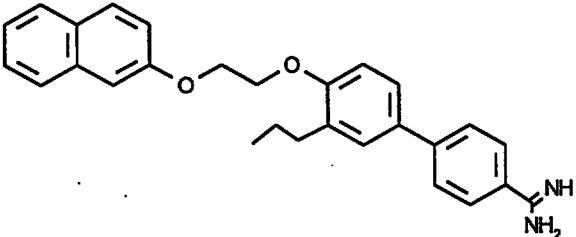
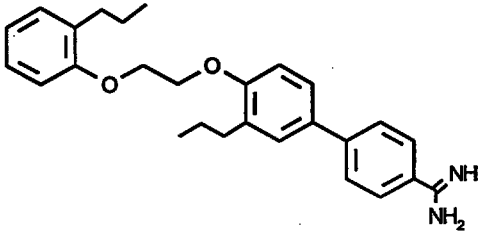
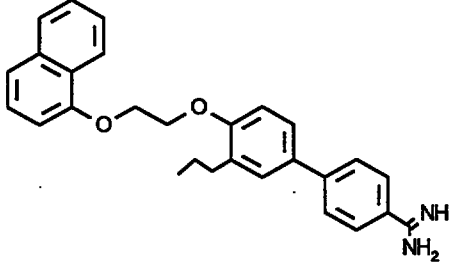
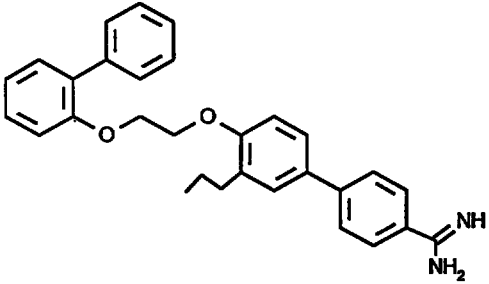
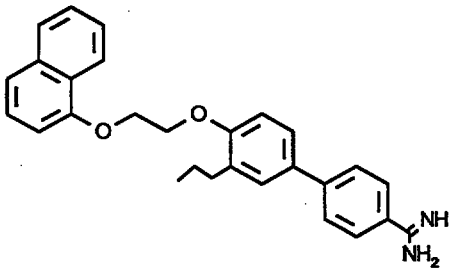
normal conditions, until 100% hydrogen uptake has occurred. After suction filtering, the filtrate is evaporated down and the residue is recrystallised from methanol. Yield: 3.8 g of the amidine compound as the methanesulphonate. Mp. 228 - 30°C.

Ethoxycarbonylamidine: $X = C(NCOOC_2H_5)-NH_2$

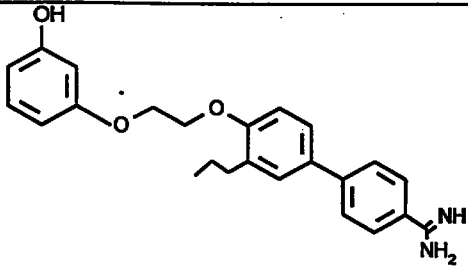
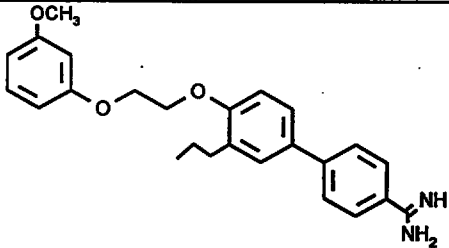
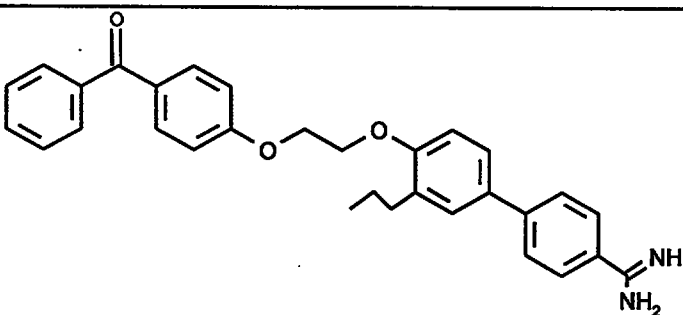
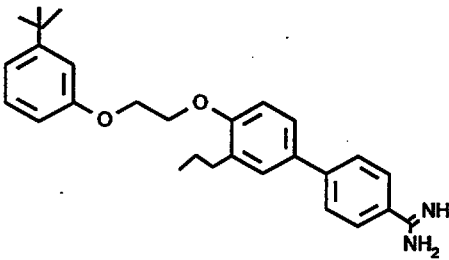
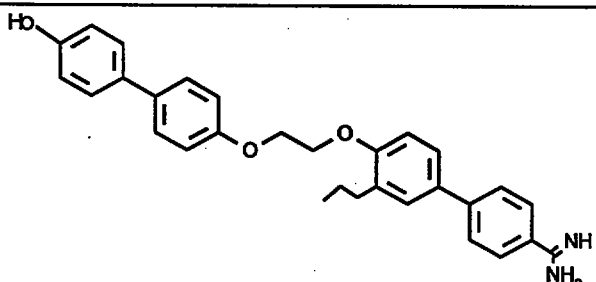
2.6 g of the amidine methanesulphonate are suspended with 1.6 ml of triethylamine in 50 ml of ethyl acetate and 0.6 ml of ethyl chloroformate in 5.5 ml of ethyl acetate is added thereto at ambient temperature over about 15 minutes. The reaction mixture is then washed three times with water, dried with Na_2SO_4 and evaporated down. After recrystallisation from acetonitrile the ethoxycarbonylamidine compound is obtained, mp. 142 - 144°C.

