

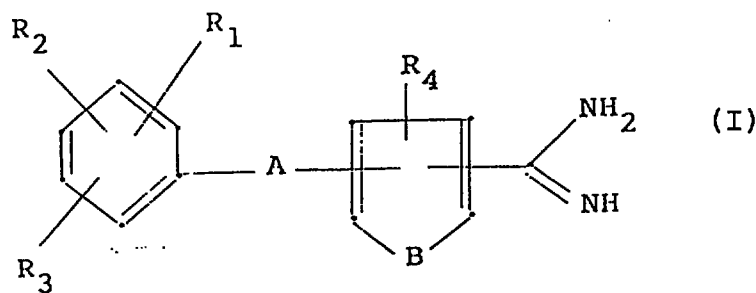
☒ Description : paged to paged
☒ Claim(s) : paged to paged
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☐ Abstract : paged to paged
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New amidine derivatives, the preparation and use
thereof as pharmaceutical compositions with LTB₄-
antagonistic activity

The invention relates to new amidine derivatives, the preparation thereof using conventional methods and their use in pharmaceutical compositions.

The new amidine derivatives correspond to the formula

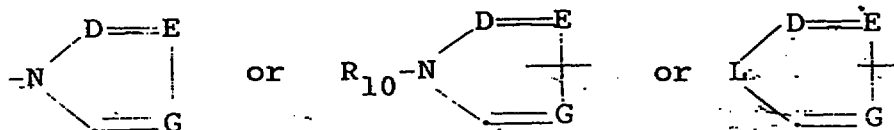


wherein

R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_{3-4}-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,

R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONR_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}-alkyl)$, SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}-alkyl)$, $NH-SO_2-(C_{1-4}-alkyl)$, NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula





(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

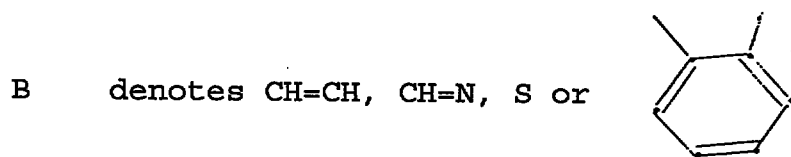
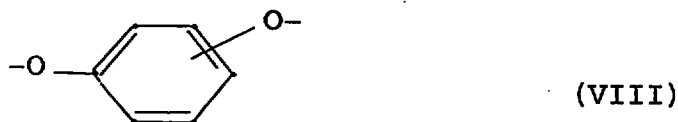
X₁-A₁-X₂ (II)

X₂-A₂-X₃ (III)

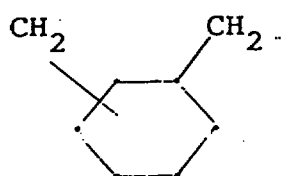
X₄-A₂-X₂ (IV)

(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)





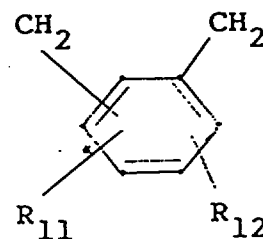
A_1 denotes C_{2-4} -alkylene, cis- or trans- $\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2$, $\text{CH}_2-\text{C}=\text{C}-\text{CH}_2$ or



(IX)



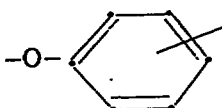
(IXa)



(IXb)

A_2 denotes C_{1-5} -alkylene,

X_1 denotes O, NH, S, SO, SO_2 , CO, CH_2 or 

X_2 denotes O, NH, S or 

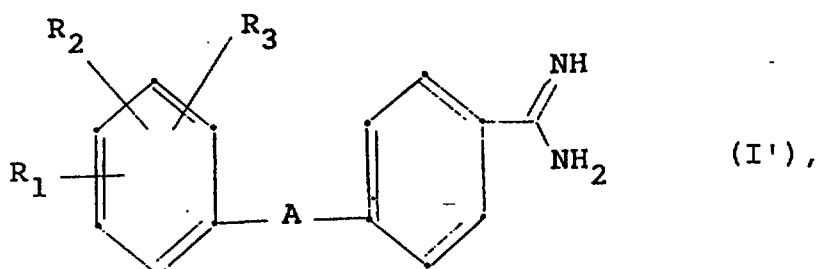
X_3 denotes NH-CO, CO-NH, SO_2 -NH or 

X_4 denotes NH-CO, CO-NH, NH- SO_2 , SO_2 -NH or NH-CO-NH,



and (if they contain one or more chiral centres), may occur in the form of racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and (if a double bond is present) in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.

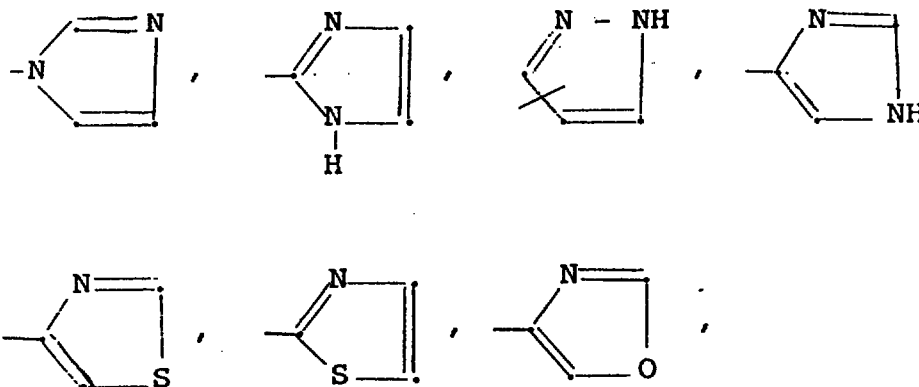
Within the scope of the above definitions, the preferred compounds are the compounds of formula



wherein

R_1, R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-CR_8=R_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-O-CHR_{10}-CH_2-$ or $-CO-CH_2-CH_2-O-$, linked with adjacent carbon atoms of the benzene ring,

R_3 denotes halogen, CF_3 , R_7 , OR_7 , $CO-(C_{1-4}\text{-alkyl})$, $NH-CO-(C_{1-4}\text{-alkyl})$, $NHSO_2-(C_{1-4}\text{-alkyl})$ or $N(R_{10})_2$ (whilst R_7 can only denote H if at least one of the substituents R_1 and R_2 does not denote H) or a heterocyclic five-membered ring such as

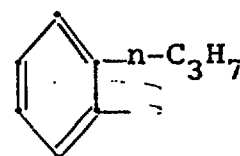
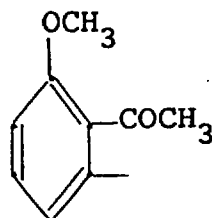
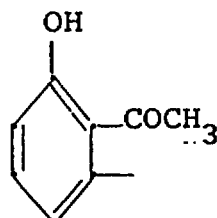
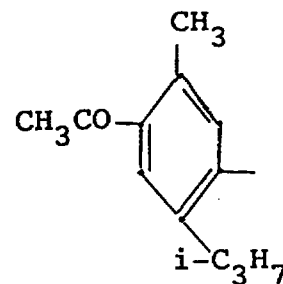
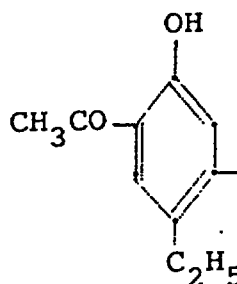
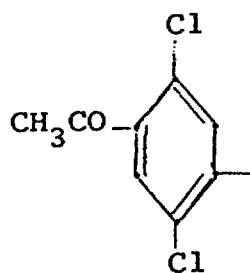
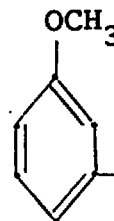
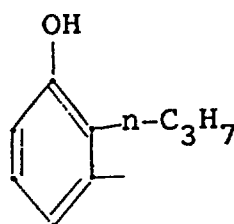
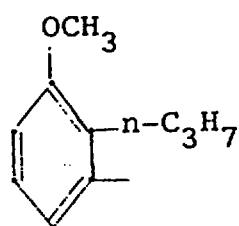


R_6 and R_7 are as hereinbefore defined,

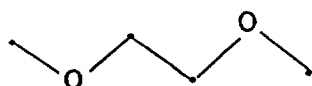
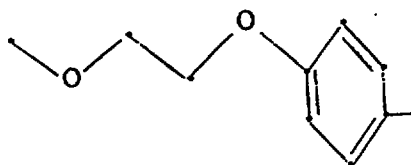
and

A denotes the group II.

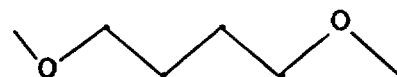
The following may be particularly mentioned as examples of the group of formula II:



Of the definitions of A particular mention may be made of:

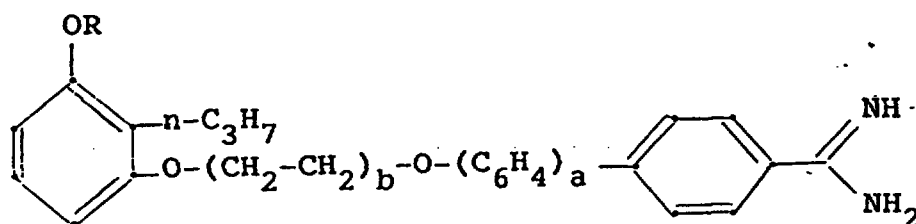


and





Special mention should also be made of the compounds of formula



wherein

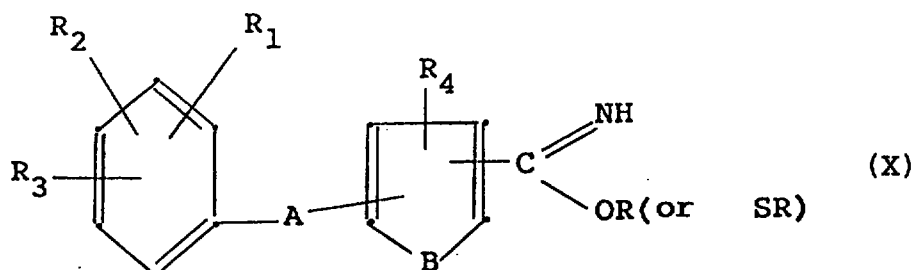
- a denotes 0 or 1,
- b denotes 1 or 2,
- R denotes C_{1-4} -alkyl, and if $a = 0$ or 1 and $b = 1$, and if $a = 1$ and $b = 2$, R may also denote hydrogen, and
- R preferably denotes CH_3 , C_2H_5 or H, and for $a = 1$, b is preferably 1.

In the above definitions, the term halogen denotes F, Cl, Br or I, preferably F, Cl. If the groups listed are alkyl chains or contain alkyl chains, these may be straight-chained or branched. The alkyl chains in R_5 , R_6 and R_7 preferably contain up to 6 carbon atoms, more particularly 1 to 4 carbon atoms. In particular, as a constituent of COR_6 , R_6 denoting alkyl may also be mono- or poly-fluorine-substituted. Particular examples of substituents of ring systems are alkyls such as methyl, ethyl and the propyls. A preferred acyl group is $COCH_3$, a preferred alkoxy group is CH_3O . The bridge A preferably contains 4 to 6 members. The group is arranged between the two ring systems in formula I and in corresponding formulae so as to correspond to the written form of formulae II to VI, whereas the groups which are valid for both R_1 and R_2 are not listed in the proper orientation. If R_1 and R_2 together denote a double bonded group, R_3 preferably denotes H or C_{2-5} -acyl, e.g. acetyl. The groups R_1 , R_2 and R_3 should not all simultaneously denote CF_3 , COR_6 , SR_6 , SOR_6 , SO_2R_6 ,

$\text{SO}_2\text{NR}_5\text{R}_7$ or $\text{C}(\text{OH})\text{R}_5\text{R}_7$, but rather these groups as well as OR_5 , with the definition phenoxy or substituted phenoxy, preferably occur only once or possibly twice, whilst alkyl, acyl and halogen, in particular, may occur as further substituents. The bonds or CH_2 groups in IX/IXa/IXb are generally in the α -position to one another. Typical groups for A are, for example, $\text{O}-(\text{CH}_2)_2-\text{O}$, $\text{O}-(\text{CH}_2)_4-\text{O}$, whilst one of the O-atoms may be replaced by S, NH or CO, as well as groups such as $\text{CH}_2-\text{CH}_2-\text{CONH}$, $\text{CH}_2-\text{CH}_2-\text{NH}-\text{CO}$, $\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2$ or $\text{NH}-\text{CO}-\text{CH}_2-\text{CH}_2$. The amidino group is usually in the para-position relative to the carbon atom to which A is linked.

The new compounds are prepared by conventional methods.

1. Reaction of imidoesters of the formula



wherein R_1 to R_4 , A and B are as hereinbefore defined and R preferably represents a C_{1-6} -alkyl group or benzyl (but if desired the man skilled in the art can also use derivatives of other alcohols), and ammonia. The reaction is preferably 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 the boiling temperature, if this is lower. Suitable solvents are polar solvents such as methanol, ethanol and propanol.

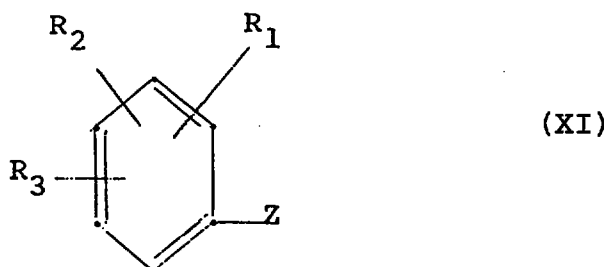


If the starting materials are sufficiently acid-resistant the reaction may be carried out via the corresponding acid imide chlorides instead of the imidoesters.

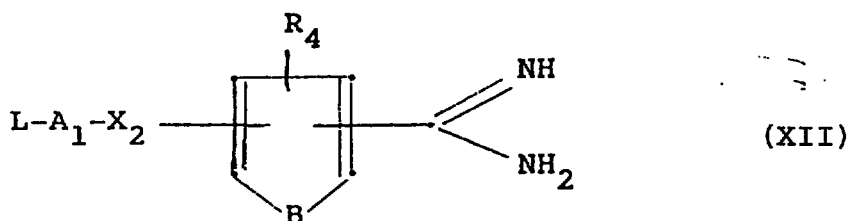
2. In order to prepare compounds of formula I wherein A is linked via O or S to at least one of the ring systems:

reaction

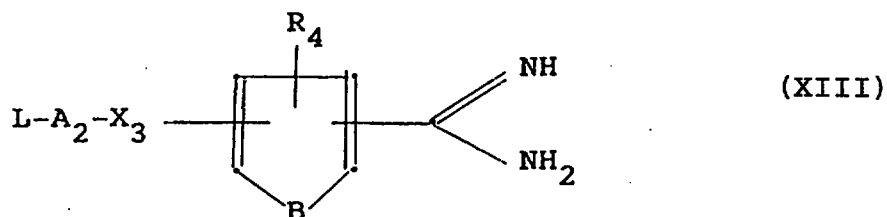
(a) of a phenol or thiophenol of formula



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



or

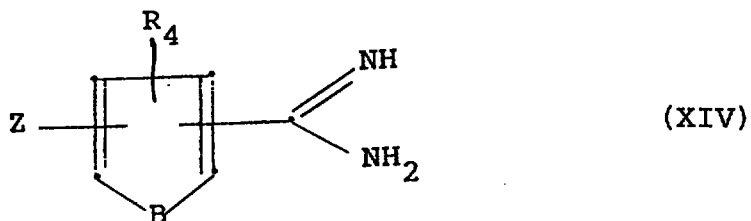


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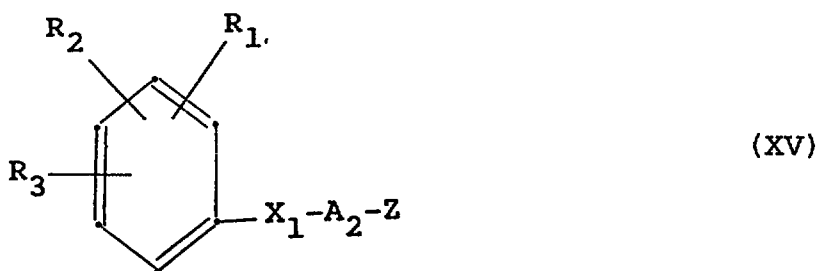


wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L represents a nucleofugic leaving group, or

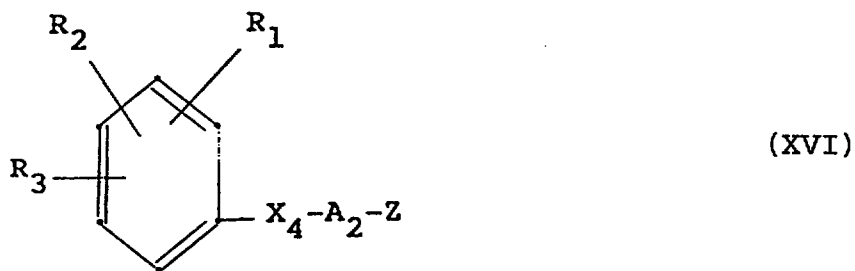
(b) of a phenol or thiophenol of the formula



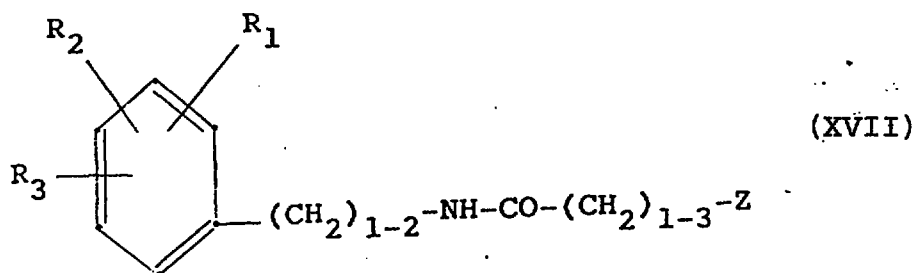
wherein B , R_4 and Z are as hereinbefore defined, with a compound of the formula



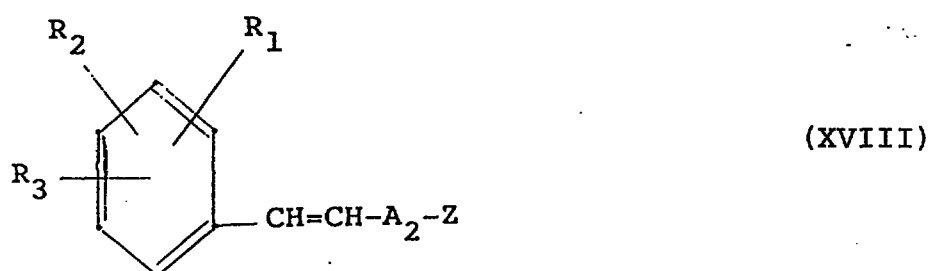
or



or



or



wherein A_1 , A_2 , R_1 , R_2 , R_3 and Z are as hereinbefore defined.

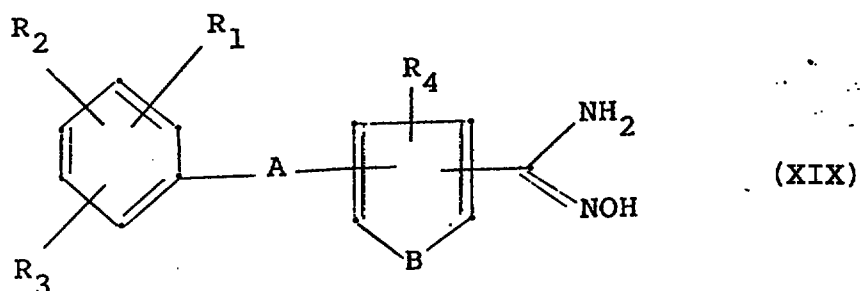
The reaction is carried out in aprotic solvents such as dimethylsulphoxide, dimethylformamide, acetonitrile or alcohols such as methanol, ethanol or propanol with the addition of a base (metal carbonates, metal hydroxides, metal hydrides) at temperatures between about 0 and 140°C or the boiling temperature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

The phenols or thiophenols may also be used in the form of salts, e.g. alkali metal salts. Examples of suitable nucleofugic leaving groups include halogens such as Br and Cl.

3. Reduction of an amidoxime of the formula

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wherein A, B and R_1 to R_4 are as hereinbefore defined.

For the reduction of XIX it is appropriate to use catalytic hydrogenation, particularly with Raney nickel in a lower alcohol such as methanol.

Conveniently, the amidoxime of formula XIX is 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. up to 5 bar, until the uptake of hydrogen has ended.

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 them with HCl via the step of the imide chlorides or directly by reacting them with, for example, C_{1-6} -alcohols or benzyl alcohol in the presence of an acid such as HCl. The reaction of the nitriles with H_2S in solvents such as pyridine or dimethylformamide in the presence of a base such as triethylamine and subsequent alkylation or benzylation result in compounds of formula X. Starting from carboxylic acid amides, which moreover

correspond to the compounds of formula X, compounds of formula X may also be obtained by reaction with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate, in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, preferably at ambient temperature.

The starting materials XIX may also be obtained by reacting corresponding amidoximes instead of amidines analogously to method 1 or 2; by analogous reaction of corresponding nitriles from which the starting materials XIX are finally obtained by the addition of hydroxylamine.

The compounds according to the invention are therapeutically useful, particularly in the light of their LTB₄-antagonistic activity. They are therefore suitable for use, particularly, in those diseases in which inflammatory and/or allergic processes are involved, such as asthma, ulcerative colitis, psoriasis and also for treating gastropathy induced by non-steroidal antiphlogistics. The new compounds may also be used in conjunction with other active substances, e.g. antiallergics, secretolytics, β_2 -adrenergics, steroids for inhalation, antihistamines and/or PAF-antagonists. They may be administered by topical, oral, transdermal, nasal or parenteral route or by inhalation.