Following these procedures, the following compounds are obtained, for example:

No.	Compound	salt form	Mp. [°C]
1		methane sulphonate	221-223
2		methane sulphonate	212-213

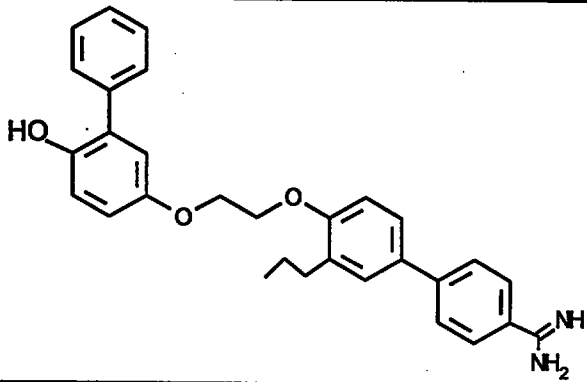
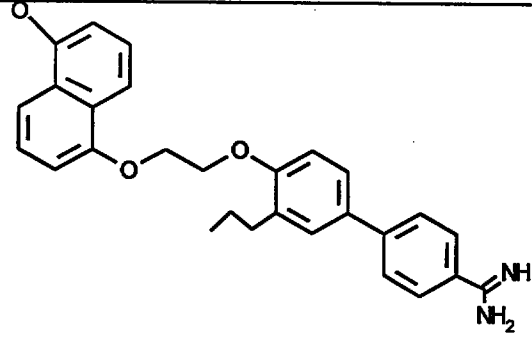
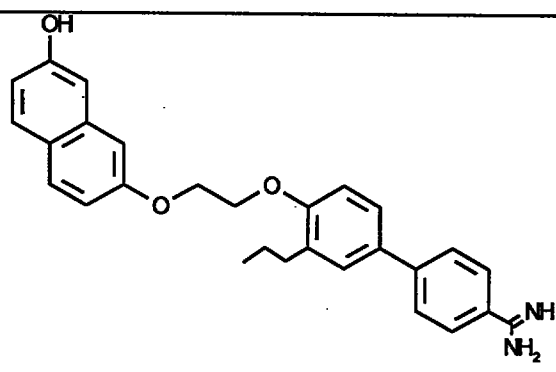
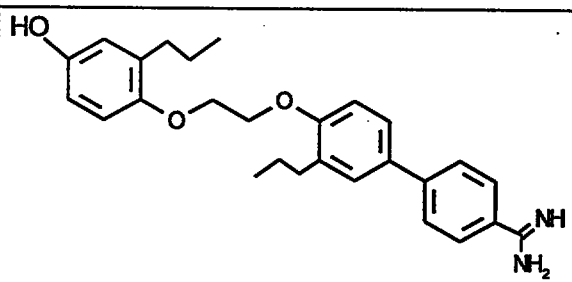
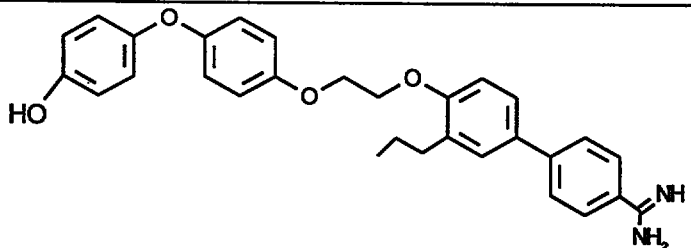
3		methane sulphonate	219-222
4		methane sulphonate	>230
5		methane sulphonate	185-188
6		methane sulphonate	228-230
7		methane sulphonate	233-234
8		methane sulphonate	211-213



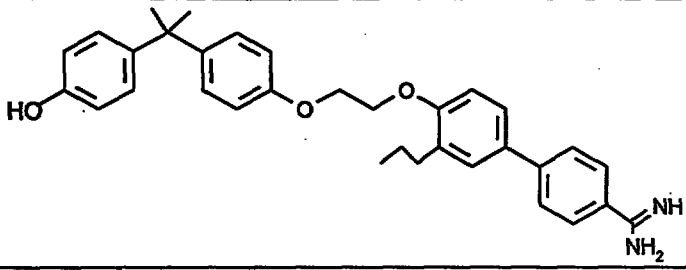
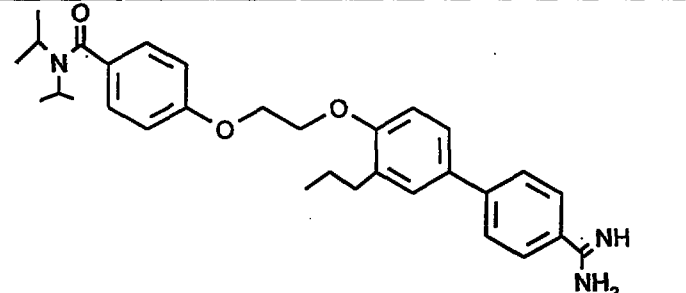
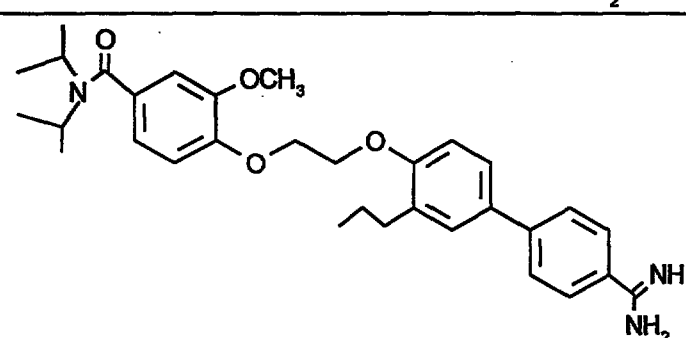
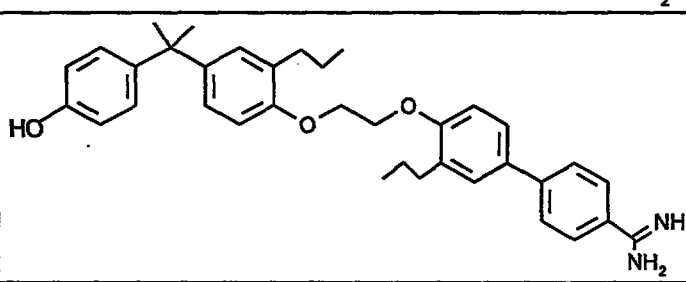
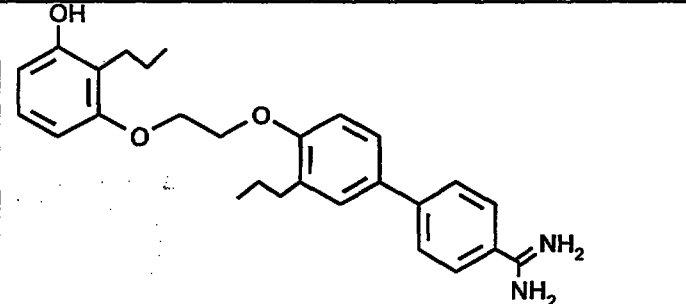
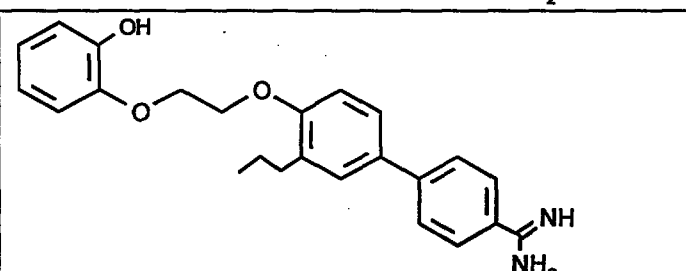
9		methane sulphonate	206-208
10		methane sulphonate	201-203
11		methane sulphonate	207-211
12		methane sulphonate	212-214
13		methane sulphonate	225-227

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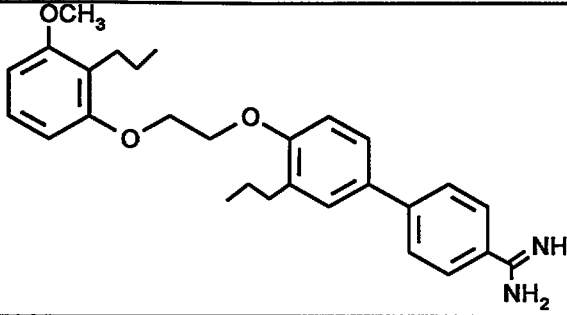
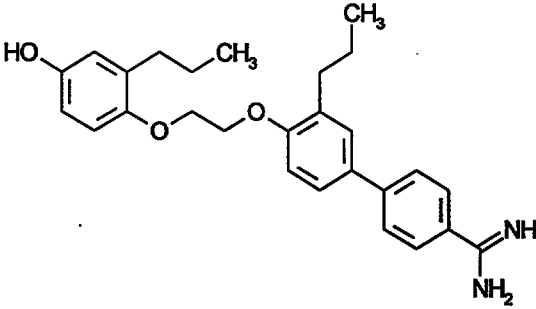
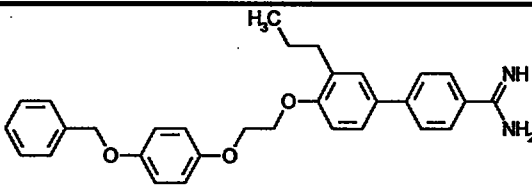
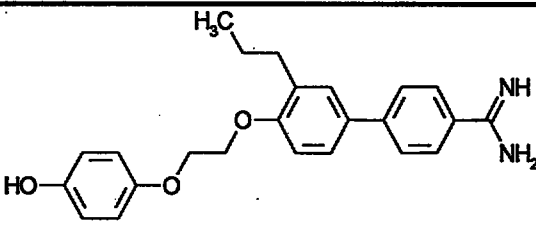
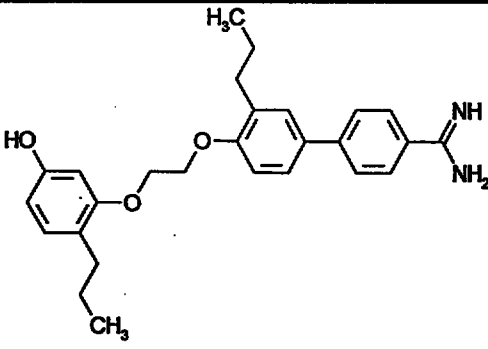
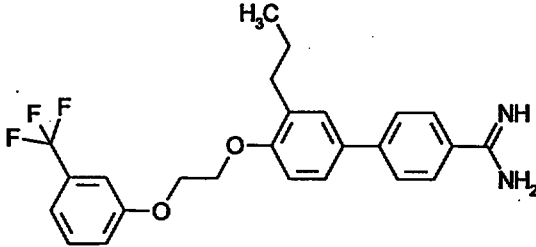