The therapeutic or prophylactic dose is dependent on the nature and gravity of the disease, as well as the potency of the individual compounds and the body weight of the patient. For oral administration the dose is between 10 and 250 mg, preferably between 20 and 200 mg. For inhalation, the patient takes between about 2 and 20 mg of active substance. The new compounds may be administered in conventional preparations such as plain or coated tablets, capsules, lozenges, powders,



granules, solutions, emulsions, syrups, aerosols for inhalation, ointments and suppositories.

The Examples which follow illustrate some possible formulations for the preparations.

Formulation Examples

1. Tablets

Composition:

Active substance according to the invention	20 parts by weight
Stearic acid	6 parts by weight
Dextrose	474 parts by weight

The constituents 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 dextrose reduced or increased accordingly.

2. Suppositories

Composition:

Active substance according to the invention	100 parts by weight
Powdered lactose	45 parts by weight
Cocoa butter	1555 parts by weight

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

3. Powder for inhalation

Micronised powdered active substance (compound of formula I; particle size about 0.5 to 7 μ m) is packed into hard gelatine capsules in a quantity of 5 mg,



optionally with the addition of micronised lactose. The powder is inhaled using conventional inhalation devices, e.g. according to DE-A 3 345 722.

The compounds according to the invention were tested inter alia for their activity in the tests described below.

a) U937 - Receptor binding test/LTB₄

The binding of ³H-LTB₄ (3nM) to vital U937 cells (differentiated human monocytary cell line with naturally expressed LTB₄ receptors) is inhibited, in dosage dependent manner, by an increasing concentration of the test substance (incubation 2 hours at 0°C). After the unbound ³H-LTB₄ has been separated off by membrane filtration, the radioactivity of the bound LTB₄ receptor/³H-LTB₄ complex is quantified by scintillation measurement. The affinity (inhibition constant K_i) was determined by repeated adaptation of a displacement curve to the measurements (program: "coupled mass equilibria" on Wang computer).

b) Aggregation of neutrophilic granulocytes in the guinea-pig

Indicated by LTB₄ in vitro (increase in light transmission in the aggregometer, recorded in mm; each experiment repeated twice): inhibition 2 minutes after incubation with test substance in polydiol/DMSO.

c) Leukotrien-B₄-indicated accumulation of neutrophiles in the mouse ear

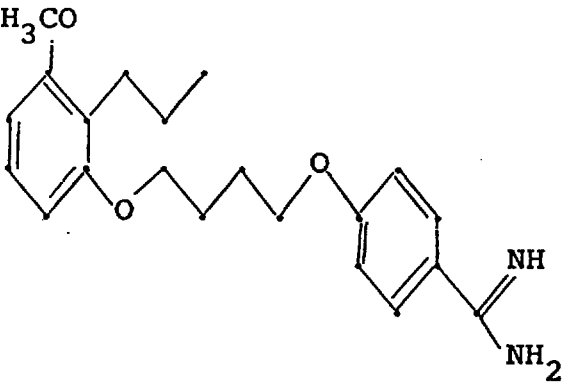
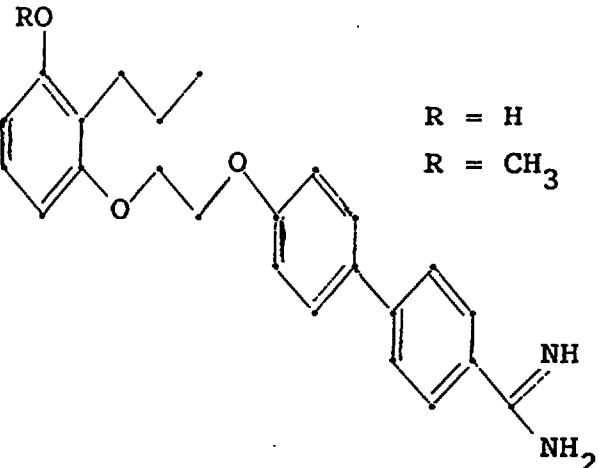
Evaluation of the neutrophilic influx by



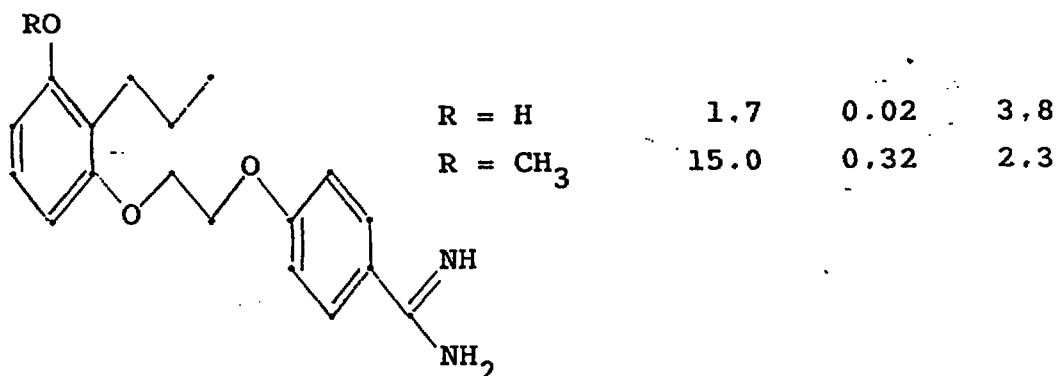
photometric measurement (mOD/min) of the myeloperoxidase activity (Bradley et al.: J. Invest. Dermatol. 78, 206, 1982) in the skin of the ear. Increase 6 hours after topical treatment of the left ear with LTB₄ (250 ng on each side) compared with the right ear (2 x 5 µl acetone as solvent).

Substance administered by oral route in 1% tylose 300, 30 minutes before the LTB₄ stimulation.

4. Results

	a)*	b)**	c)***
	12.0	1.9	0.8
			
R = H	3.8	0.06	1.2
R = CH ₃	6.3	0.31	0.9





- * Receptor binding U937-8 K₁ [nM] (1)
- ** LTB₄-induced neutroph. Aggr. EC₅₀ [μM] (2)
- *** LTB₄-induced neutroph. Accum. p.o. ED₅₀ [mg/kg]

The ³H-LTB₄-receptor binding to guinea-pig spleen cells in the presence of 10% blood plasma yielded K₁-values of, in some cases, far less than 1 μM, more particularly between 0.2 and 0.02. Inhibition of the LTB₄-induced aggregation of neutrophiles resulted in EC₅₀-values between about 0.5 and 0.05 μM.

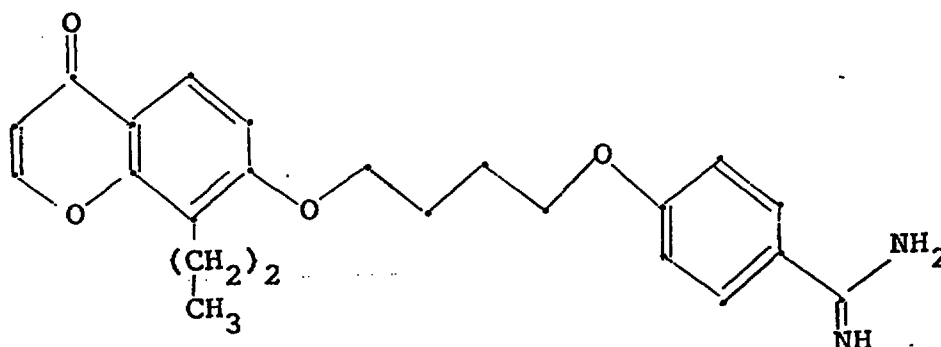
Particular mention should be made of the compounds according to Examples 1 and 5 and Nos. 10, 11, 13, 19, 20, 22 and 23 from Table I, No. 1 from Table II, No. 2 from Table III.

The Examples which follow illustrate the possible methods of preparing the compounds according to the invention.



Process 1:

Example 1



To a solution of 2.0 g of 7-[4-(4-cyano-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one in 50 ml of chloroform and 1.5 ml of ethanol are added 5 ml of a solution of hydrogen chloride in diethylether (17%). The mixture is left to stand for 14 days at ambient temperature and the product is precipitated with diethylether. 1.15 g of 7-[4-(4-imidacaroxyethyl-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained. The imidoester is mixed with 50 ml of ethanolic ammonia solution (5 M) and heated for 3 hours to 70°C. The mixture is evaporated down and the residue is chromatographed (chloroform/methanol 7:3, silica gel). After recrystallisation from dichloromethane/diethylether, 0.6 g of 7-[4-(4-amidino-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained (m.p. 144 - 148°C).

Example 2

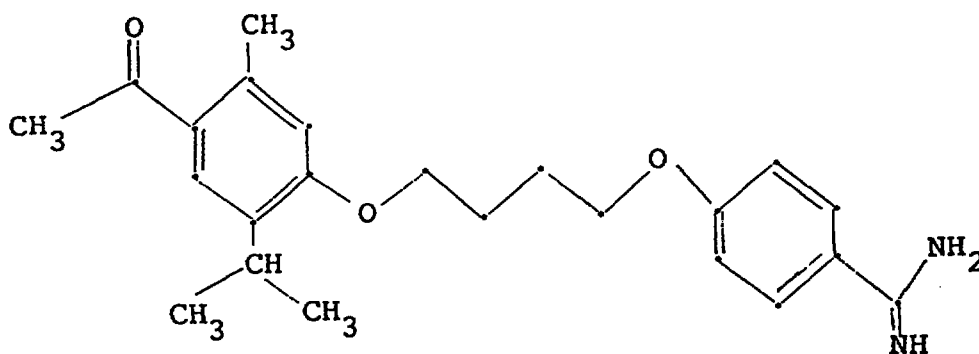
To a solution of 2.5 g of 4-[4-(2-propyl-3-methoxy-phenoxy)-butyloxy]-benzonitrile, prepared from 2-propyl-3-methoxy-phenol and 4-bromobutoxybenzonitrile, in 40 ml of ethanol, hydrogen chloride is introduced at -20°C



with stirring for 1 hour and the mixture is left to stand at ambient temperature for 16 hours.

The solvent is distilled off in vacuo and the residue is taken up in 50 ml of ethanol. A mixture of 14 ml of ethanolic ammonia solution and 50 ml of ethanol is added dropwise thereto and the mixture is left to stand for 24 hours at ambient temperature. The solvent is evaporated off and the residue is chromatographed (chloroform/methanol 8:2; silica gel 60). 1.8 g of 4-[4-(2-propyl-3-methoxy-phenoxy)-butyloxy]-benzamidinium-hydrochloride-hemihydrate are obtained. (M.p. 117-121°C).

Example 3

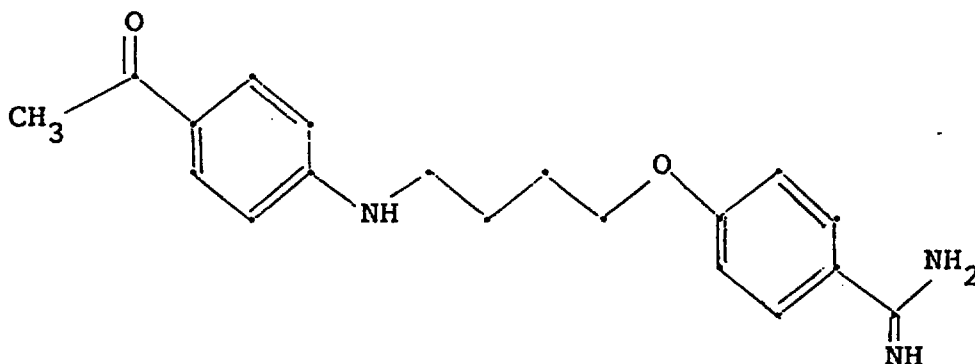


Hydrogen chloride is introduced at -20°C into a solution of 32.0 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzonitrile in 350 ml of ethanol and the resulting mixture is stirred for 48 hours. The crystals precipitated are suction filtered and washed with diethylether. 41.0 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzimidooethylester-hydrochloride are obtained (m.p. 100 - 102°C decomp.). 15.0 g of the imidoester are added at ambient temperature in several batches to 33 ml of ethanolic ammonia solution (5 M) and 100 ml of ethanol. The mixture is stirred for 36 hours at ambient temperature,



evaporated down and the residue is stirred with 50 ml of water. The residue is suction filtered, recrystallised from 30 ml of ethanol and washed with diethylether. 11.5 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzamidinium-hydrochloride are obtained (m.p. 182 - 183°C decomp.).

Example 4

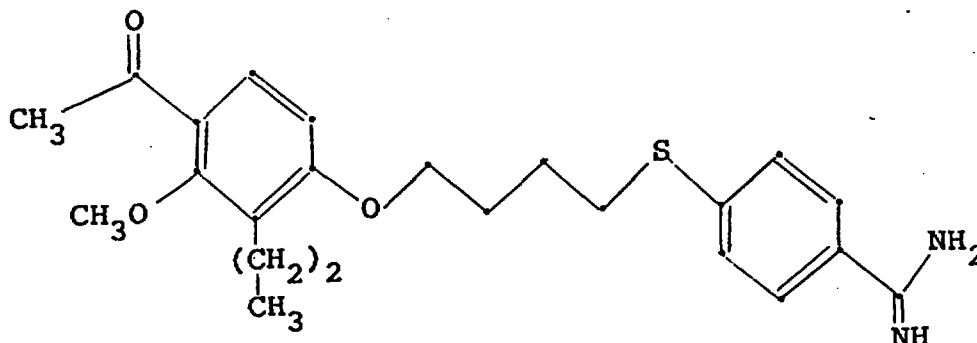


Hydrogen chloride is introduced at -20°C into a solution of 3.0 g of 4-[4-(4-cyano-phenoxy)-butylamino]-acetophenone in 40 ml of ethanol, with stirring, for 4 hours and the mixture is left to stand at ambient temperature for 16 hours. The solvent is distilled off in vacuo and the residue is taken up in 50 ml of ethanol. A mixture of 14 ml of ethanolic ammonia solution and 50 ml of ethanol is added dropwise thereto and the mixture is left to stand for 24 hours at ambient temperature. The solvent is evaporated off and the residue is chromatographed (chloroform/methanol 7:3, silica gel 60). 0.3 g of 4-[4-(4-amidino-phenoxy)butylamino]-acetophenone are obtained (m.p. 200 - 202°C).



Process 2:

Example 6



8.2 g of 4-acetyl-3-methoxy-2-propyl-phenol are dissolved in 80 ml of dimethylformamide and 1.1 g of sodium hydride is added in batches to the solution (as an 80% dispersion in white oil). The mixture is heated to 80°C for 30 minutes and combined with a solution of 5.75 g of 4-(4-bromopropylthio)-benzamidinium (prepared from dibromobutane and 4-cyanobenzothiol by means of 4-(4-bromobutyl-thio)-benzonitrile) in 40 ml of dimethylformamide. After 5 hours at 80°C the mixture is allowed to cool, acidified with ethereal hydrochloric acid and the solvents are distilled off in vacuo. The residue is taken up in ethanol and filtered. The filtrate is concentrated by evaporation. The process is repeated with chloroform and acetonitrile. The residue is stirred with diethylether. After decanting, 5.65 g of a brownish-yellow oil are left. The product is chromatographed (chloroform/methanol 7:3, silica gel). 2.4 g of an oil are obtained which is crystallised from toluene. The product is dissolved in acetonitrile, acidified with ethereal hydrochloric acid. The crystals are suction filtered, washed with cold acetonitrile, dissolved in water and crystallised once more after the addition of 2 N hydrochloric acid. 0.8 g of 4-[4-(4-acetyl-3-methoxy-2-propylphenoxy)-butylthio]-benzamidinium-hydrochloride are obtained (m.p.



120 - 122°C).

Process 3:

Example 7

a) 4-[4-(4-Acetylphenoxy-butoxy)-benzamidoxime

45.6 g (0.3 mol) of 4-hydroxybenzamidoxime and 81.3 g (0.3 mol) of 4-bromo-butoxy-acetophenone are dissolved in 300 ml of dimethylformamide. After the addition of 55.2 g (0.4 mol) of anhydrous potassium carbonate the mixture is heated to 80°C for 2 hours. The inorganic salts are suction filtered, evaporated down in vacuo and recrystallised from acetonitrile.

Yield: 47.8 g

M.p.: 164.5 - 165.5°C.

b) 3-[4-(4-Acetylphenoxy)butoxy]-benzamidine-methanesulphonate

47.8 g of the compound synthesised according to a) are dissolved in 10 times the quantity of methanol with the addition of the calculated amount of methanesulphonic acid. After the addition of Raney nickel, the mixture is hydrogenated at 5 bar until the uptake of hydrogen has ended. The mixture is suction filtered, the solvent is distilled off in vacuo and the residue is recrystallised from ethanol.

Yield: 45.2 g

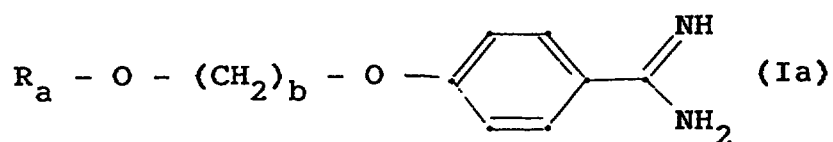
M.p.: 204 - 204.5°C.

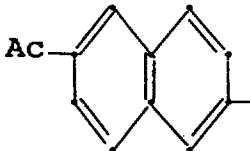
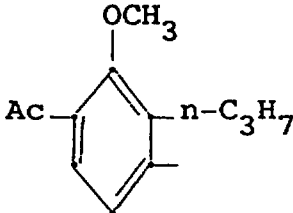
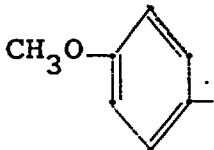
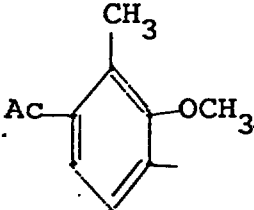
The other compounds of formula I can be obtained according to the processes described above. "Ac" hereinafter denotes CH₃CO-.



TABLE I

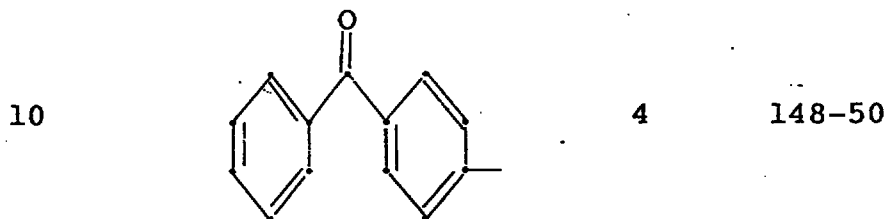
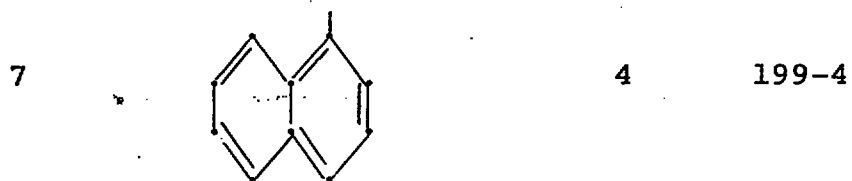
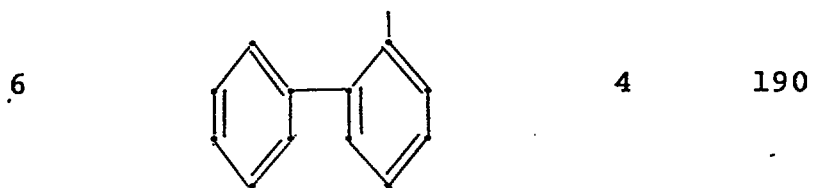
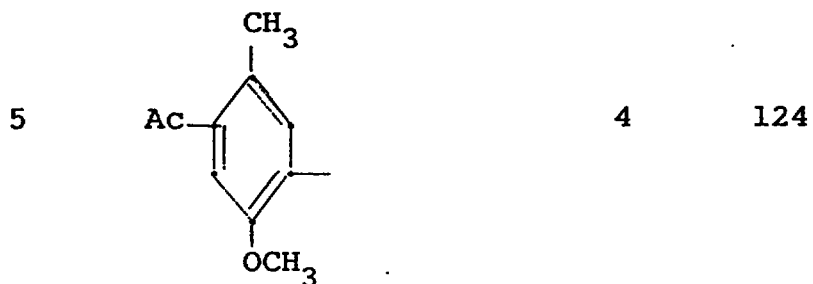
Compounds of formula



No.	R_a	b	M.p. [°C] (Hydrochloride)
1		2	240
2		2	209-10
3		4	
4		4	143

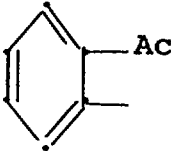
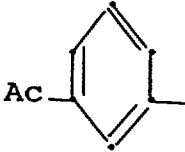
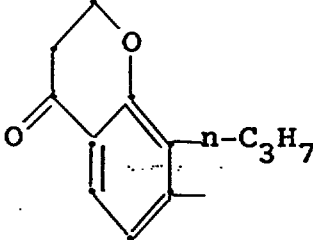
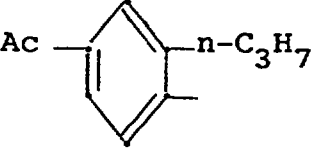
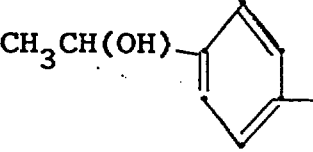