14		methane sulphonate	198-200
15		methane sulphonate	>230
16		methane sulphonate	209-211
17		methane sulphonate	188-190
18			



19		methane sulphonate	>230°
20			
21			
22			
23			
24		chloride	302 (decomposition)



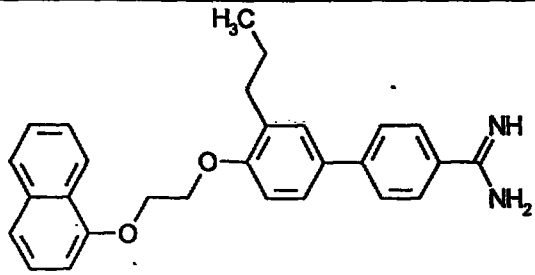
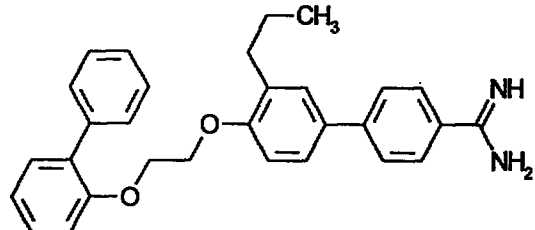
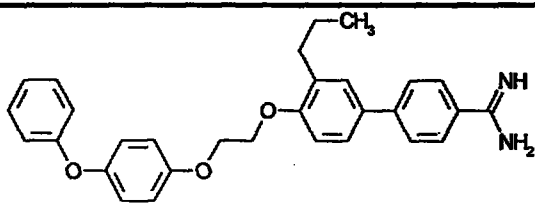
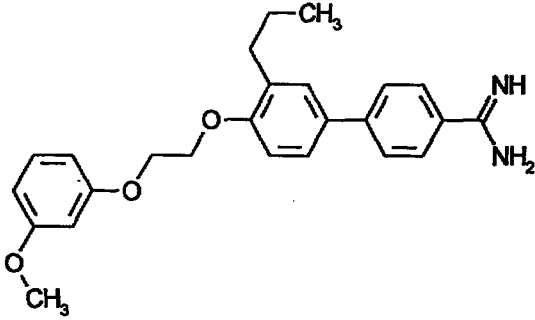
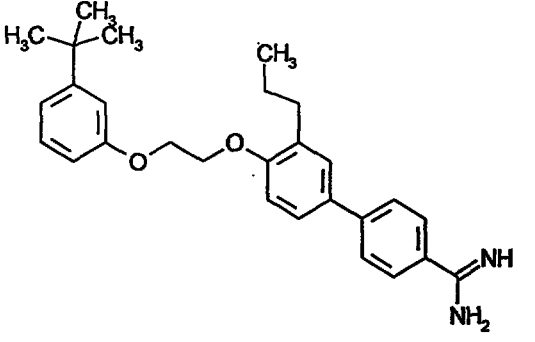
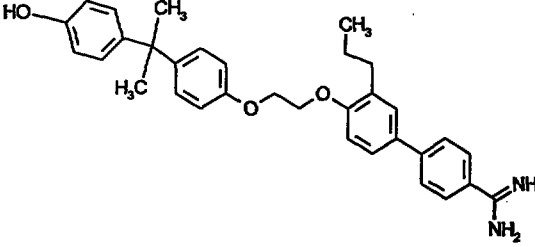
25		methane sulphonate	221-223
26		methane sulphonate	188-190
27		methane sulphonate	216-219
28		methane sulphonate	219-222
29		methane sulphonate	176
30		methane sulphonate	212-213

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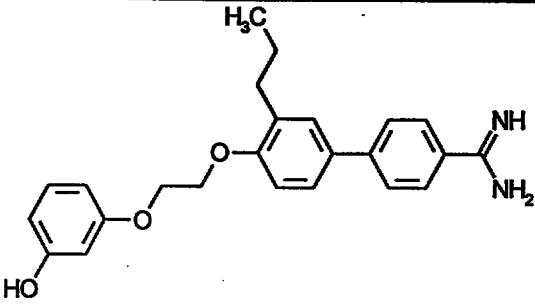
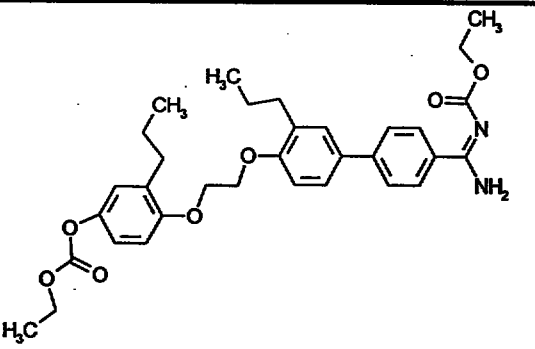
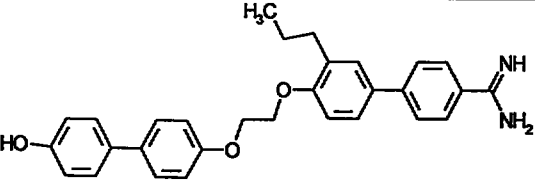
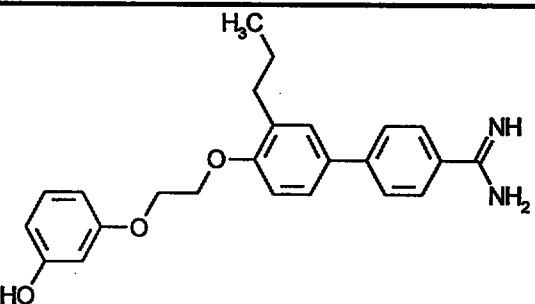
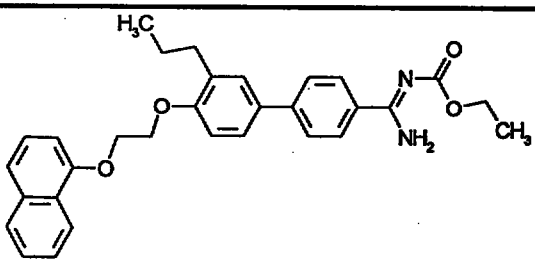
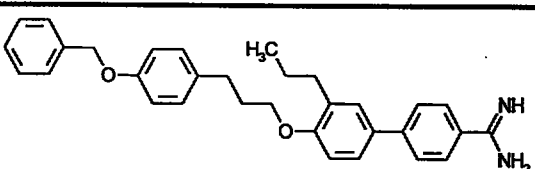
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36		methane sulphonate	228-230
37		methane sulphonate	233-234
38		methane sulphonate	211-213
39		methane sulphonate	201-203
40		methane sulphonate	212-214
41		methane sulphonate	230

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42		methane sulphonate	206-208
43			84-86
44		methane sulphonate	225-227
45		methane sulphonate	207-211
46			142-144
47		methane sulphonate	215-221



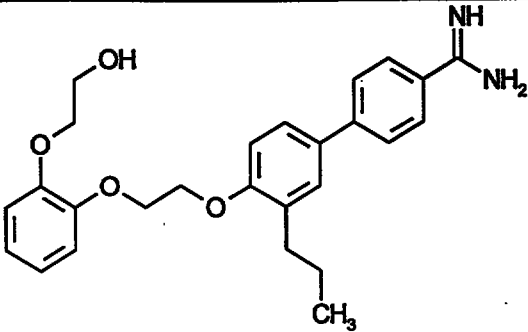
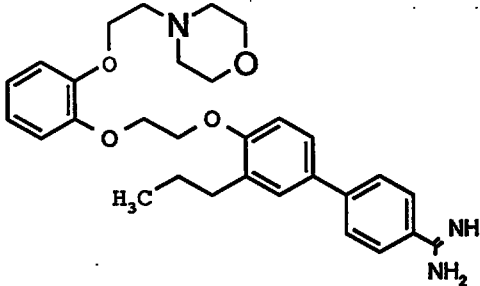
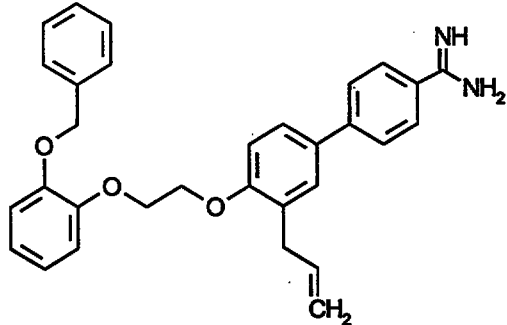
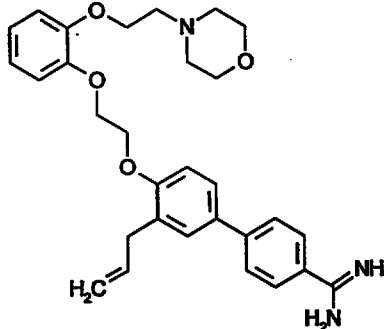
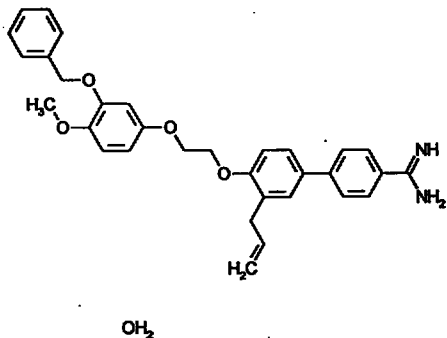
48		methane sulphonate	209-211
49		methane sulphonate	>230
50		methane sulphonate	>230
51		methane sulphonate	>230
52		methane sulphonate	198-200
53		methane sulphonate	218-222