No.	R _a	b	M.p. [°C] (Hydrochloride)
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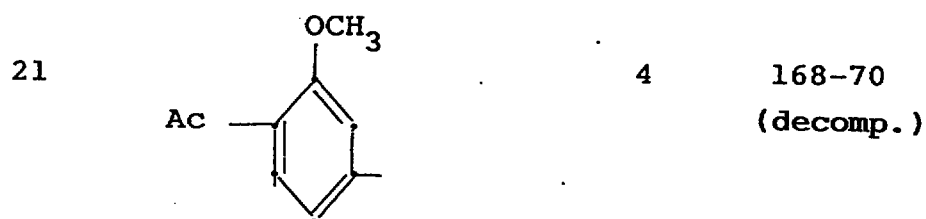
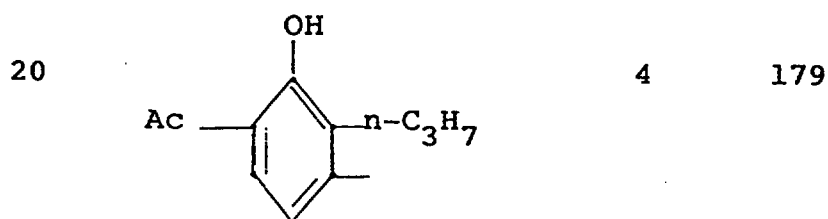
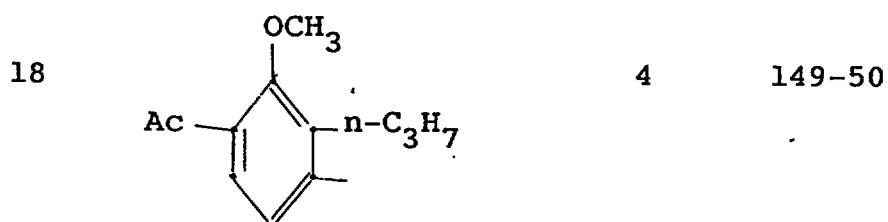
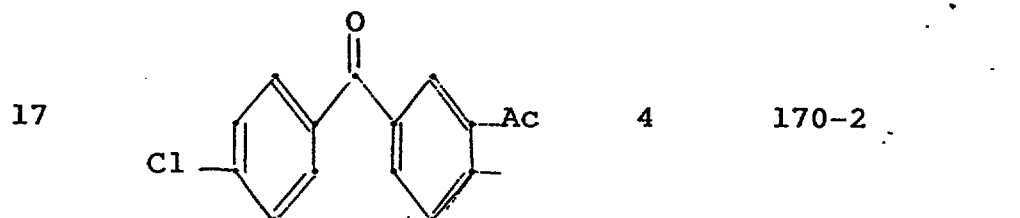
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No.	R_a	b	M.p. [°C] (Hydrochloride)
11		4	132-40
12		4	160-3
13		4	160-5
14		4	228-31
15		4	140-6
16		4	

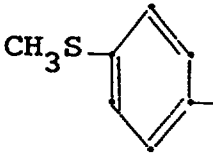
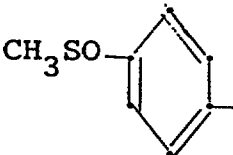
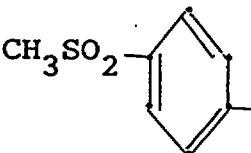
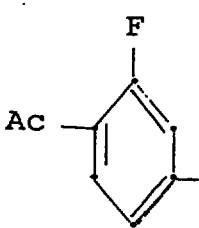
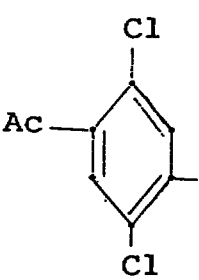
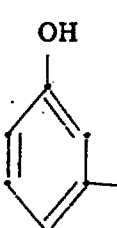


No.	R _a	b	M.p. [°C] (Hydrochloride)
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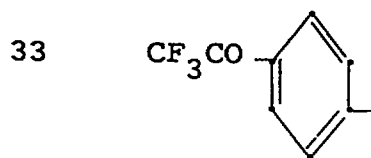
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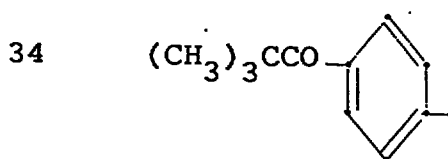
No.	R_a	b	M.p. [°C] (Hydrochloride)
27		4	
28		4	
29		4	174-5
30		4	155-60
31		4	194-60
32		4	214-23



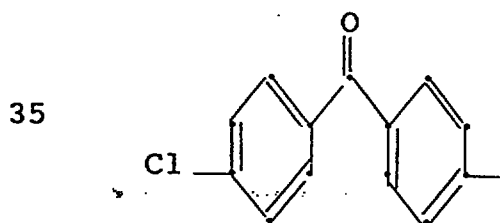
No.	R _a	b	M.p. [°C] (Hydrochloride)
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4

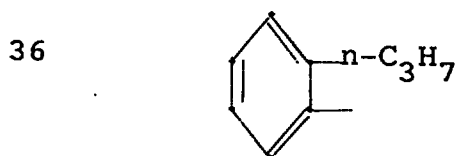


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4

145-8

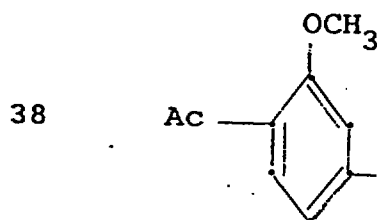


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128-31



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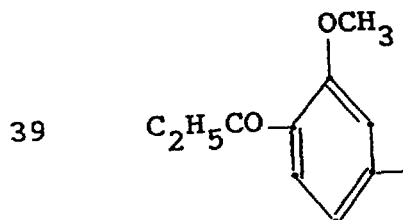


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No.	R _a	b	M.p. [°C] (Hydrochloride)
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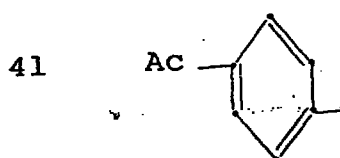


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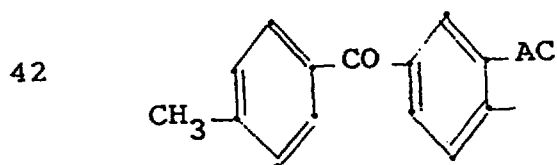
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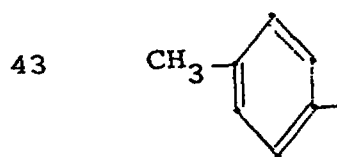


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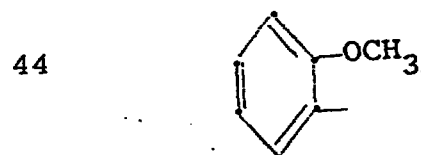
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4



4



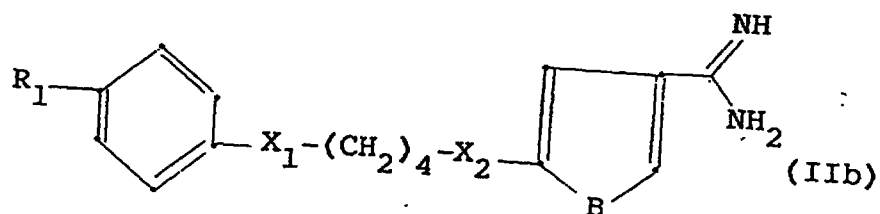
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TABLE II

Compounds of formula

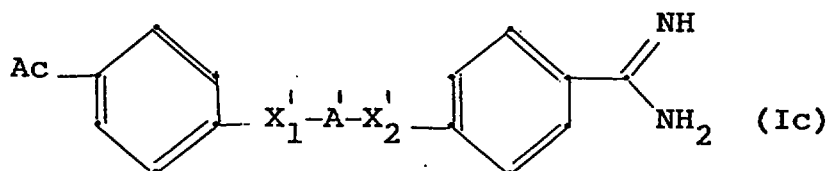


No.	B	R ₁	X ₁	X ₂	M.p. [°C] (Hydrochloride)
1	CH=CH	Ac	O	S	
2	CH=CH	Ac	O	SO	
3	CH=CH	Ac	O	SO ₂	160-2 (Base)
4	CH=CH	Ac	S	S	
5	N=CH	Ac	O	S	152-60
6	CH=CH	Ac	O	NH	200-2
7	CH=CH	Ac	S	O	196-7
8	CH=CH	Ac	SO	O	
9	CH=CH	Ac	SO ₂	O	208



TABLE III

Compounds of formula



No.	A'	X' ₁	X' ₂	M.p. [°C] (Hydrochloride)
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1	CH ₂ -CH=CH-CH ₂	O	O	215-8
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2		O	O	196-202
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3		O	O	205-9
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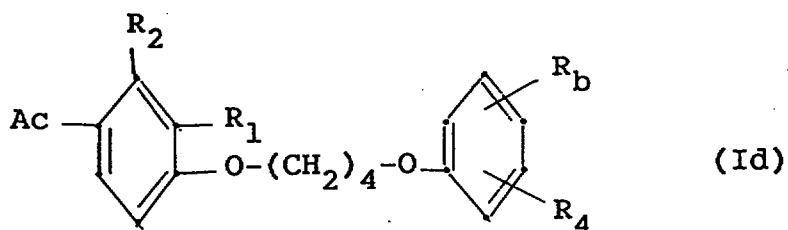
4		O	O	183
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TABLE IV

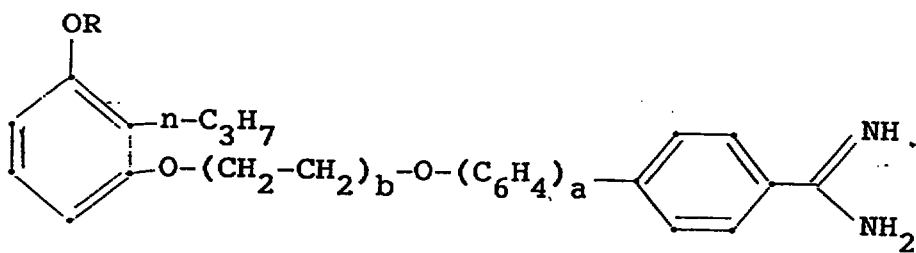
Compounds of formula



No.	R _b	R ₁	R ₂	R ₄	M.p. [°C] (Hydrochloride)
1	$\begin{array}{c} \text{NH} \\ \parallel \\ 2-\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	H	H	H	
2	$\begin{array}{c} \text{NH} \\ \parallel \\ 3-\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	H	H	H	174-6
3	$\begin{array}{c} \text{NH} \\ \parallel \\ 4-\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	n-C ₃ H ₇	OCH ₃	2-OCH ₃	124-7

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No.	R	a	b	M.p. [°C]
1	H	0	1	178-80 (Hydrochloride)
2	H	1	1	248-51 (Hydrochloride)
3	H	1	2	
4	CH ₃	0	1	176-8 (Hydrochloride)
5	CH ₃	1	1	236-40 (Methanesulphonate)
6	C ₂ H ₅	0	1	
7	C ₂ H ₅	0	2	
8	n-C ₃ H ₇	0	2	
9	n-C ₃ H ₇	1	1	
10	i-C ₃ H ₇	1	1	
11	n-C ₄ H ₉	0	1	144-7 (Hydrochloride)
12	n-C ₄ H ₉	0	2	

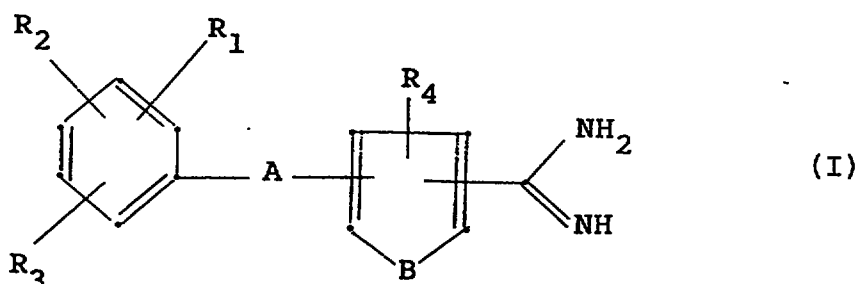
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Claims

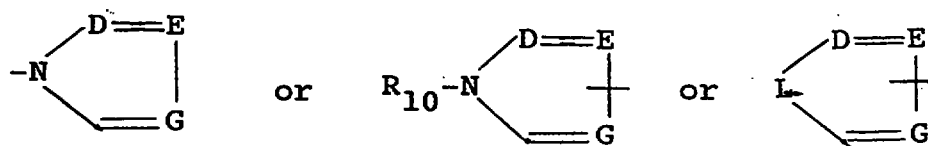
1. Compounds of the formula



wherein

R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_{3-4}-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,

R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONH_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}-alkyl)$, SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}-alkyl)$, $NH-SO_2-(C_{1-4}-alkyl)$, NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula





(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

X₁-A₁-X₂ (II)

X₂-A₂-X₃ (III)

X₄-A₂-X₂ (IV)

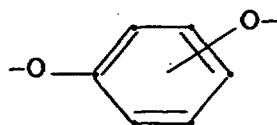
(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)

-CH=CH-A₂-X₂ (VI)



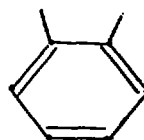
(VII)



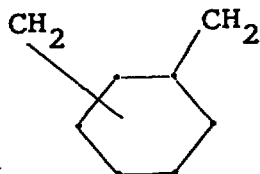


(VIII)

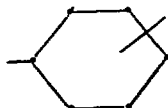
B denotes CH=CH, CH=N, S or



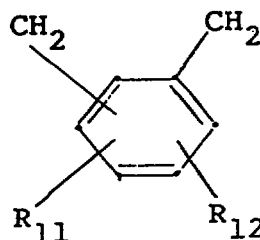
A₁ denotes C₂₋₄-alkylene, cis- or trans-CH₂-CH=CH-CH₂, CH₂-C=C-CH₂ or



(IX)



(IXa)



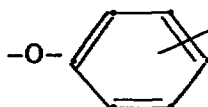
(IXb)

A₂ denotes C₁₋₅-alkylene,

X₁ denotes O, NH, S, SO, SO₂, CO, CH₂ or



X₂ denotes O, NH, S or



X₃ denotes NH-CO, CO-NH, SO₂-NH or



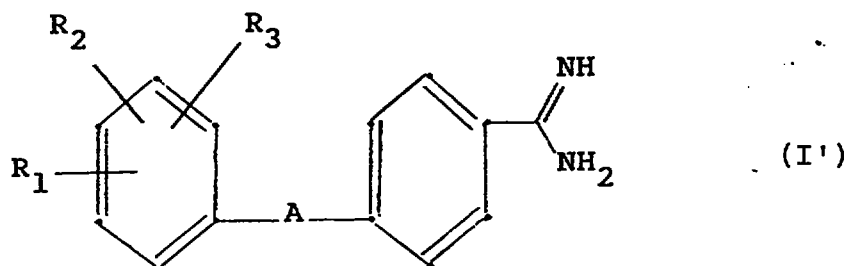
X₄ denotes NH-CO, CO-NH, NH-SO₂, SO₂-NH or NH-CO-NH,

as racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.





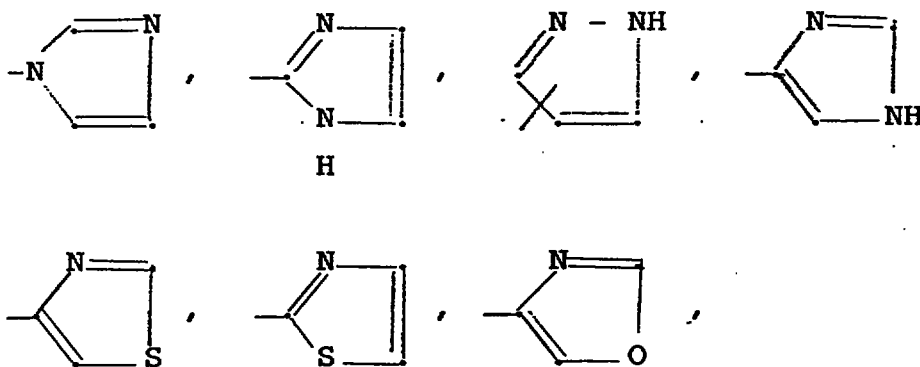
2. Compounds of the formula



wherein

R_1 , R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-CR_8=R_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-O-CHR_{10}-CH_2-$ or $-CO-CH_2-CH_2-O-$, linked with adjacent carbon atoms of the benzene ring,

R_3 denotes halogen, CF_3 , R_7 , OR_7 , $CO-(C_{1-4}-alkyl)$, $NH-CO-(C_{1-4}-alkyl)$, $NHSO_2-(C_{1-4}-alkyl)$ or $N(R_{10})_2$ (whilst R_7 can only denote H if at least one of the substituents R_1 and R_2 does not denote H) or a heterocyclic five-membered ring such as



R_6 and R_7 are as hereinbefore defined,



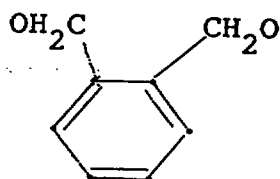


and

A denotes the group II.

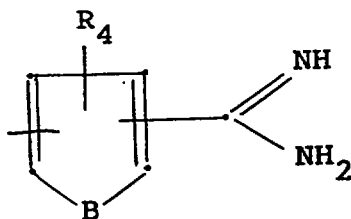
3. Compounds according to claim 1 or 2, wherein
 $R_1/R_2/R_3$ have the meanings C_{2-5} -acyl/H/H;
 C_6H_5CO /H/H; C_{1-4} -alkyl/OH/H;
 C_{2-5} -acyl/ C_{1-4} -alkyl/H;
 C_{2-5} -acyl/OH/ C_{1-4} -alkyl;
OH/ C_{2-5} -acyl/ C_{1-4} -alkyl.

4. Compounds according to claim 1, 2 and 3,
characterised in that A denotes

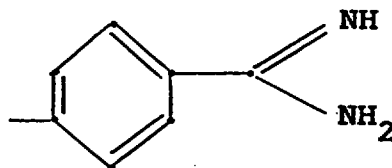


5. Compounds according to claim 1, 2, 3 or 4,
characterised in that the group II is acetylphenyl.

6. Compounds according to claim 1, 2, 3, 4 or 5,
characterised in that the group

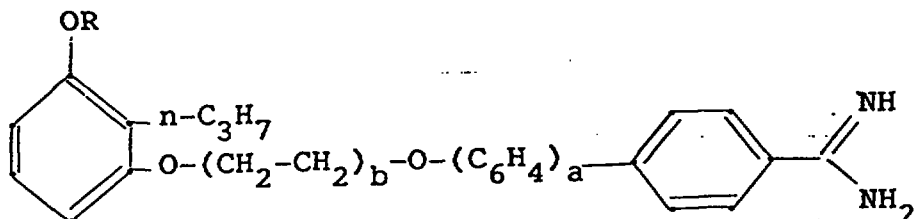


represents





7. Compounds of the formula



wherein

a denotes 0 or 1,

b denotes 1 or 2,

R denotes C_{1-4} -alkyl, and if $a = 0$ or 1 and $b = 1$ and if $a = 1$ and $b = 2$ it may also denote hydrogen, in the form of free bases or acid addition salts.

8. Compounds according to claim 7, wherein $a = 0$ or 1 and $b = 1$ or $a = 0$ and $b = 2$ as free bases or as acid addition salts.

9. Compounds according to claim 8, wherein R denotes H, CH_3 or C_2H_5 , a denotes 0 or 1 and b denotes 1, as free bases or as acid addition salts.

10. Compounds according to claim 8, wherein a denotes 0, b denotes 2 and R denotes CH_3 , as free bases or as acid addition salts.

11. Pharmaceutical compositions, characterised in that they contain a compound according to claims 1 to 10.

12. Use of compounds according to claims 1 to 10 in the preparation of pharmaceutical compositions for the treatment of diseases in which inflammatory and/or allergic processes are involved, especially asthma, ulcerative colitis, psoriasis and for treating gastropathy induced by non-steroidal antiphlogistics.



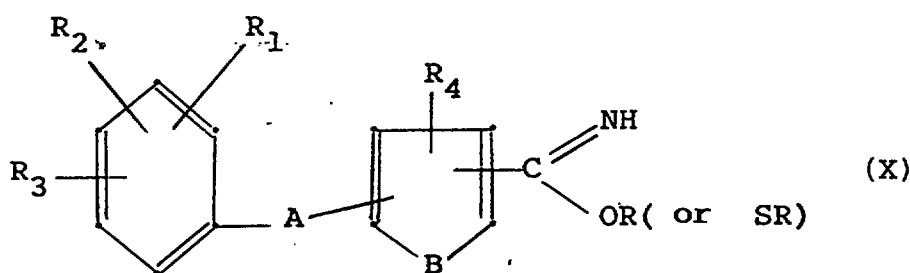


13. Use of an effective dose of a compound according to claims 1 to 10 for treating diseases in which LTB₄-antagonistic compounds can be used.

14. Use of an effective dose of a compound according to claims 1 to 10 for the treatment of diseases in which inflammatory and/or allergic processes are involved, particularly asthma, ulcerative colitis, psoriasis, and for treating gastropathy induced by non-steroidal antiphlogistics.

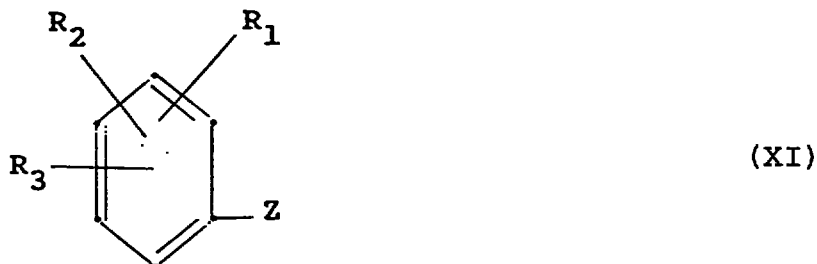
15. Process for preparing compounds according to claims 1 to 10, characterised in that

a) an imidoester of the formula



wherein R₁ to R₄, A and B are as hereinbefore defined and R preferably represents a C₁₋₆-alkyl group or benzyl, is reacted with ammonia, or

b1) a phenol or thiophenol of the formula

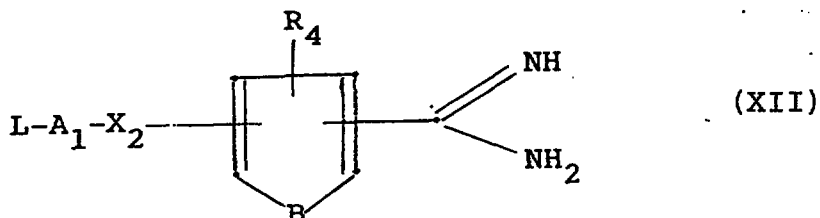


wherein Z denotes OH or SH and R₁, R₂ and R₃ are as

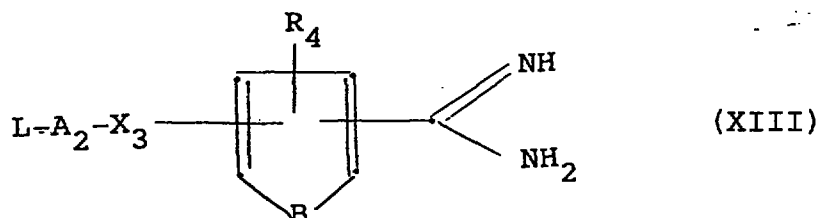




hereinbefore defined, is reacted with a compound of formula

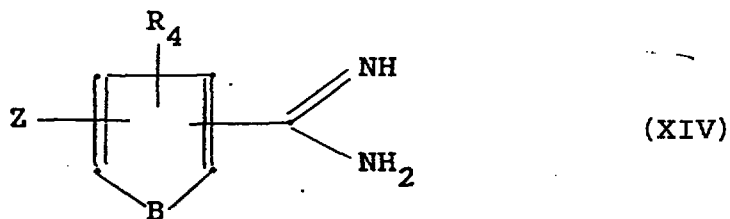


or

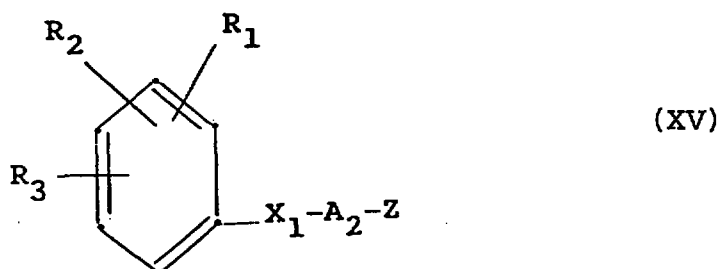


wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L denotes a nucleofugic leaving group, or

b2) a phenol or thiophenol of formula

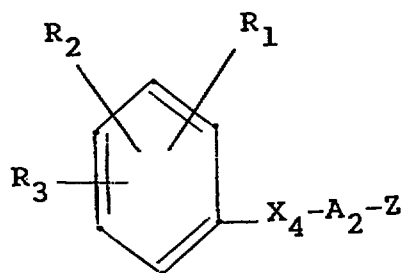


wherein B , R_4 and Z are as hereinbefore defined, is reacted with a compound of formula

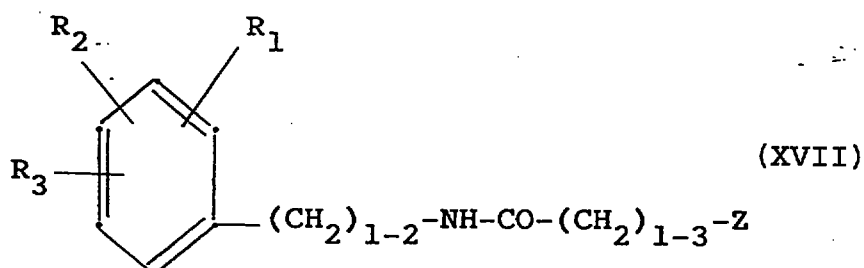




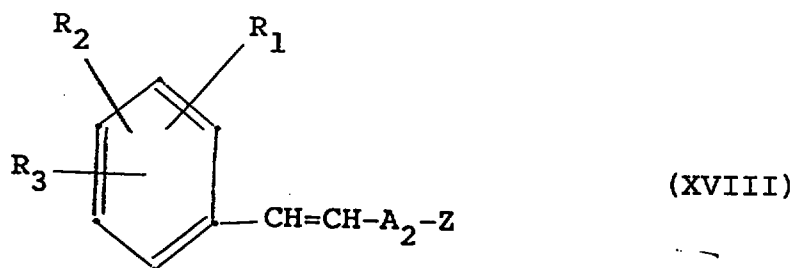
or



or

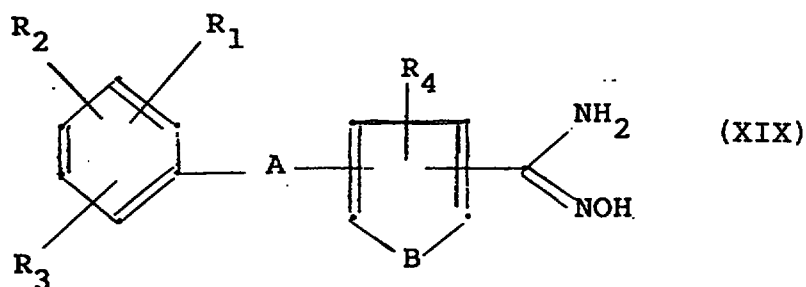


or



wherein A_1 , A_2 , R_1 , R_2 , R_3 and Z are as hereinbefore defined; or

c) an amidoxime of the formula





- 43 -

wherein A, B and R_1 to R_4 are as hereinbefore defined, is reduced to form the corresponding amidine.

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REPLACED SHEETS		SG
☒	Description	: paged1..... to paged33.....
☒	Claim(s)	: paged34..... to paged43.....
☐	Drawing(s)	: paged to paged
☒	Abstract	: paged44..... to paged
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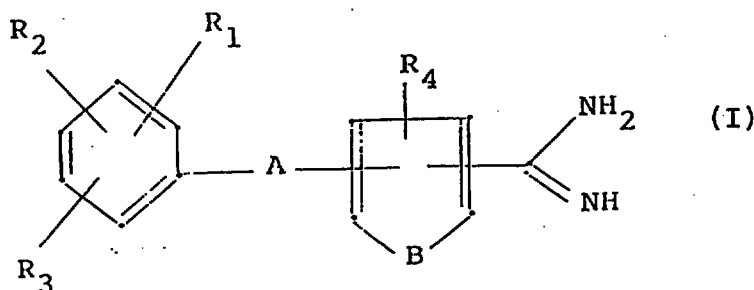
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REPLACEMENT SHEETS		SG
☒	Description	: paged1..... to paged33.....
☒	Claim(s)	: paged34..... to paged43.....
☐	Drawing(s)	: paged to paged
☒	Abstract	: paged44..... to paged
DATE OF RECEIPT2/11/96.....		

New amidine derivatives, the preparation and use thereof as pharmaceutical compositions with LTB₄-antagonistic activity

The invention relates to new amidine derivatives, the preparation thereof using conventional methods and their use in pharmaceutical compositions.

The new amidine derivatives correspond to the formula



wherein

R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_{3-4}-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,

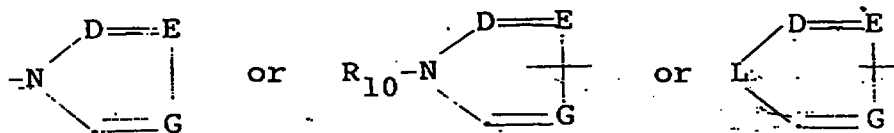
R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONR_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}-alkyl)$, SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}-alkyl)$, $NH-SO_2-(C_{1-4}-alkyl)$, NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula

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(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

X₁-A₁-X₂ (II)

X₂-A₂-X₃ (III)

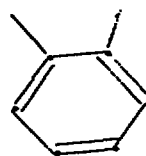
X₄-A₂-X₂ (IV)

(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)

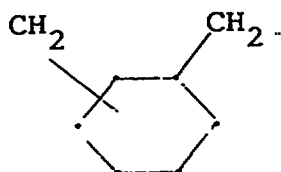




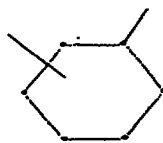
B denotes $\text{CH}=\text{CH}$, $\text{CH}=\text{N}$, S or



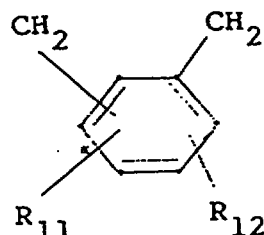
A_1 denotes C_{2-4} -alkylene, cis- or trans- $\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2$, $\text{CH}_2-\text{C}=\text{C}-\text{CH}_2$ or



(IX)



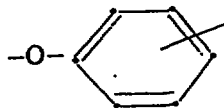
(IXa)



(IXb)

A_2 denotes C_{1-5} -alkylene,

X_1 denotes O, NH, S, SO, SO_2 , CO, CH_2 or ,

X_2 denotes O, NH, S or 

X_3 denotes NH-CO, CO-NH, SO_2 -NH or ,

X_4 denotes NH-CO, CO-NH, NH- SO_2 , SO_2 -NH or NH-CO-NH,

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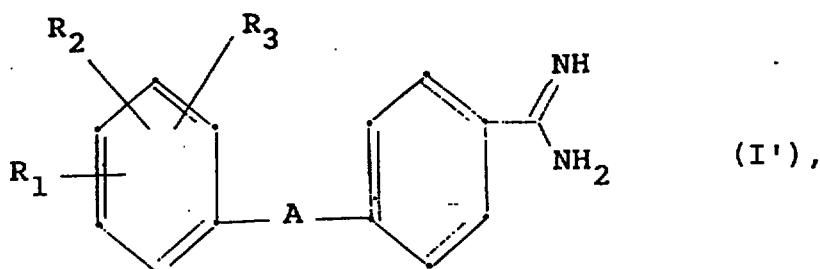


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and (if they contain one or more chiral centres), may occur in the form of racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and (if a double bond is present) in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.

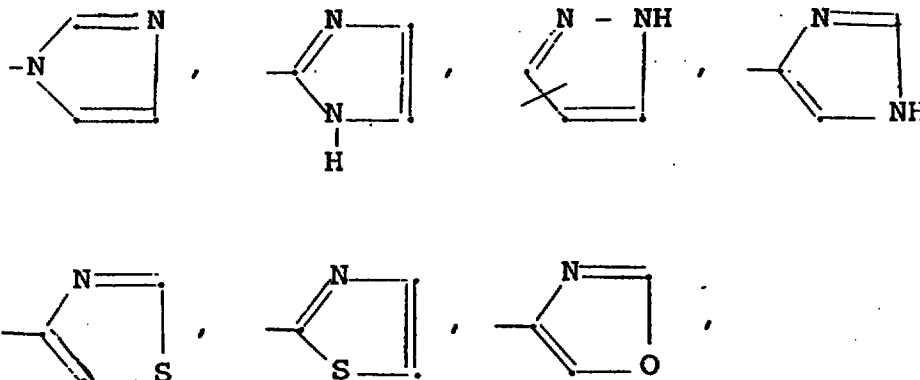
Within the scope of the above definitions, the preferred compounds are the compounds of formula



wherein

R_1 , R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-CR_8=R_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-O-CHR_{10}-CH_2-$ or $-CO-CH_2-CH_2-O-$, linked with adjacent carbon atoms of the benzene ring,

R_3 denotes halogen, CF_3 , R_7 , OR_7 , $CO-(C_{1-4}-alkyl)$, $NH-CO-(C_{1-4}-alkyl)$, $NHSO_2-(C_{1-4}-alkyl)$ or $N(R_{10})_2$ (whilst R_7 can only denote H if at least one of the substituents R_1 and R_2 does not denote H) or a heterocyclic five-membered ring such as



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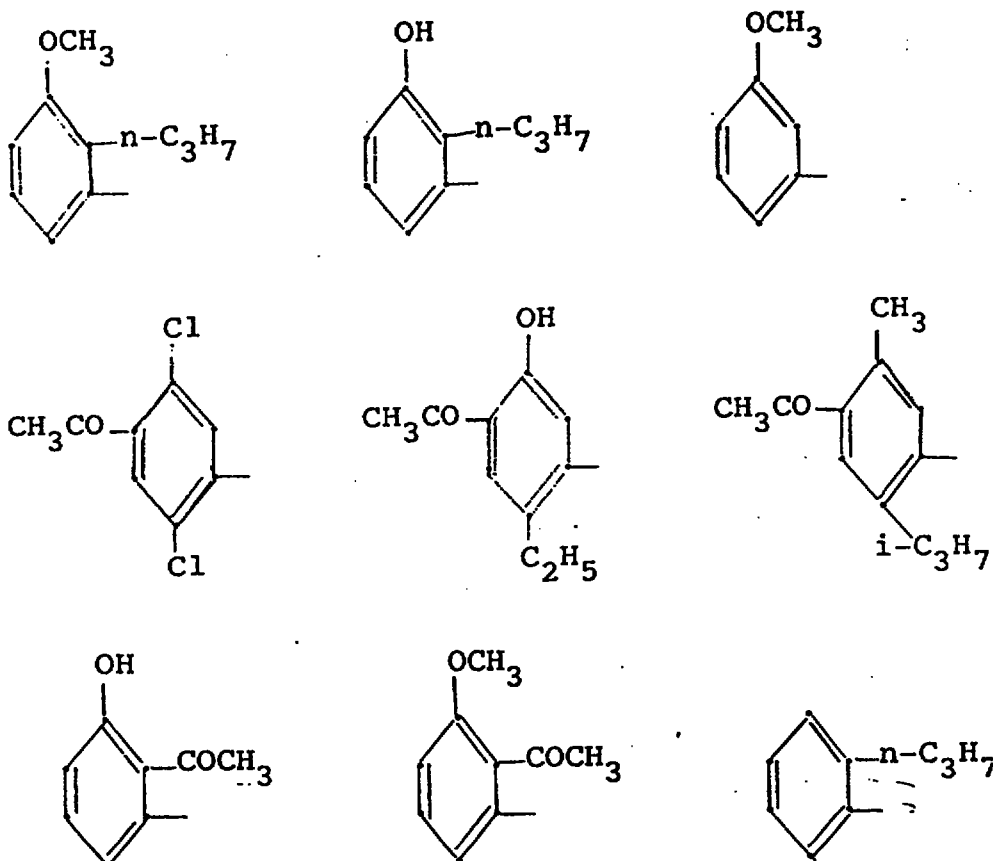
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R_6 and R_7 are as hereinbefore defined,

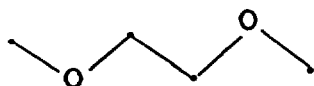
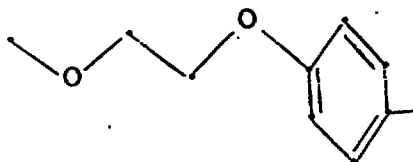
and

A denotes the group II.

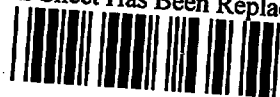
The following may be particularly mentioned as examples of the group of formula II:



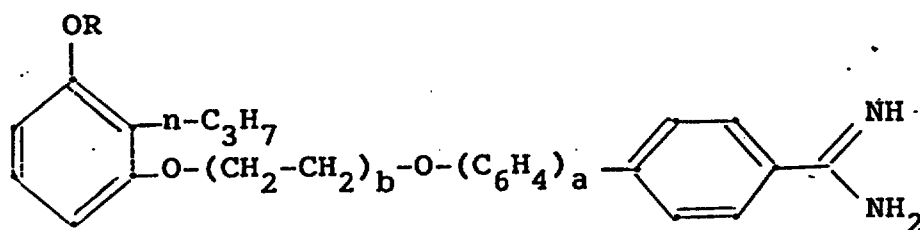
Of the definitions of A particular mention may be made of:



and



Special mention should also be made of the compounds of formula



wherein

- a denotes 0 or 1,
- b denotes 1 or 2,
- R denotes C₁₋₄-alkyl, and if a = 0 or 1 and b = 1, and if a = 1 and b = 2, R may also denote hydrogen, and
- R preferably denotes CH₃, C₂H₅ or H, and for a = 1, b is preferably 1.

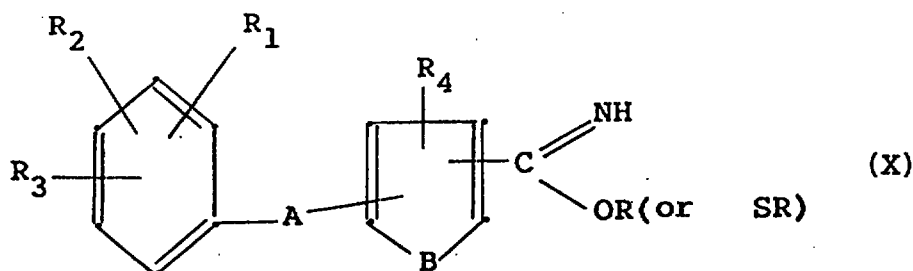
In the above definitions, the term halogen denotes F, Cl, Br or I, preferably F, Cl. If the groups listed are alkyl chains or contain alkyl chains, these may be straight-chained or branched. The alkyl chains in R₅, R₆ and R₇ preferably contain up to 6 carbon atoms, more particularly 1 to 4 carbon atoms. In particular, as a constituent of COR₆, R₆ denoting alkyl may also be mono- or poly-fluorine-substituted. Particular examples of substituents of ring systems are alkyls such as methyl, ethyl and the propyls. A preferred acyl group is COCH₃, a preferred alkoxy group is CH₃O. The bridge A preferably contains 4 to 6 members. The group is arranged between the two ring systems in formula I and in corresponding formulae so as to correspond to the written form of formulae II to VI, whereas the groups which are valid for both R₁ and R₂ are not listed in the proper orientation. If R₁ and R₂ together denote a double bonded group, R₃ preferably denotes H or C₂₋₅-acyl, e.g. acetyl. The groups R₁, R₂ and R₃ should not all simultaneously denote CF₃, COR₆, SR₆, SOR₆, SO₂R₆,



$\text{SO}_2\text{NR}_5\text{R}_7$, or $\text{C}(\text{OH})\text{R}_5\text{R}_7$, but rather these groups as well as OR_5 , with the definition phenoxy or substituted phenoxy, preferably occur only once or possibly twice, whilst alkyl, acyl and halogen, in particular, may occur as further substituents. The bonds or CH_2 groups in IX/IXa/IXb are generally in the α -position to one another. Typical groups for A are, for example, $\text{O}-(\text{CH}_2)_2-\text{O}$, $\text{O}-(\text{CH}_2)_4-\text{O}$, whilst one of the O-atoms may be replaced by S, NH or CO, as well as groups such as $\text{CH}_2-\text{CH}_2-\text{CONH}$, $\text{CH}_2-\text{CH}_2-\text{NH}-\text{CO}$, $\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2$ or $\text{NH}-\text{CO}-\text{CH}_2-\text{CH}_2$. The amidino group is usually in the para-position relative to the carbon atom to which A is linked.

The new compounds are prepared by conventional methods.

1. Reaction of imidoesters of the formula



wherein R_1 to R_4 , A and B are as hereinbefore defined and R preferably represents a C_{1-6} -alkyl group or benzyl (but if desired the man skilled in the art can also use derivatives of other alcohols), and ammonia. The reaction is preferably 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 the boiling temperature, if this is lower. Suitable solvents are polar solvents such as methanol, ethanol and propanol.

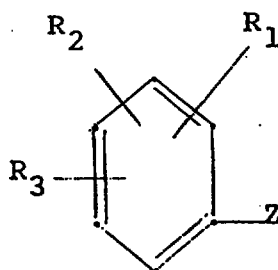


If the starting materials are sufficiently acid-resistant the reaction may be carried out via the corresponding acid imide chlorides instead of the imidoesters.