54			144-147
55		methane sulphonate	185-191
56		dichloride	150-154
57		methane sulphonate	220
58		di-methane sulphonate	198-202
59		chloride	302

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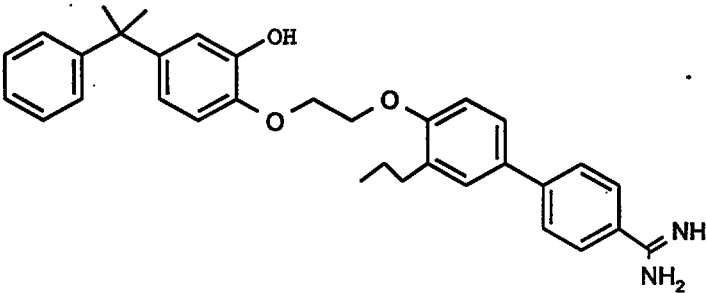
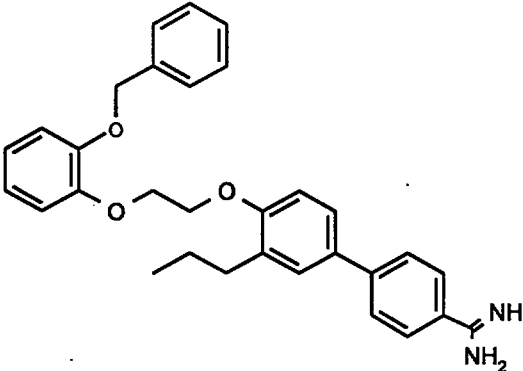
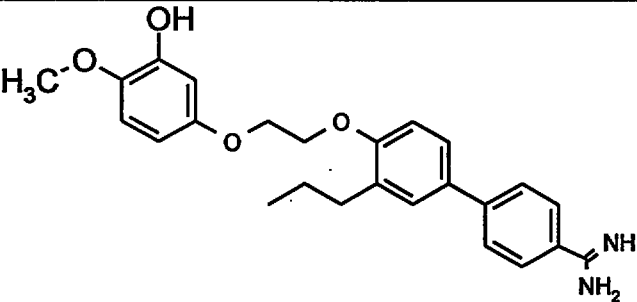
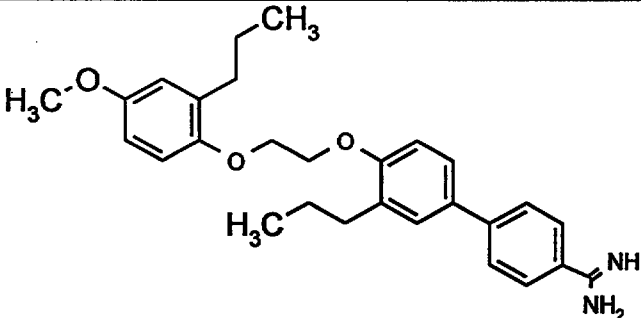


60		methane sulphonate	158
61		methane sulphonate	151
62		chloride	170-175
63		methane sulphonate	135-142
64		chloride	178



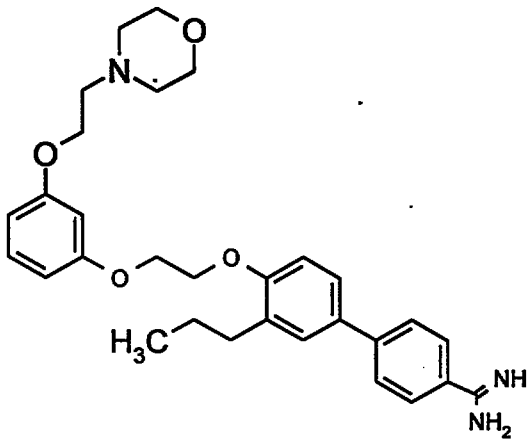
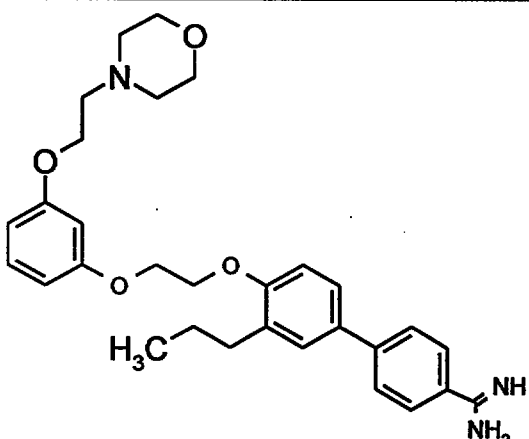
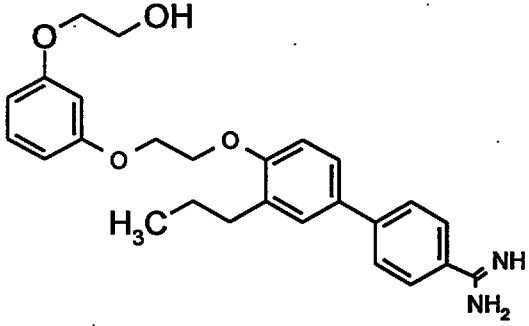
65		chloride	138-145
66		chloride	209-210
67		chloride	182-183
68		chloride	211-216
69		methane sulphonate	168-175
70		methane sulphonate	170-174