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:

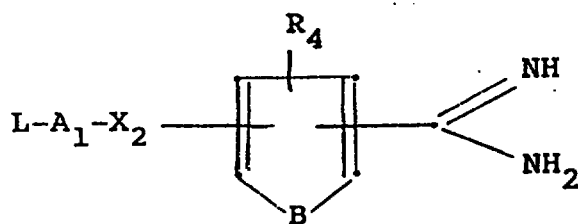
reaction

(a) of a phenol or thiophenol of formula



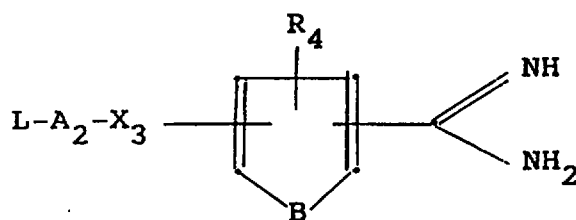
(XI)

wherein Z denotes OH or SH and R₁, R₂ and R₃ are as hereinbefore defined, with a compound of the formula



(XII)

or



(XIII)

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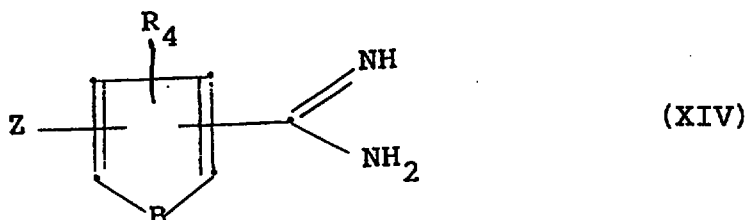


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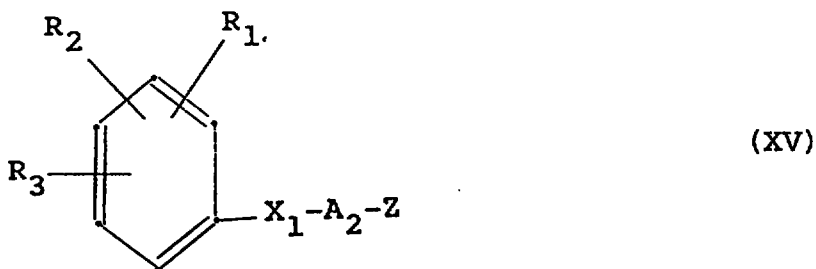
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wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L represents a nucleofugic leaving group, or

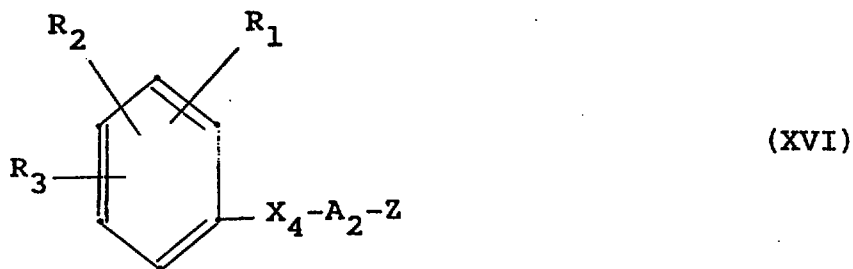
(b) of a phenol or thiophenol of the formula



wherein B , R_4 and Z are as hereinbefore defined, with a compound of the formula

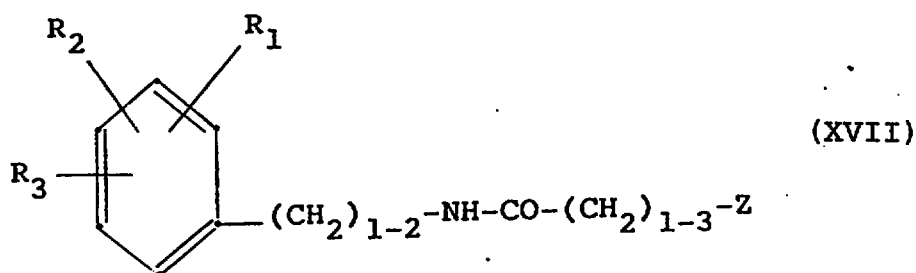


or

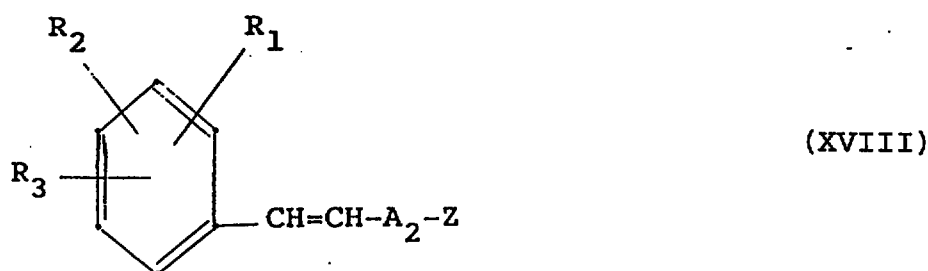


or





or



wherein A_1 , A_2 , R_1 , R_2 , R_3 and Z 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 with the addition of a base (metal carbonates, metal hydroxides, metal hydrides) 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. alkali metal salts. Examples of suitable nucleofugic leaving groups include halogens such as Br and Cl.

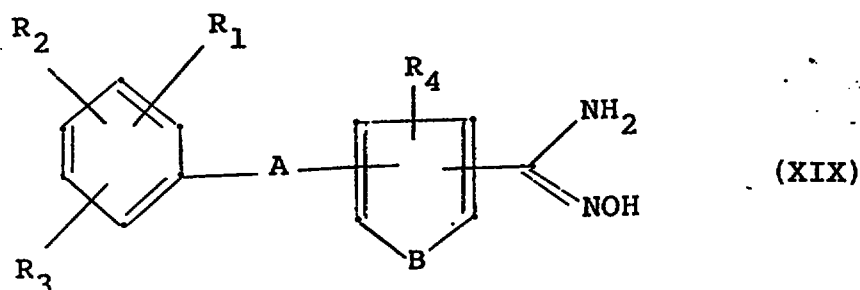
3. Reduction of an amidoxime of the formula

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wherein A, B and R_1 to R_4 are as hereinbefore defined.

For the reduction of XIX it is appropriate to use catalytic hydrogenation, particularly with Raney nickel in a lower alcohol such as methanol.

Conveniently, the amidoxime of formula XIX is 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. up to 5 bar, until the uptake of hydrogen has ended.

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 them with HCl via the step of the imide chlorides or directly by reacting them with, for example, C_{1-6} -alcohols or benzyl alcohol in the presence of an acid such as HCl. The reaction of the nitriles with H_2S in solvents such as pyridine or dimethylformamide in the presence of a base such as triethylamine and subsequent alkylation or benzylation result in compounds of formula X. Starting from carboxylic acid amides, which moreover

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correspond to the compounds of formula X, compounds of formula X may also be obtained by reaction with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate, in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, preferably at ambient temperature.

The starting materials XIX may also be obtained by reacting corresponding amidoximes instead of amidines analogously to method 1 or 2; by analogous reaction of corresponding nitriles from which the starting materials XIX are finally obtained by the addition of hydroxylamine.

The compounds according to the invention are therapeutically useful, particularly in the light of their LTB₄-antagonistic activity. They are therefore suitable for use, particularly, in those diseases in which inflammatory and/or allergic processes are involved, such as asthma, ulcerative colitis, psoriasis and also for treating gastropathy induced by non-steroidal antiphlogistics. The new compounds may also be used in conjunction with other active substances, e.g. antiallergics, secretolytics, β_2 -adrenergics, steroids for inhalation, antihistamines and/or PAF-antagonists. They may be administered by topical, oral, transdermal, nasal or parenteral route or by inhalation.

The therapeutic or prophylactic dose is dependent on the nature and gravity of the disease, as well as the potency of the individual compounds and the body weight of the patient. For oral administration the dose is between 10 and 250 mg, preferably between 20 and 200 mg. For inhalation, the patient takes between about 2 and 20 mg of active substance. The new compounds may be administered in conventional preparations such as plain or coated tablets, capsules, lozenges, powders,

granules, solutions, emulsions, syrups, aerosols for inhalation, ointments and suppositories.

The Examples which follow illustrate some possible formulations for the preparations.

Formulation Examples

1. Tablets

Composition:

Active substance according to the invention	20 parts by weight
Stearic acid	6 parts by weight
Dextrose	474 parts by weight

The constituents 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 dextrose reduced or increased accordingly.

2. Suppositories

Composition:

Active substance according to the invention	100 parts by weight
Powdered lactose	45 parts by weight
Cocoa butter	1555 parts by weight

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

3. Powder for inhalation

Micronised powdered active substance (compound of formula I; particle size about 0.5 to 7 μm) is packed into hard gelatine capsules in a quantity of 5 mg,



optionally with the addition of micronised lactose. The powder is inhaled using conventional inhalation devices, e.g. according to DE-A 3 345 722.

The compounds according to the invention were tested inter alia for their activity in the tests described below.

a) U937 - Receptor binding test/LTB₄

The binding of ³H-LTB₄ (3nM) to vital U937 cells (differentiated human monocytary cell line with naturally expressed LTB₄ receptors) is inhibited, in dosage dependent manner, by an increasing concentration of the test substance (incubation 2 hours at 0°C). After the unbound ³H-LTB₄ has been separated off by membrane filtration, the radioactivity of the bound LTB₄ receptor/³H-LTB₄ complex is quantified by scintillation measurement. The affinity (inhibition constant K_i) was determined by repeated adaptation of a displacement curve to the measurements (program: "coupled mass equilibria" on Wang computer).

b) Aggregation of neutrophilic granulocytes in the guinea-pig

Indicated by LTB₄ in vitro (increase in light transmission in the aggregometer, recorded in mm; each experiment repeated twice): inhibition 2 minutes after incubation with test substance in polydiol/DMSO.

c) Leukotrien-B₄-indicated accumulation of neutrophiles in the mouse ear

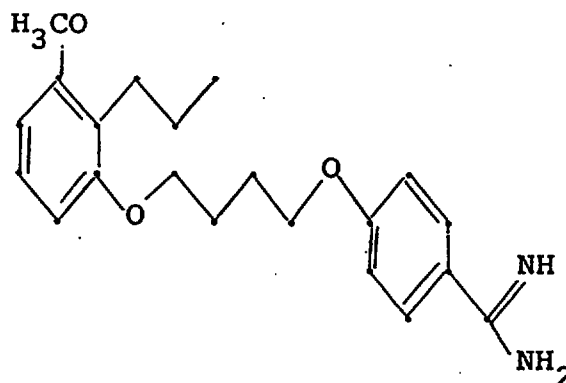
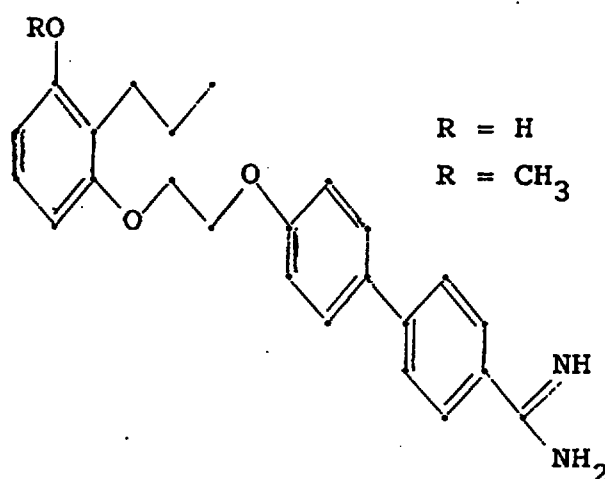
Evaluation of the neutrophilic influx by



photometric measurement (mOD/min) of the myeloperoxidase activity (Bradley et al.: J. Invest. Dermatol. 78, 206, 1982) in the skin of the ear. Increase 6 hours after topical treatment of the left ear with LTB₄ (250 ng on each side) compared with the right ear (2 x 5 µl acetone as solvent).

Substance administered by oral route in 1% tylose 300, 30 minutes before the LTB₄ stimulation.

4. Results

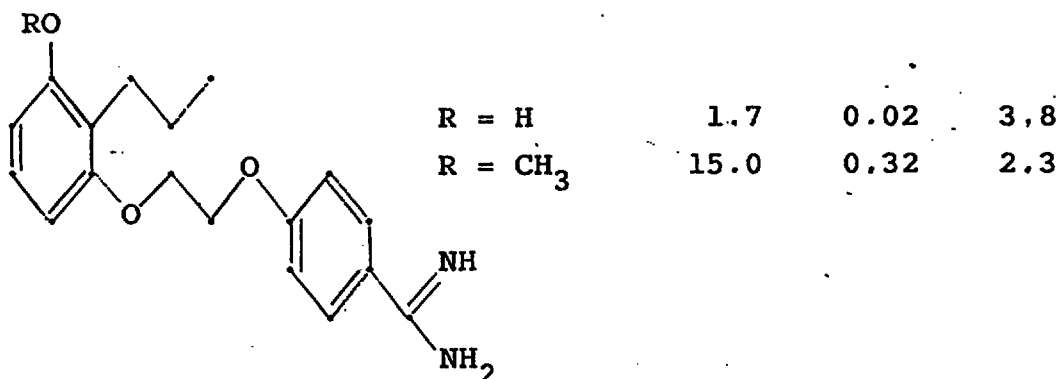
	a)*	b)**	c)***
	12.0	1.9	0.8
			
R = H	3.8	0.06	1.2
R = CH ₃	6.3	0.31	0.9

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- * Receptor binding U937-8 K_i [nM] (1)
- ** LTB₄-induced neutroph. Aggr. EC₅₀ [μM] (2)
- *** LTB₄-induced neutroph. Accum. p.o. ED₅₀ [mg/kg]

The ³H-LTB₄-receptor binding to guinea-pig spleen cells in the presence of 10% blood plasma yielded K_i-values of, in some cases, far less than 1 μM, more particularly between 0.2 and 0.02. Inhibition of the LTB₄-induced aggregation of neutrophils resulted in EC₅₀-values between about 0.5 and 0.05 μM.

Particular mention should be made of the compounds according to Examples 1 and 5 and Nos. 10, 11, 13, 19, 20, 22 and 23 from Table I, No. 1 from Table II, No. 2 from Table III.

The Examples which follow illustrate the possible methods of preparing the compounds according to the invention.

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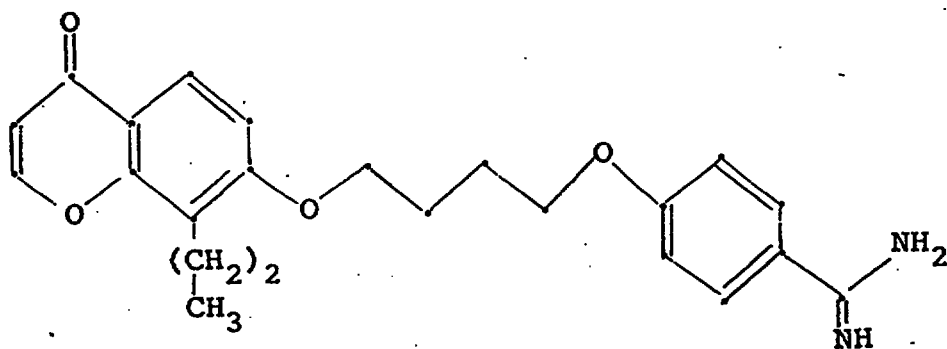


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Process 1:

Example 1



To a solution of 2.0 g of 7-[4-(4-cyano-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one in 50 ml of chloroform and 1.5 ml of ethanol are added 5 ml of a solution of hydrogen chloride in diethylether (17%). The mixture is left to stand for 14 days at ambient temperature and the product is precipitated with diethylether. 1.15 g of 7-[4-(4-imidacarboxyethyl-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained. The imidoester is mixed with 50 ml of ethanolic ammonia solution (5 M) and heated for 3 hours to 70°C. The mixture is evaporated down and the residue is chromatographed (chloroform/methanol 7:3, silica gel). After recrystallisation from dichloromethane/diethylether, 0.6 g of 7-[4-(4-amidino-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained (m.p. 144 - 148°C).

Example 2

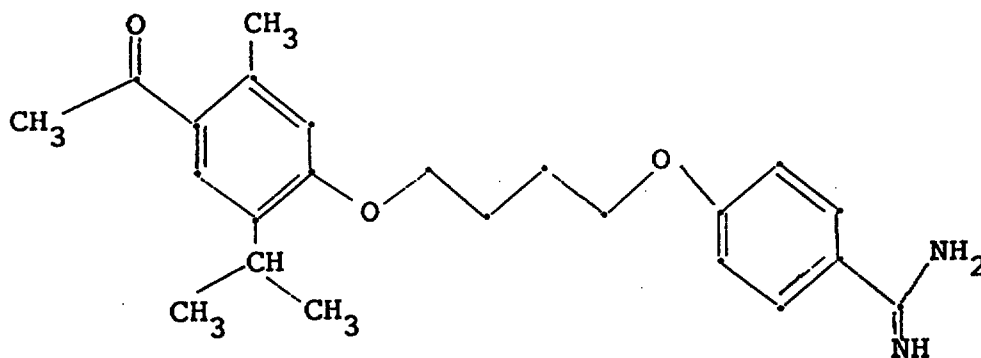
To a solution of 2.5 g of 4-[4-(2-propyl-3-methoxy-phenoxy)-butyloxyl-benzonitrile, prepared from 2-propyl-3-methoxy-phenol and 4-bromobutoxybenzonitrile, in 40 ml of ethanol, hydrogen chloride is introduced at -20°C



with stirring for 1 hour and the mixture is left to stand at ambient temperature for 16 hours.

The solvent is distilled off in vacuo and the residue is taken up in 50 ml of ethanol. A mixture of 14 ml of ethanolic ammonia solution and 50 ml of ethanol is added dropwise thereto and the mixture is left to stand for 24 hours at ambient temperature. The solvent is evaporated off and the residue is chromatographed (chloroform/methanol 8:2; silica gel 60). 1.8 g of 4-[4-(2-propyl-3-methoxy-phenoxy)-butyloxy]-benzamidinium-hydrochloride-hemihydrate are obtained. (M.p. 117-121°C).

Example 3

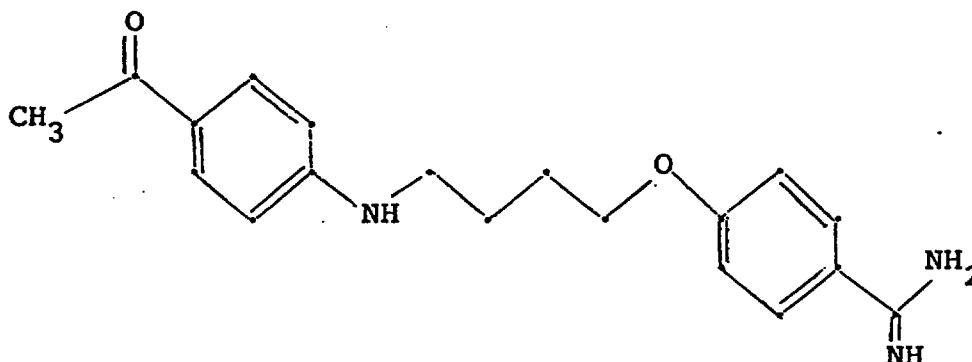


Hydrogen chloride is introduced at -20°C into a solution of 32.0 g of 4-[(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzonitrile in 350 ml of ethanol and the resulting mixture is stirred for 48 hours. The crystals precipitated are suction filtered and washed with diethylether. 41.0 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzimidazole-hydrochloride are obtained (m.p. 100 - 102°C decomp.). 15.0 g of the imidoester are added at ambient temperature in several batches to 33 ml of ethanolic ammonia solution (5 M) and 100 ml of ethanol. The mixture is stirred for 36 hours at ambient temperature,



evaporated down and the residue is stirred with 50 ml of water. The residue is suction filtered, recrystallised from 30 ml of ethanol and washed with diethylether. 11.5 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzamidine-hydrochloride are obtained (m.p. 182 - 183°C decomp.).

Example 4

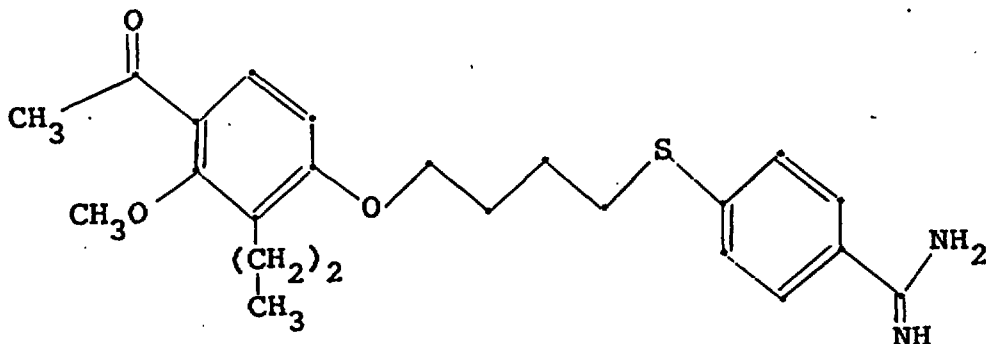


Hydrogen chloride is introduced at -20°C into a solution of 3.0 g of 4-[4-(4-cyano-phenoxy)-butylamino]-acetophenone in 40 ml of ethanol, with stirring, for 4 hours and the mixture is left to stand at ambient temperature for 16 hours. The solvent is distilled off in vacuo and the residue is taken up in 50 ml of ethanol. A mixture of 14 ml of ethanolic ammonia solution and 50 ml of ethanol is added dropwise thereto and the mixture is left to stand for 24 hours at ambient temperature. The solvent is evaporated off and the residue is chromatographed (chloroform/methanol 7:3, silica gel 60). 0.3 g of 4-[4-(4-amidino-phenoxy)butylamino]-acetophenone are obtained (m.p. 200 - 202°C).



Process 2:

Example 6



8.2 g of 4-acetyl-3-methoxy-2-propyl-phenol are dissolved in 80 ml of dimethylformamide and 1.1 g of sodium hydride is added in batches to the solution (as an 80% dispersion in white oil). The mixture is heated to 80°C for 30 minutes and combined with a solution of 5.75 g of 4-(4-bromopropylthio)-benzamidinium (prepared from dibromobutane and 4-cyanobenzothiol by means of 4-(4-bromobutyl-thio)-benzonitrile) in 40 ml of dimethylformamide. After 5 hours at 80°C the mixture is allowed to cool, acidified with ethereal hydrochloric acid and the solvents are distilled off in vacuo. The residue is taken up in ethanol and filtered. The filtrate is concentrated by evaporation. The process is repeated with chloroform and acetonitrile. The residue is stirred with diethylether. After decanting, 5.65 g of a brownish-yellow oil are left. The product is chromatographed (chloroform/methanol 7:3, silica gel). 2.4 g of an oil are obtained which is crystallised from toluene. The product is dissolved in acetonitrile, acidified with ethereal hydrochloric acid. The crystals are suction filtered, washed with cold acetonitrile, dissolved in water and crystallised once more after the addition of 2 N hydrochloric acid. 0.8 g of 4-[4-(4-acetyl-3-methoxy-2-propylphenoxy)-butylthio]-benzamidinium-hydrochloride are obtained (m.p.



120 - 122°C).

Process 3:

Example 7

a) 4-[4-(4-Acetylphenoxy-butoxy)-benzamidoxime

45.6 g (0.3 mol) of 4-hydroxybenzamidoxime and 81.3 g (0.3 mol) of 4-bromo-butoxy-acetophenone are dissolved in 300 ml of dimethylformamide. After the addition of 55.2 g (0.4 mol) of anhydrous potassium carbonate the mixture is heated to 80°C for 2 hours. The inorganic salts are suction filtered, evaporated down in vacuo and recrystallised from acetonitrile.

Yield: 47.8 g

M.p.: 164.5 - 165.5°C.

b) 3-[4-(4-Acetylphenoxy)butoxy]-benzamidine-methanesulphonate

47.8 g of the compound synthesised according to a) are dissolved in 10 times the quantity of methanol with the addition of the calculated amount of methanesulphonic acid. After the addition of Raney nickel, the mixture is hydrogenated at 5 bar until the uptake of hydrogen has ended. The mixture is suction filtered, the solvent is distilled off in vacuo and the residue is recrystallised from ethanol.

Yield: 45.2 g

M.p.: 204 - 204.5°C.

The other compounds of formula I can be obtained according to the processes described above. "Ac" hereinafter denotes CH₃CO-.

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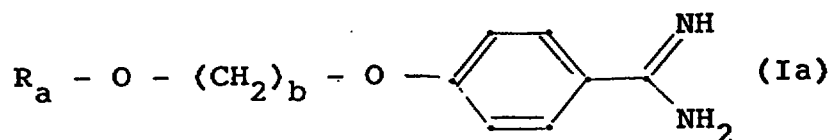


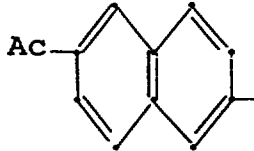
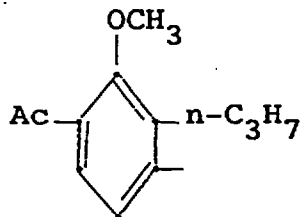
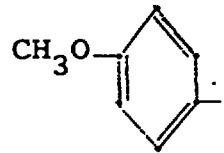
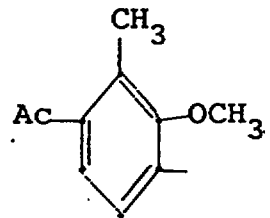
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TABLE I

Compounds of formula



No.	R_a	b	M.p. [°C] (Hydrochloride)
1		2	240
2		2	209-10
3		4	
4		4	143

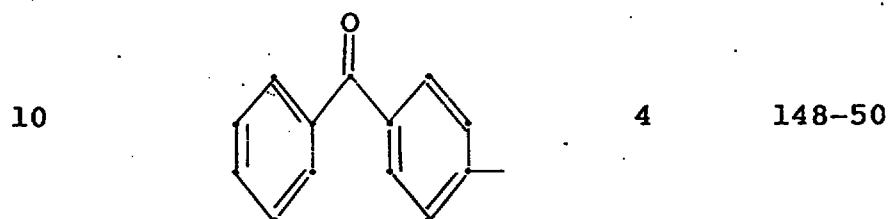
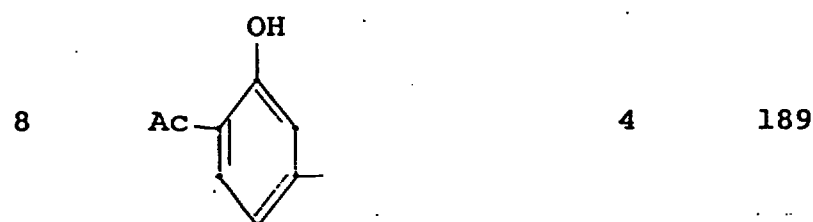
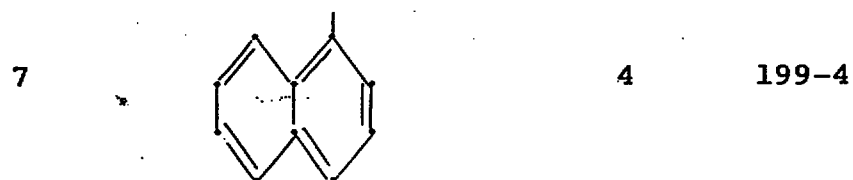
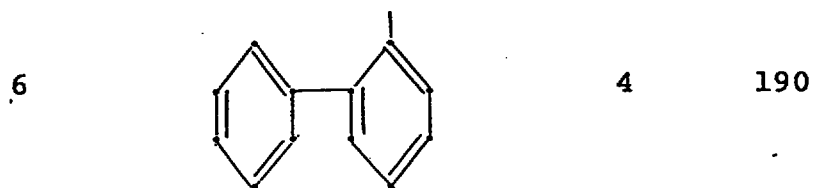
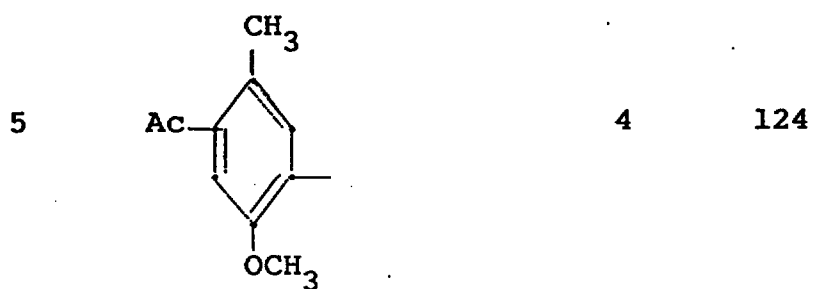
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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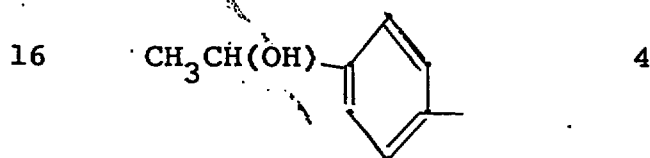
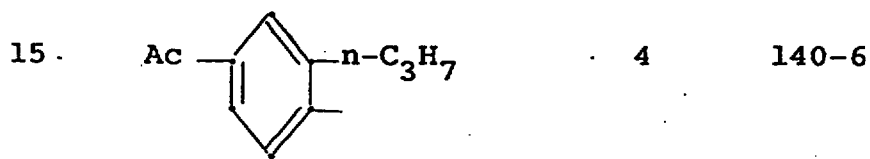
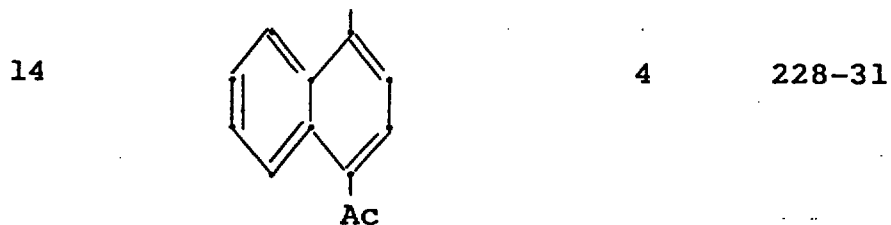
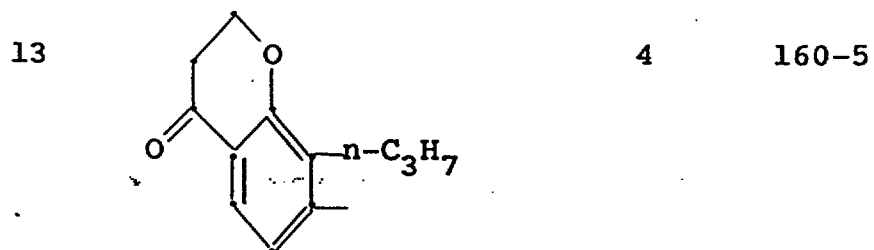
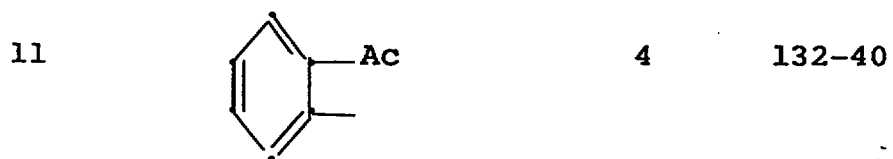
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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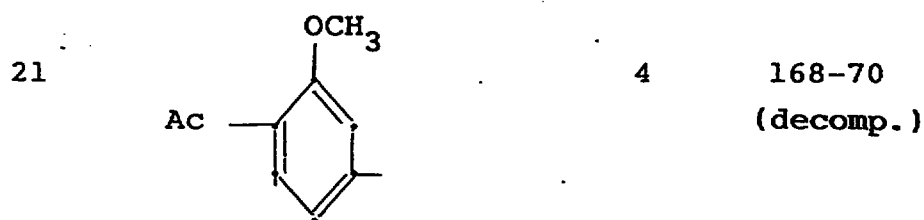
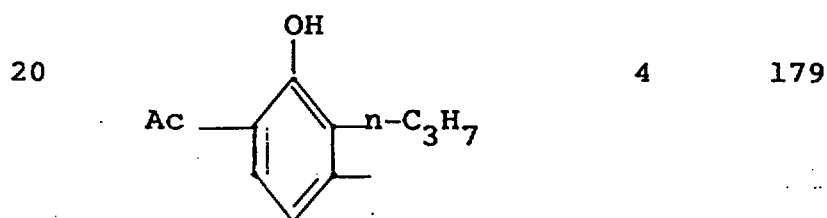
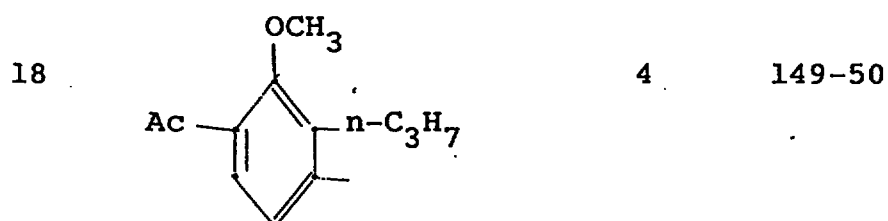
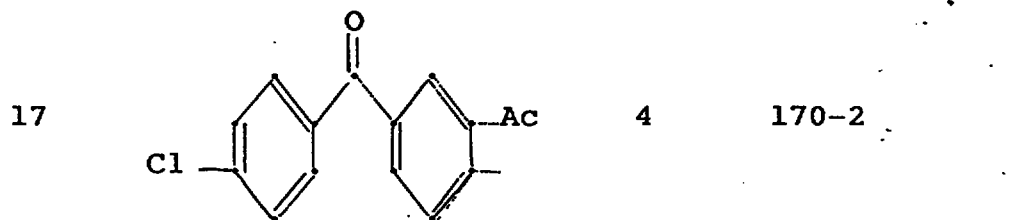
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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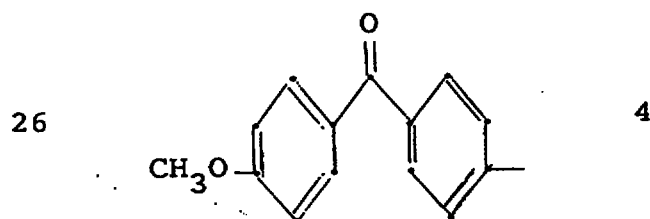
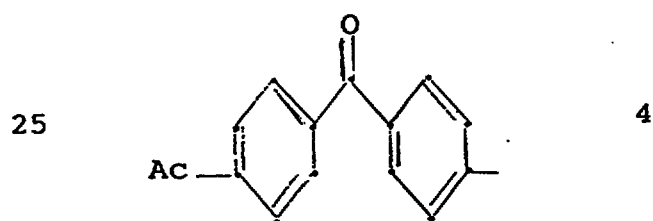
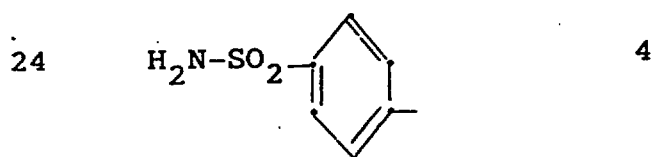
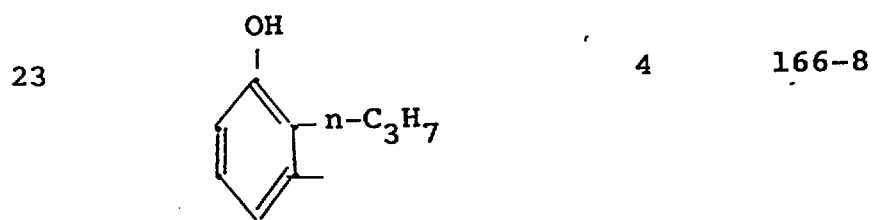
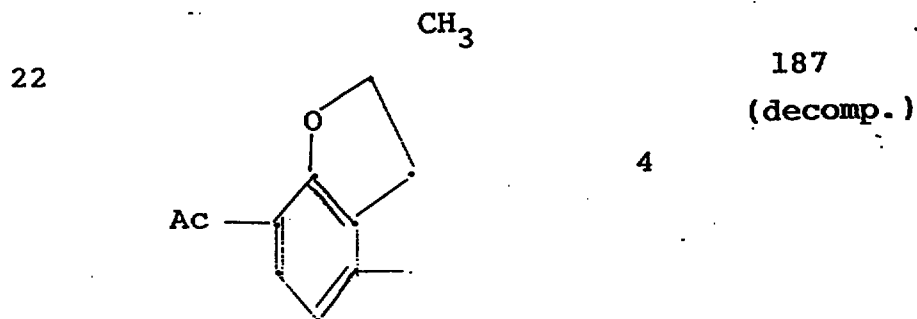


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No.	R _a	b	M.p. [°C] (Hydrochloride)
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No.	R_a	b	M.p. [°C] (Hydrochloride)
27		4	
28		4	
29		4	174-5
30		4	155-60
31		4	194-60
32		4	214-23

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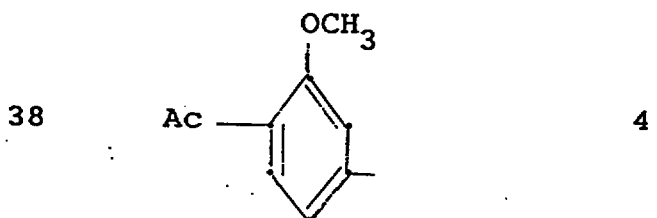
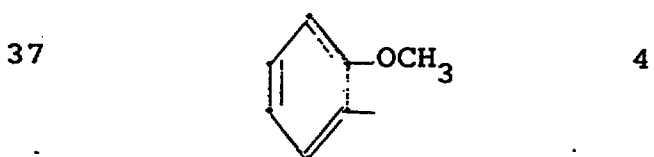
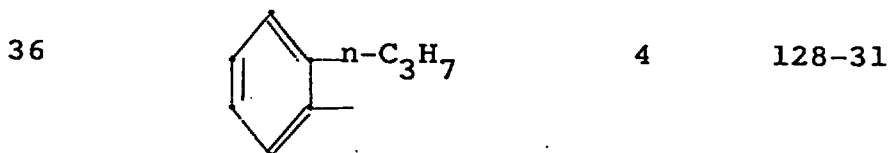
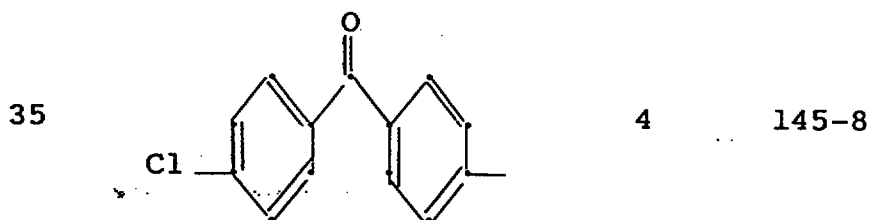
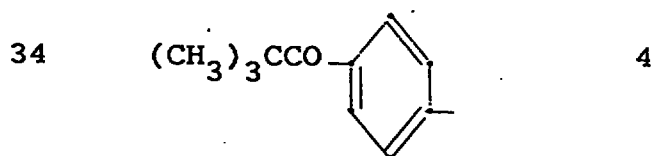
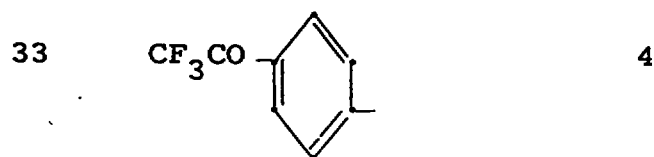


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No.	R _a	b	M.p. [°C] (Hydrochloride)
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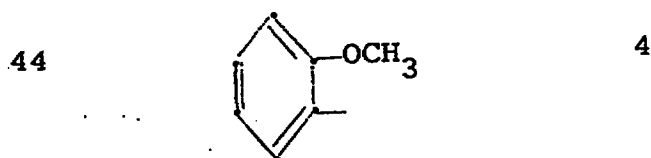
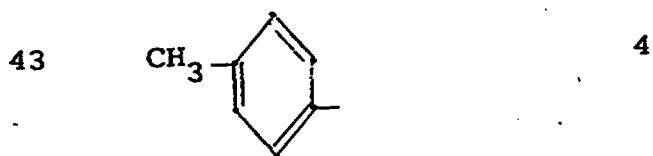
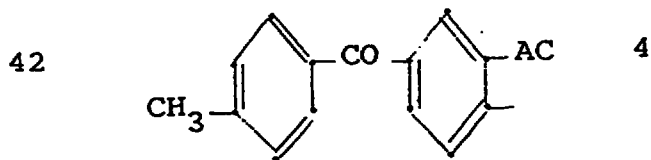
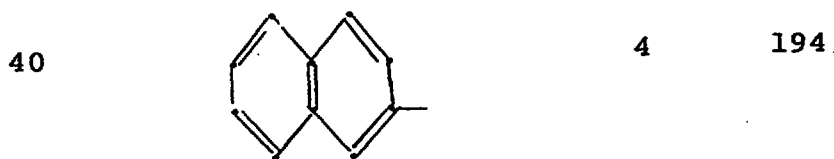
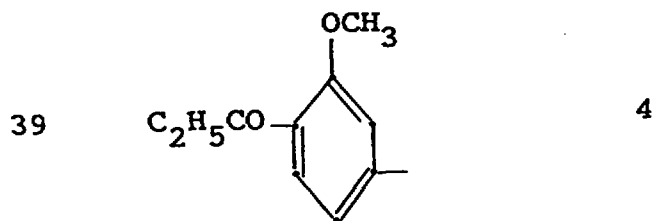
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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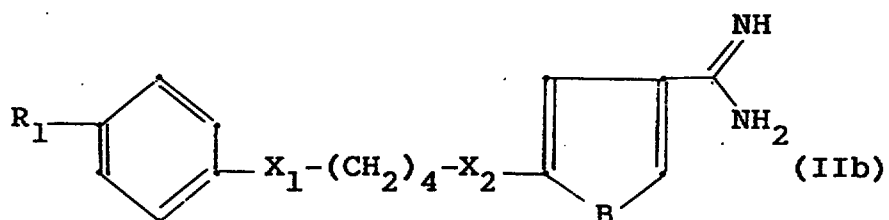


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TABLE II

Compounds of formula



No.	B	R ₁	X ₁	X ₂	M.p. [°C] (Hydrochloride)
1	CH=CH	Ac	O	S	
2	CH=CH	Ac	O	SO	
3	CH=CH	Ac	O	SO ₂	160-2 (Base)
4	CH=CH	Ac	S	S	
5	N=CH	Ac	O	S	152-60
6	CH=CH	Ac	O	NH	200-2
7	CH=CH	Ac	S	O	196-7
8	CH=CH	Ac	SO	O	
9	CH=CH	Ac	SO ₂	O	208

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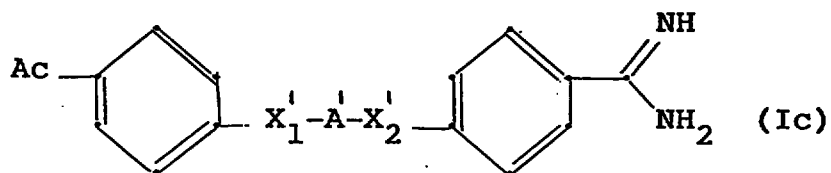


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TABLE III

Compounds of formula



No.	A'	X' ₁	X' ₂	M.p. [°C] (Hydrochloride)
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1	CH ₂ -CH=CH-CH ₂	O	O	215-8
---	--	---	---	-------