71			
72		Chloride	171-175
73		chloride	180-188
74		chloride	126-129

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75		methane sulphonate	158-166
76		methane sulphonate	175-183
77		methane sulphonate	180

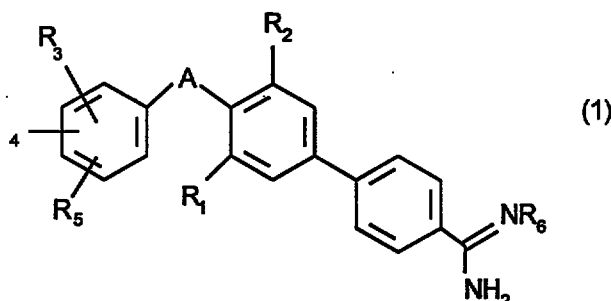
For additional information we hereby draw attention to the full disclosure of German Patent Application No.: 196 36 689.5, from which the present application claims priority.

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Patent Claims

1. Benzamidine derivatives of general formula 1



wherein

A denotes -O-C₂₋₄-alkylene-O- or -C₁₋₃-alkylene-O-

R₁ denotes branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, or F, Cl, Br, I;

R₂ denotes hydrogen, branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, or F, Cl, Br, I;

R₃ and R₄, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₆-alkyl, branched or unbranched C₃₋₆-alkenyl, preferably allyl, C₁₋₆-alkoxy, (C₁₋₄alkyl)OC(O)O, OH or CF₃ or together denote a fused-on mono- or dinuclear ring system which may be wholly or partially conjugated and may optionally contain one or more heteroatoms selected from the group comprising oxygen, sulphur or nitrogen, which may be identical or different, which may optionally be substituted by OH, C₁₋₄-alkoxy or C_{1-C4}-alkyl;

R₅ denotes hydrogen, aryl, preferably phenyl, -O-phenyl, -CR₇R₈-phenyl, -C(O)phenyl, -SO₂phenyl, -CH(OH)phenyl, wherein the phenyl ring may be substituted by OH, -C₁₋₄-alkoxy, or -C(O)NR₉R₁₀;

R₆ denotes hydrogen, C₁₋₆-alkoxycarbonyl or (C₁₋₅alkyl)carbonyl or -C(O)-O-(C₁₋₆alkylene)-NR₁₁R₁₂;

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R₇ and R₈, which may be identical or different, denote hydrogen or branched or unbranched C₁₋₈-alkyl;

R₉ and R₁₀, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₈-alkyl;

R₁₁ and R₁₂, which may be identical or different, independently of one another denote hydrogen, branched or unbranched C₁₋₈-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.

2. Compounds of general formula 1 according to claim 1, wherein

A denotes -OCH₂CH₂O-, -CH₂O-, -CH₂CH₂CH₂O-;

R₁ denotes branched or unbranched C₁₋₅-alkyl or allyl;

R₂ denotes hydrogen;

R₃ denotes hydrogen, C₁₋₆-alkyl, OCH₃, C₂H₅OC(O)O, OH, Cl, F, CF₃;

R₄ denotes hydrogen, -OCH₃, OH;

R₃ and R₄ together denote a fused-on benzene ring, a 3,4-dihydrocumarin system or a 1,3-dioxolane system which may be substituted by OH, C₁₋₃-alkyl or OCH₃;

R₅ denotes hydrogen, phenyl, O-phenyl, -CR₇R₈-phenyl, wherein the phenyl ring may be substituted by OH or OCH₃, or it denotes -C(O)NR₉R₁₀;

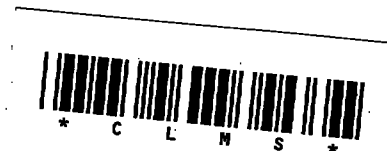
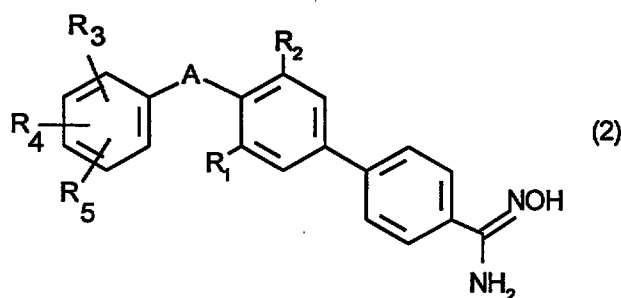
R₆ denotes hydrogen or C₁₋₄-alkoxycarbonyl or -C(O)-O-(CH₂)₂-N(C₂H₅)₂;

R₇ and R₈, which may be identical or different, independently of one another denote hydrogen, CH₃ or CF₃;

R₉ and R₁₀, which may be identical or different, denote hydrogen or branched or unbranched C_{1-C8}-alkyl.

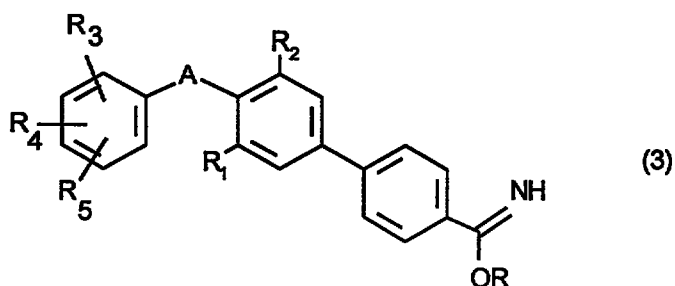


3. Process for preparing compounds of general formula 1, characterised in that an amidoxime of general formula 2



wherein R_1 to R_5 and A are defined as in claim 1, is reduced in a manner known per se.