2		O	O	196-202
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3		O	O	205-9
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4		O	O	183
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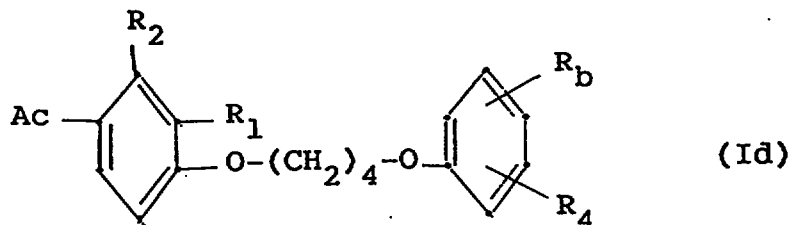


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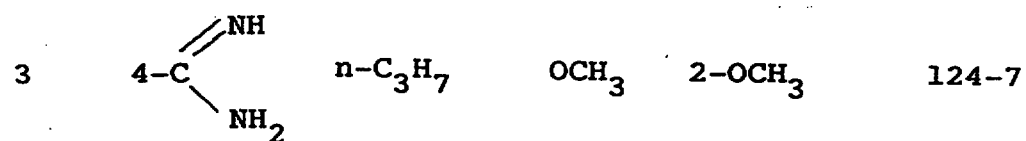
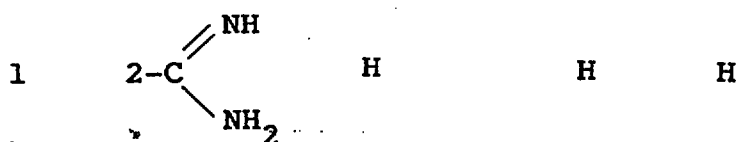
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TABLE IV

Compounds of formula



No.	R _b	R ₁	R ₂	R ₄	M.p. [°C] (Hydrochloride)
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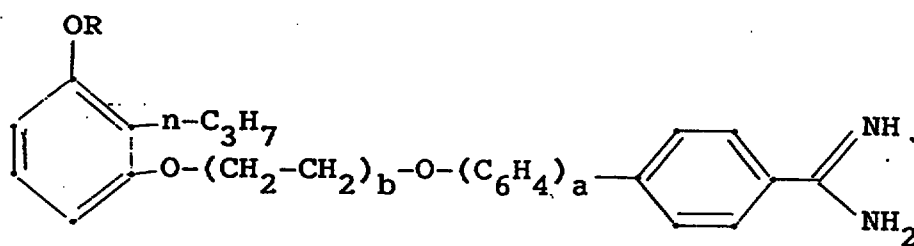


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No.	R	a	b	M.p. [°C]
1	H	0	1	178-80 (Hydrochloride)
2	H	1	1	248-51 (Hydrochloride)
3	H	1	2	
4	CH_3	0	1	176-8 (Hydrochloride)
5	CH_3	1	1	236-40 (Methanesulphonate)
6	C_2H_5	0	1	
7	C_2H_5	0	2	
8	$n\text{-C}_3\text{H}_7$	0	2	
9	$n\text{-C}_3\text{H}_7$	1	1	
10	$i\text{-C}_3\text{H}_7$	1	1	
11	$n\text{-C}_4\text{H}_9$	0	1	144-7 (Hydrochloride)
12	$n\text{-C}_4\text{H}_9$	0	2	

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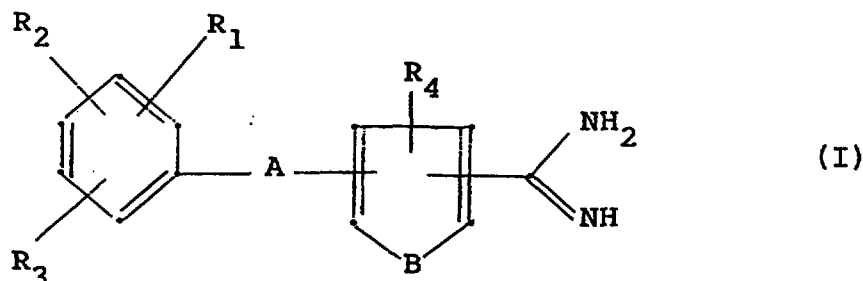
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Claims

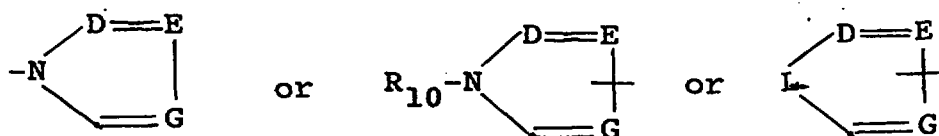
1. Compounds of the formula



wherein

R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_{3-4}-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,

R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONH_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}$ -alkyl), SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}$ -alkyl), $NH-SO_2-(C_{1-4}$ -alkyl), NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula





(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

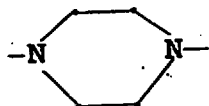
X₁-A₁-X₂ (II)

X₂-A₂-X₃ (III)

X₄-A₂-X₂ (IV)

(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)

-CH=CH-A₂-X₂ (VI)



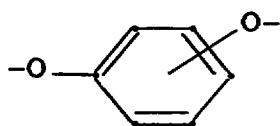
(VII)

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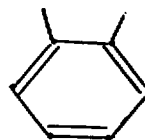
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Date: 02 NOV 1996

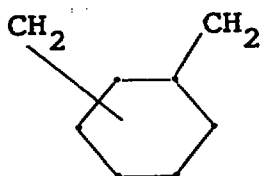


(VIII)

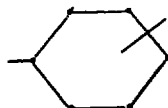
B denotes CH=CH, CH=N, S or



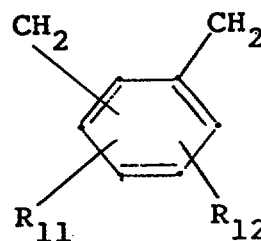
A₁ denotes C₂₋₄-alkylene, cis- or trans-CH₂-CH=CH-CH₂, CH₂-C=C-CH₂ or



(IX)



(IXa)



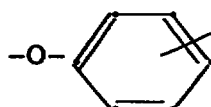
(IXb)

A₂ denotes C₁₋₅-alkylene,

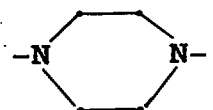
X₁ denotes O, NH, S, SO, SO₂, CO, CH₂ or



X₂ denotes O, NH, S or



X₃ denotes NH-CO, CO-NH, SO₂-NH or



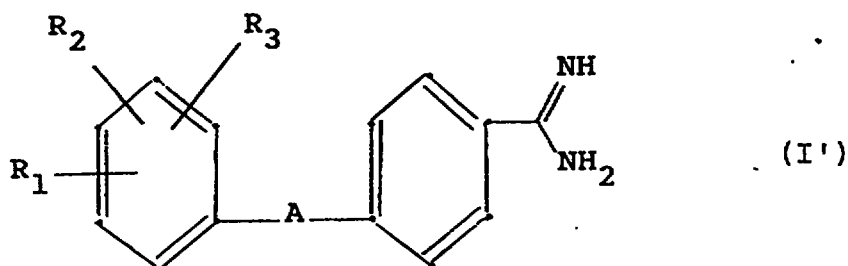
X₄ denotes NH-CO, CO-NH, NH-SO₂, SO₂-NH or NH-CO-NH,

as racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.





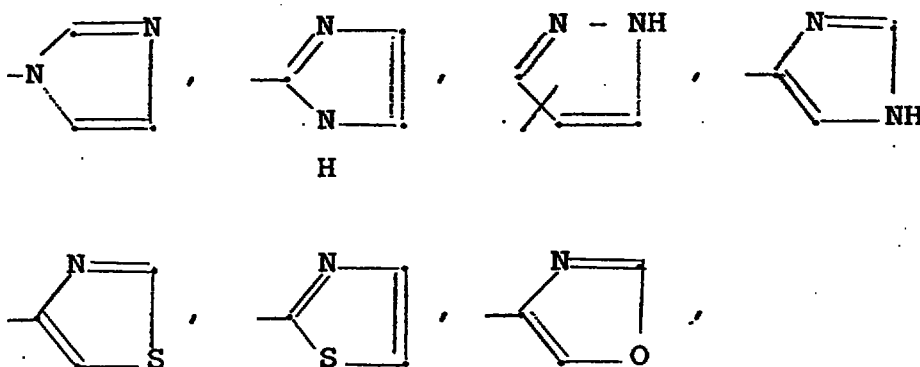
2. Compounds of the formula



wherein

R_1 , R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-CR_8=R_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-O-CHR_{10}-CH_2-$ or $-CO-CH_2-CH_2-O-$, linked with adjacent carbon atoms of the benzene ring,

R_3 denotes halogen, CF_3 , R_7 , OR_7 , $CO-(C_{1-4}-alkyl)$, $NH-CO-(C_{1-4}-alkyl)$, $NHSO_2-(C_{1-4}-alkyl)$ or $N(R_{10})_2$ (whilst R_7 can only denote H if at least one of the substituents R_1 and R_2 does not denote H) or a heterocyclic five-membered ring such as



R_6 and R_7 are as hereinbefore defined,

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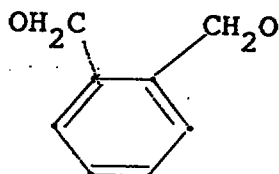
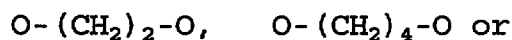


and

A denotes the group II.

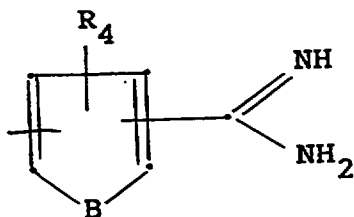
3. Compounds according to claim 1 or 2, wherein
 $R_1/R_2/R_3$ have the meanings C_{2-5} -acyl/H/H;
 C_6H_5CO /H/H; C_{1-4} -alkyl/OH/H;
 C_{2-5} -acyl/ C_{1-4} -alkyl/H;
 C_{2-5} -acyl/OH/ C_{1-4} -alkyl;
OH/ C_{2-5} -acyl/ C_{1-4} -alkyl.

4. Compounds according to claim 1, 2 and 3,
characterised in that A denotes

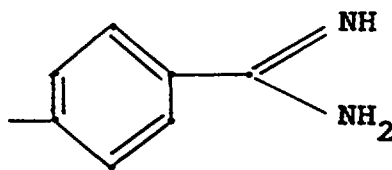


5. Compounds according to claim 1, 2, 3 or 4,
characterised in that the group II is acetylphenyl.

6. Compounds according to claim 1, 2, 3, 4 or 5,
characterised in that the group



represents



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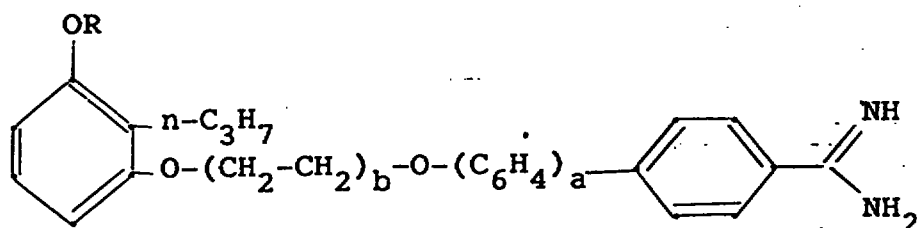


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7. Compounds of the formula



wherein

- a denotes 0 or 1,
b denotes 1 or 2,
R denotes C₁₋₄-alkyl, and if a = 0 or 1 and b = 1 and if a = 1 and b = 2 it may also denote hydrogen, in the form of free bases or acid addition salts.
8. Compounds according to claim 7, wherein a = 0 or 1 and b = 1 or a = 0 and b = 2 as free bases or as acid addition salts.
9. Compounds according to claim 8, wherein R denotes H, CH₃ or C₂H₅, a denotes 0 or 1 and b denotes 1, as free bases or as acid addition salts.
10. Compounds according to claim 8, wherein a denotes 0, b denotes 2 and R denotes CH₃, as free bases or as acid addition salts.
11. Pharmaceutical compositions, characterised in that they contain a compound according to claims 1 to 10.
12. Use of compounds according to claims 1 to 10 in the preparation of pharmaceutical compositions for the treatment of diseases in which inflammatory and/or allergic processes are involved, especially asthma, ulcerative colitis, psoriasis and for treating gastropathy induced by non-steroidal antiphlogistics.

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Date: 02 NOV 1996

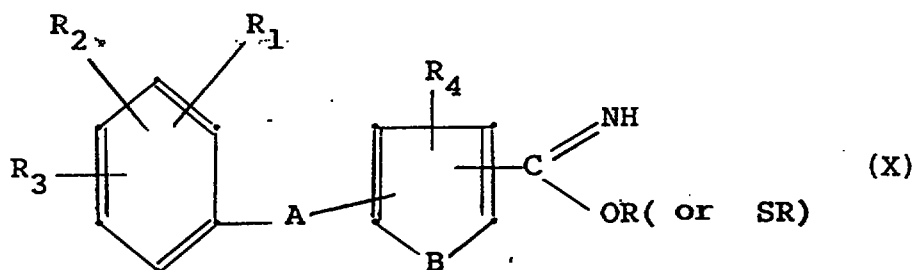


13. Use of an effective dose of a compound according to claims 1 to 10 for treating diseases in which LTB_4 -antagonistic compounds can be used.

14. Use of an effective dose of a compound according to claims 1 to 10 for the treatment of diseases in which inflammatory and/or allergic processes are involved, particularly asthma, ulcerative colitis, psoriasis, and for treating gastropathy induced by non-steroidal antiphlogistics.

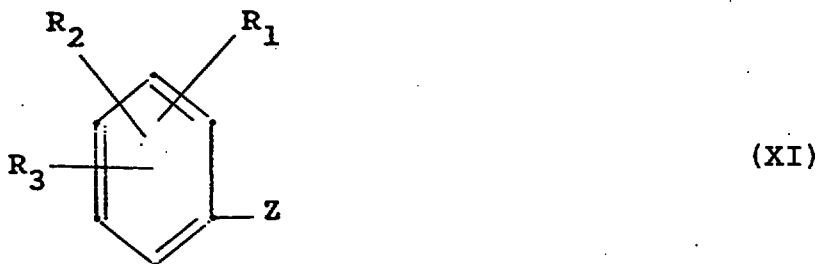
15. Process for preparing compounds according to claims 1 to 10, characterised in that

a) an imidoester of the formula



wherein R_1 to R_4 , A and B are as hereinbefore defined and R preferably represents a C_{1-6} -alkyl group or benzyl, is reacted with ammonia, or

b1) a phenol or thiophenol of the formula

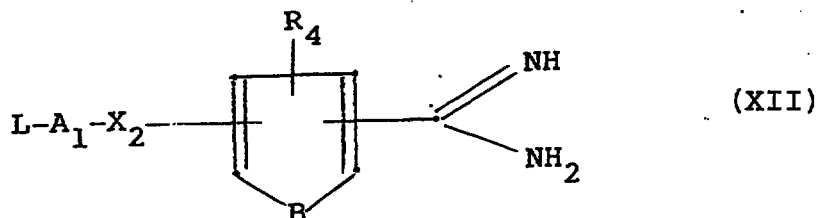


wherein Z denotes OH or SH and R_1 , R_2 and R_3 are as

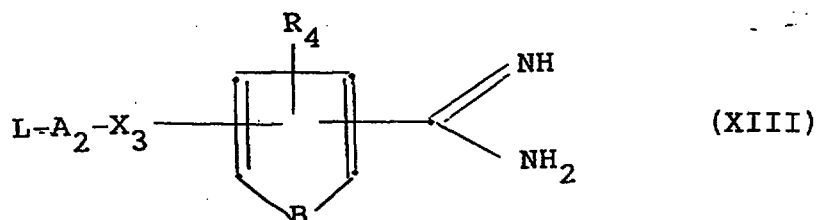




hereinbefore defined, is reacted with a compound of formula

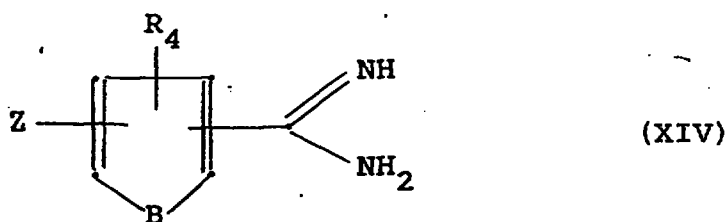


or

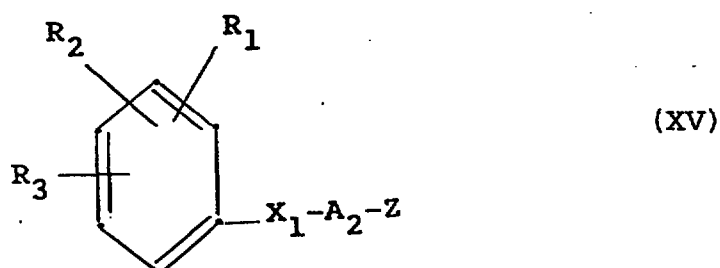


wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L denotes a nucleofugic leaving group, or

b2) a phenol or thiophenol of formula



wherein B , R_4 and Z are as hereinbefore defined, is reacted with a compound of formula



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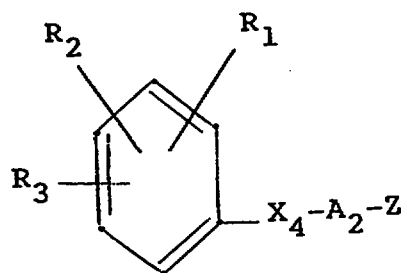


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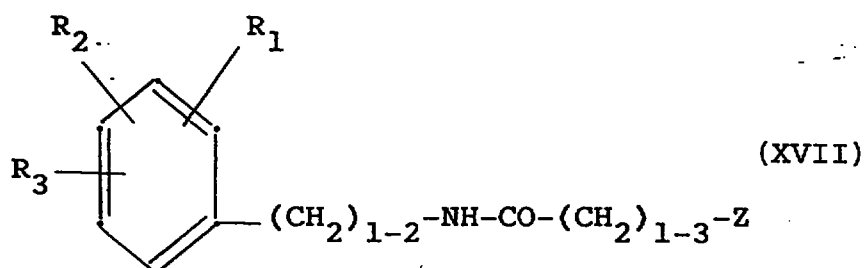
Date: 02 NOV 1996



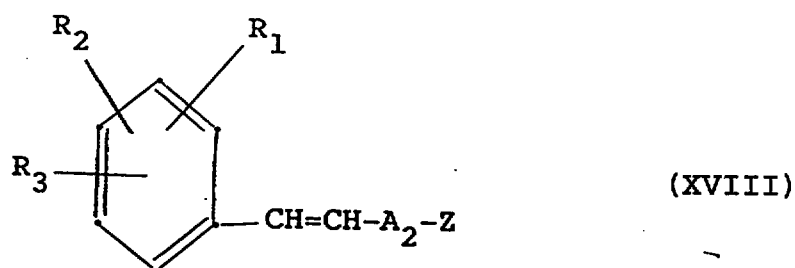
or



or

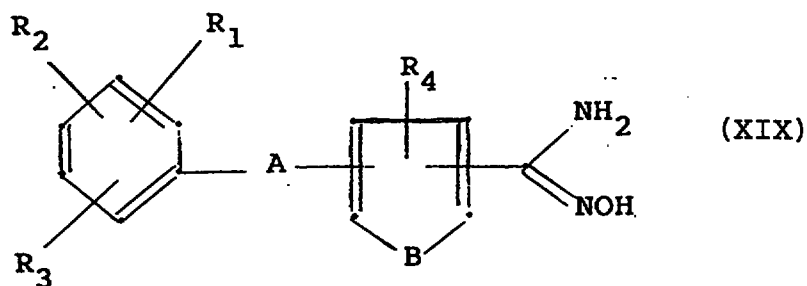


or



wherein A_1 , A_2 , R_1 , R_2 , R_3 and Z are as hereinbefore defined; or

c) an amidoxime of the formula





* C L M S *

- 43 -

wherein A, B and R_1 to R_4 are as hereinbefore defined, is reduced to form the corresponding amidine.

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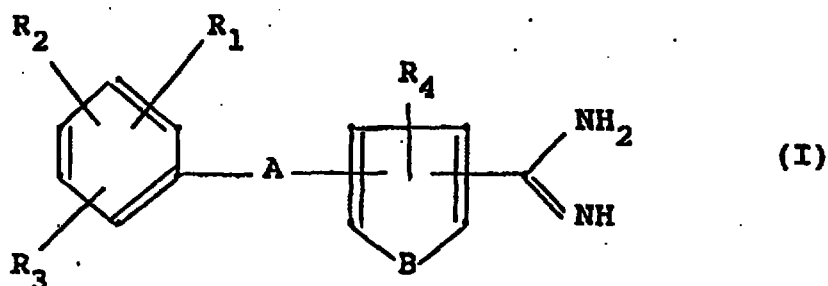
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Date: 02 NOV 1996

New amidine derivatives, the preparation and use thereof as pharmaceutical compositions with LTB₄-antagonistic activity

Abstract

Compounds of the formula



which is explained more fully in the specification, may be prepared by conventional methods and used therapeutically in conventional galenic preparations.