4. Process according to claim 3, characterised in that the reduction is carried out catalytically, preferably in the presence of Raney nickel.
5. Process according to claim 3 or 4, characterised in that the catalytic reduction of the amidoxime is carried out in a lower alcohol, preferably in methanol.
6. Process for preparing compounds of general formula 1, characterised in that



wherein R_1 to R_5 and A wherein R_1 to R_5 and A [sic] are defined as in claim 1, is reacted with ammonia.

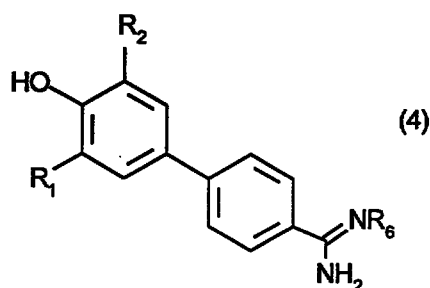
7. Process according to claim 6, characterised in that the reaction is carried out in an organic solvent at temperatures between about 0°C and the boiling temperature of



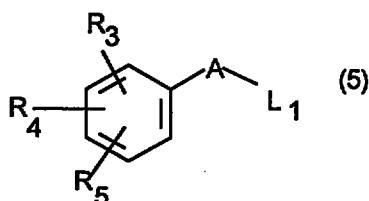
the reaction mixture, preferably in a temperature range of between ambient temperature and about 100°C or at the boiling temperature, if this is lower.

8. Process according to claim 6 or 7, characterised in that the reaction is carried out in a polar solvent, preferably methanol, ethanol or a propanol.

9. Process for preparing compounds of general formula 1, characterised in that a phenol of general formula 4



wherein R₁, R₂ and R₆ are defined as in claim 1, is reacted with a compound of formula 5



wherein A, R₃, R₄ and R₅ are defined as in claim 1 and L₁ denotes a nucleofugal leaving group, preferably a halogen atom or a sulphonic acid group, in an aprotic solvent.

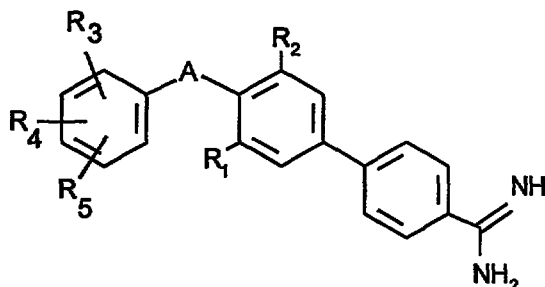
10. Process according to claim 9, characterised in that the solvent is dimethylsulphoxide, dimethylformamide, acetonitrile or an alcohol, preferably methanol, ethanol or a propanol.



11. Process according to claim 9 or 10, characterised in that the reaction is carried out in the presence of a base, preferably in the presence of an alkali metal or alkaline earth metal carbonate, metal hydroxide or metal hydride.

12. Process according to one of claims 9 to 11, characterised in that the reaction is carried out at a temperature in the range between 0 °C and the boiling point of the reaction mixture and preferably in the temperature range from 0 to 140°C.

13. Process for preparing compounds of general formula 1, characterised in that an amidine of general formula 6



wherein R_1 to R_5 and A are defined as in claim 1, is reacted with a compound of general formula 7



wherein R_6' denotes C_1 - C_6 -alkoxycarbonyl or C_1 - C_6 -acyl and L_2 denotes a nucleofugal leaving group, preferably chlorine, bromine or acyloxy.

14. Process according to claim 13, characterised in that the reaction is carried out in a polar solvent.

15. Process according to claim 14, characterised in that the solvent is tetrahydrofuran, methylene chloride, chloroform or dimethylformamide.





16. Process according to claim 14 or 15, characterised in that the reaction is carried out in the presence of an inorganic base, preferably sodium carbonate, potassium carbonate or sodium hydroxide solution, or in the presence of a tertiary organic base, preferably triethylamine, N-ethyl-diisopropylamine, N-methylmorpholine or pyridine.
17. Process according to one of claims 14 to 16, characterised in that the reaction is carried out in a temperature range of between -30 and 100°C, preferably in a temperature range of between -10 and 80°C.
18. Pharmaceutical preparation, characterised in that it contains a compound according to one of claims 1 and 2 and the acid addition salts thereof together with excipients and/or carriers.
19. Use of compounds according to one of claims 1 and 2 as pharmaceutical compositions.
20. Use of compounds according to claim 19 as pharmaceutical compositions with an LTB₄-antagonistic activity.
21. Use of compounds of general formula 1, the stereoisomers and the acid addition salts thereof for the preparation of a medicament for the therapeutic treatment of arthritis, asthma, chronic obstructive lung diseases such as chronic bronchitis, psoriasis, ulcerative colitis, gastropathy or enteropathy induced by nonsteroidal antiinflammatories, cystic fibrosis, Alzheimer's disease, shock, reperfusion damage/ischaemia, atherosclerosis and multiple sclerosis.