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REPLACED SHEETS SG
☒ Description : paged 1 to paged 10
☒ Claim(s) : paged 39 to paged 40
☐ Drawing(s) : paged 41 to paged 42
☐ Abstract : paged 43 to paged 44

DATE OF RECEIPT 5/1/98

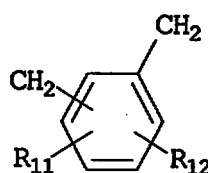
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- 4 -

REPLACED SHEETS SG
☒ Description : paged 1 to paged 10
☒ Claim(s) : paged 39 to paged 40
☐ Drawing(s) : paged 41 to paged 42
☐ Abstract : paged 43 to paged 44
 DATE OF RECEIPT

- then if any one of R_1 , R_2 or R_3 denotes $O-C_{1-12}$ -alkyl or $O-(C_{1-4}$ -alkyl)-phenyl then at least one of the remaining substituents R_1 , R_2 and R_3 is not H, halogen, OH, CF_3 , C_{1-12} -alkyl, phenyl- C_{1-4} -alkyl, $O-C_{1-12}$ -alkyl or $O-(C_{1-4}$ -alkyl)-phenyl;
- and if R_3 denotes $CONR_5R_7$, wherein R_5 denotes C_{1-12} -alkyl, phenyl, phenyl optionally substituted by halogen, C_{1-4} -alkyl or C_{1-4} -alkoxy, or phenyl- $(C_{1-4}$ -alkyl), and R_7 is as defined above, then A_1 does not denote C_{2-4} alkylene or

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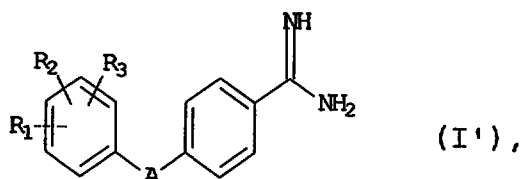
(IXb);

or when B denotes $-CH=CH-$, R_4 denotes hydrogen, X_1 and X_2 denote oxygen, A_1 denotes a C_3 or C_4 -alkylene and the amidino group is in the meta position to the group A,

- then R_1 , R_2 or R_3 do not denote NH_2 , chlorine, methoxy or CF_3 .

and (if they contain one or more chiral centres), may occur in the form of racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and (if a double bond is present) in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.

Within the scope of the above definitions, the preferred compounds are the compounds of formula



(I'),

wherein

R_1 , R_2 , which may be identical or different, denote

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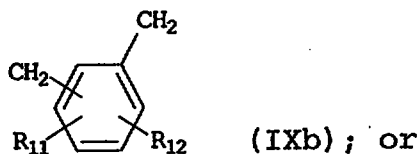
Date: 05 JUN 1998



With the proviso that when

B denotes $-\text{CH}=\text{CH}-$ and A denotes the group $\text{X}_1-\text{A}_1-\text{X}_2$, wherein X_1 denotes O or S, X_2 denotes O or S and A_1 is as defined above,

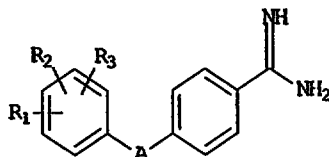
- then if any one of R_1 , R_2 or R_3 denotes O- C_{1-12} -alkyl or O-(C_{1-4} -alkyl)-phenyl then at least one of the remaining substituents R_1 , R_2 and R_3 is not H, halogen, OH, CF_3 , C_{1-12} -alkyl, phenyl- C_{1-4} -alkyl, O- C_{1-12} -alkyl or O-(C_{1-4} -alkyl)-phenyl;
- and if R_3 denotes CONR_5R_7 , wherein R_5 denotes C_{1-12} -alkyl, phenyl, phenyl optionally substituted by halogen, C_{1-4} -alkyl or C_{1-4} -alkoxy, or phenyl-(C_{1-4} -alkyl), and R_7 is as defined above, then A_1 does not denote C_{2-4} alkylene or



B denotes $-\text{CH}=\text{CH}-$, R_4 denotes hydrogen, X_1 and X_2 denote oxygen, A_1 denotes a C_3 or C_4 -alkylene and the amidino group is in the meta position to the group A,

- then R_1 , R_2 or R_3 do not denote NH_2 , chlorine, methoxy or CF_3 .

2. Compounds of the formula



(I')

wherein

R_1 , R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-\text{CR}_8=\text{R}_9-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CR}_8-\text{CR}_9=\text{CH}-$,

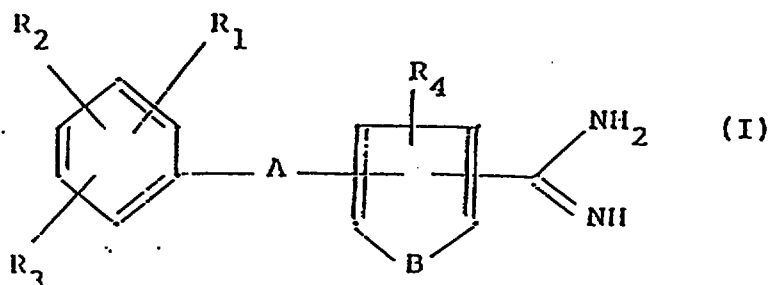
REPLACEMENT SHEETS SG
☒ Description : paged ... to paged ...
☒ Claim(s) : paged 35 to paged 45
☐ Drawing(s) : paged ... to paged ...
☒ Abstract : paged 46 to paged ...

DATE OF RECEIPT 1/11/98

New amidine derivatives, the preparation and use thereof as pharmaceutical compositions with LTB₄-antagonistic activity

The invention relates to new amidine derivatives, the preparation thereof using conventional methods and their use in pharmaceutical compositions.

The new amidine derivatives correspond to the formula

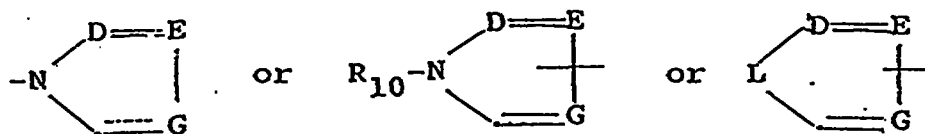


wherein

- R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,
- R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONR_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}\text{-alkyl})$, SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}\text{-alkyl})$, $NH-SO_2-(C_{1-4}\text{-alkyl})$, NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula

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Date: 01 NOV 1998



(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes hydrogen, halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

X₁-A₁-X₂ (II)

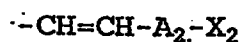
X₂-A₂-X₃ (III)

X₄-A₂-X₂ (IV)

(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)

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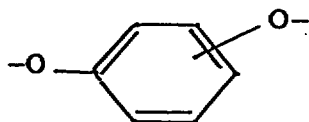
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(VI)

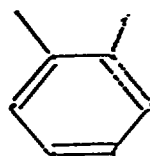


(VII)

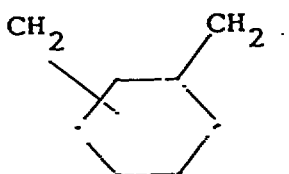


(VIII)

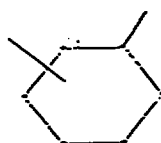
B denotes $\text{CH}=\text{CH}$, $\text{CH}=\text{N}$, S or



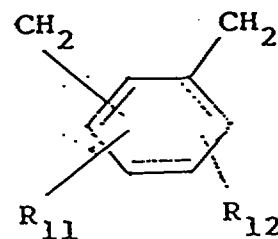
A_1 denotes C_{2-4} -alkylene, cis- or trans- $\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2$, $\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$ or



(IX)



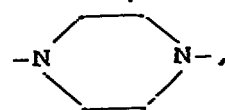
(IXa)



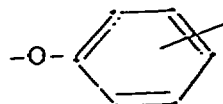
(IXb)

A_2 denotes C_{1-5} -alkylene,

X_1 denotes O, NH, S, SO, SO_2 , CO, CH_2 or



X_2 denotes O, NH, S or



X_3 denotes NH-CO, CO-NH, SO_2 -NH or



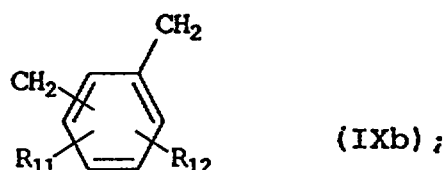
X_4 denotes NH-CO, CO-NH, NH- SO_2 , SO_2 -NH or NH-CO-NH,

With the proviso that when B denotes $-\text{CH}=\text{CH}-$ and A denotes the group $\text{X}_1-\text{A}_1-\text{X}_2$, wherein X_1 denotes O or S, X_2 denotes O or S and A_1 is as defined above,

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- then if any one of R_1 , R_2 or R_3 denotes O- C_{1-12} -alkyl or O-(C_{1-4} -alkyl)-phenyl then at least one of the remaining substituents R_1 , R_2 and R_3 is not H, halogen, OH, CF_3 , C_{1-12} -alkyl, phenyl- C_{1-4} -alkyl, O- C_{1-12} -alkyl or O-(C_{1-4} -alkyl)-phenyl;
- and if R_3 denotes $CONR_5R_7$, wherein R_5 denotes C_{1-12} -alkyl, phenyl, phenyl optionally substituted by halogen, C_{1-4} -alkyl or C_{1-4} -alkoxy, or phenyl-(C_{1-4} -alkyl), and R_7 is as defined above, then A_1 does not denote C_{2-4} alkylene or

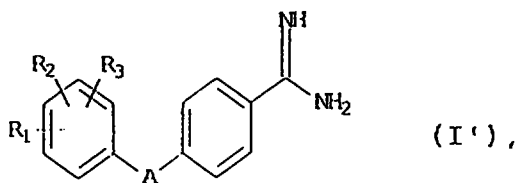


or when B denotes $-CH=CH-$, R_4 denotes hydrogen, X_1 and X_2 denote oxygen, A_1 denotes a C_3 or C_4 -alkylene and the amidino group is in the meta position to the group A,

- then R_1 , R_2 or R_3 do not denote NH_2 , chlorine, methoxy or CF_3 .

and (if they contain one or more chiral centres), may occur in the form of racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and (if a double bond is present) in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids.

Within the scope of the above definitions, the preferred compounds are the compounds of formula

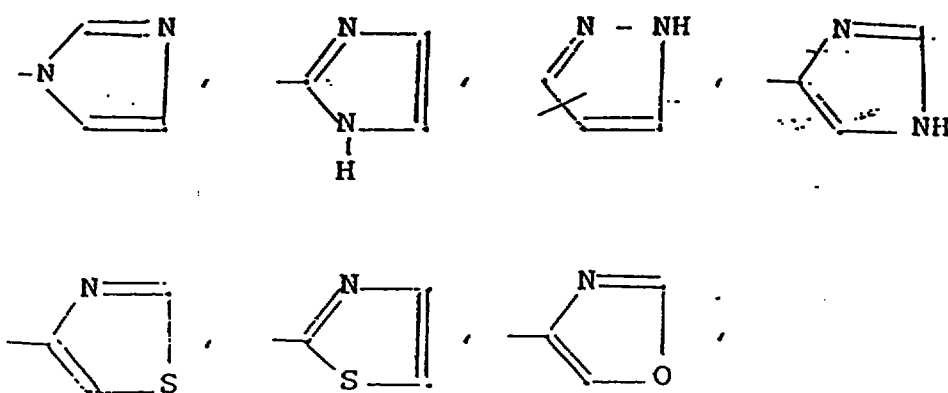


wherein

R_1 , R_2 , which may be identical or different, denote

R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-O-CHR_{10}-CH_2-$ or $-CO-CH_2-CH_2-O-$, linked with adjacent carbon atoms of the benzene ring,

R_3 denotes halogen, CF_3 , R_7 , OR_7 , $CO-(C_{1-4}-alkyl)$, $NH-CO-(C_{1-4}-alkyl)$, $NHSO_2-(C_{1-4}-alkyl)$ or $N(R_{10})_2$ (whilst R_7 can only denote H if at least one of the substituents R_1 and R_2 does not denote H) or a heterocyclic five-membered ring such as

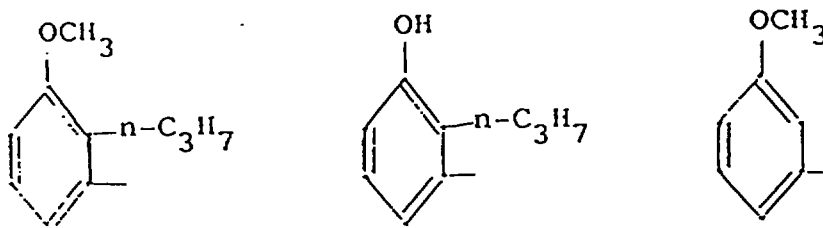


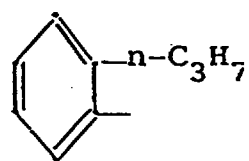
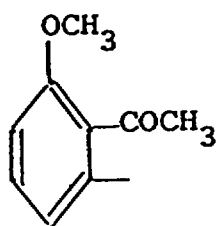
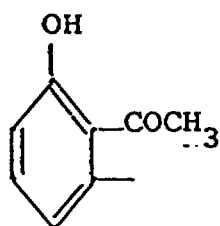
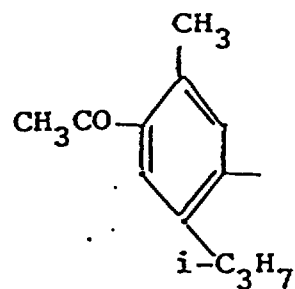
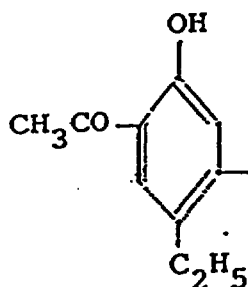
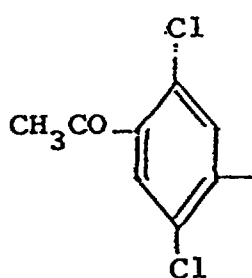
R_6 and R_7 are as hereinbefore defined,

and

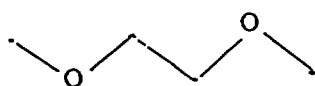
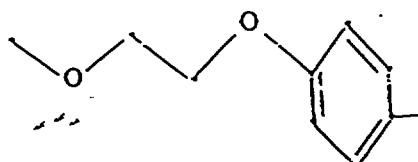
A denotes the group II.

The following may be particularly mentioned as examples of the group of formula II:

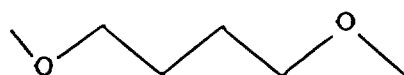




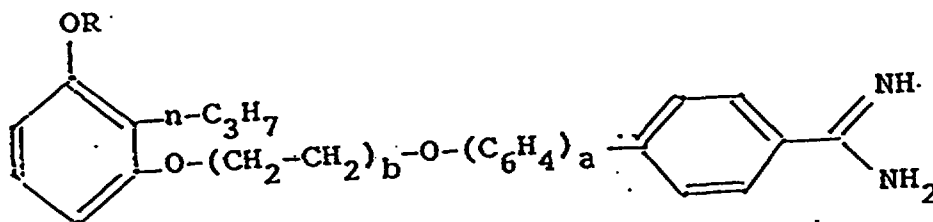
Of the definitions of A particular mention may be made of:



and



Special mention should also be made of the compounds of formula



wherein

- a denotes 0, b denotes 1 and R denotes H, or a denotes 1, b denotes 1 or 2, and
- R denotes C₁₋₄-alkyl, and if b = 2, R may also denote hydrogen, and
- R preferably denotes CH₃, C₂H₅ or H, and for a = 1, b is preferably 1.

In the above definitions, the term halogen denotes F, Cl, Br or I, preferably F, Cl. If the groups listed are alkyl chains or contain alkyl chains, these may be straight-chained or branched. The alkyl chains in R₅, R₆ and R₇ preferably contain up to 6 carbon atoms, more particularly 1 to 4 carbon atoms. In particular, as a constituent of COR₆, R₆ denoting alkyl may also be mono- or poly-fluorine-substituted. Particular examples of substituents of ring systems are alkyls such as methyl, ethyl and the propyls. A preferred acyl group is COCH₃, a preferred alkoxy group is CH₃O. The bridge A preferably contains 4 to 6 members. The group is arranged between the two ring systems in formula I and in corresponding formulae so as to correspond to the written form of formulae II to VI, whereas the groups which are valid for both R₁ and R₂ are not listed in the proper orientation. If R₁ and R₂ together denote a double bonded group, R₃ preferably denotes H or C₂₋₅-acyl, e.g. acetyl. The groups R₁, R₂ and R₃ should not all simultaneously denote CF₃, COR₆, SR₆, SOR₆, SO₂R₆,

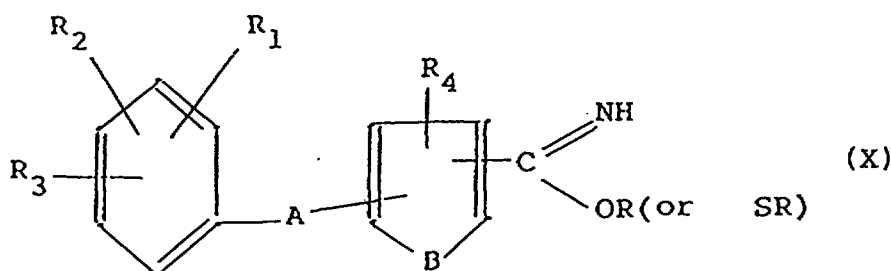
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$\text{SO}_2\text{NR}_5\text{R}_7$ or $\text{C}(\text{OH})\text{R}_5\text{R}_7$, but rather these groups as well as OR_5 , with the definition phenoxy or substituted phenoxy, preferably occur only once or possibly twice, whilst alkyl, acyl and halogen, in particular, may occur as further substituents. The bonds or CH_2 groups in IX/IXa/IXb are generally in the α -position to one another. Typical groups for A are, for example, $\text{O}-(\text{CH}_2)_2-\text{O}$, $\text{O}-(\text{CH}_2)_4-\text{O}$, whilst one of the O-atoms may be replaced by S, NH or CO, as well as groups such as $\text{CH}_2-\text{CH}_2-\text{CONH}$, $\text{CH}_2-\text{CH}_2-\text{NH}-\text{CO}$, $\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2$ or $\text{NH}-\text{CO}-\text{CH}_2-\text{CH}_2$. The amidino group is usually in the para-position relative to the carbon atom to which A is linked.

The new compounds are prepared by conventional methods.

1. Reaction of imidoesters of the formula



wherein R_1 to R_4 , A and B are as hereinbefore defined and R preferably represents a C_{1-6} -alkyl group or benzyl (but if desired the man skilled in the art can also use derivatives of other alcohols), and ammonia. The reaction is preferably 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 the boiling temperature, if this is lower. Suitable solvents are polar solvents such as methanol, ethanol and propanol.

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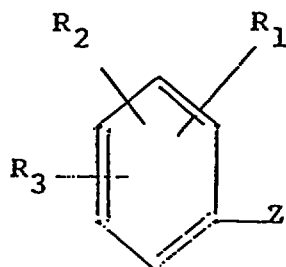
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If the starting materials are sufficiently acid-resistant the reaction may be carried out via the corresponding acid imide chlorides instead of the imidoesters.

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:

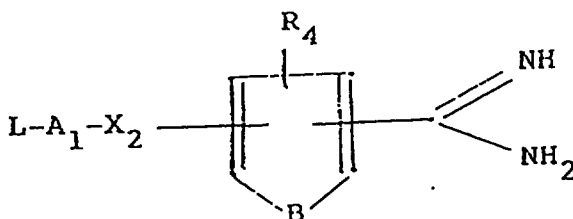
reaction

(a) of a phenol or thiophenol of formula



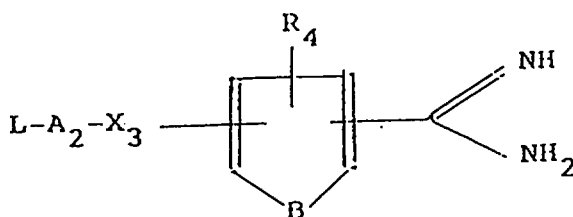
(XI)

wherein Z denotes OH or SH and R₁, R₂ and R₃ are as hereinbefore defined, with a compound of the formula



(XII)

or



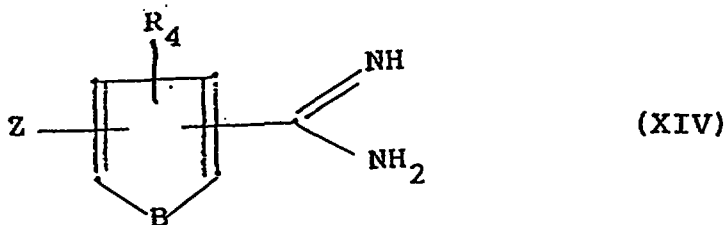
(XIII)

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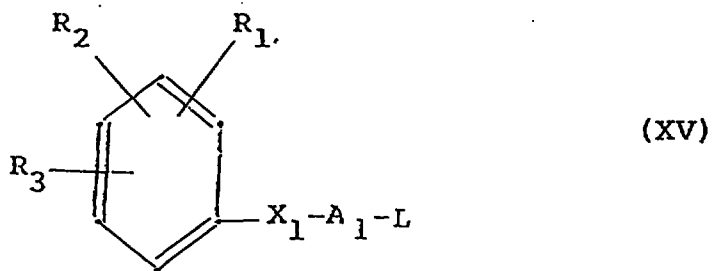
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wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L represents a nucleofugic leaving group, or

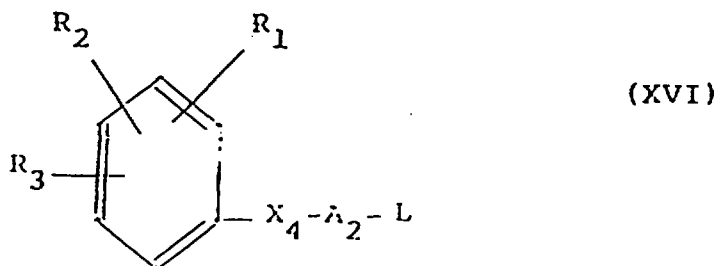
(b) of a phenol or thiophenol of the formula



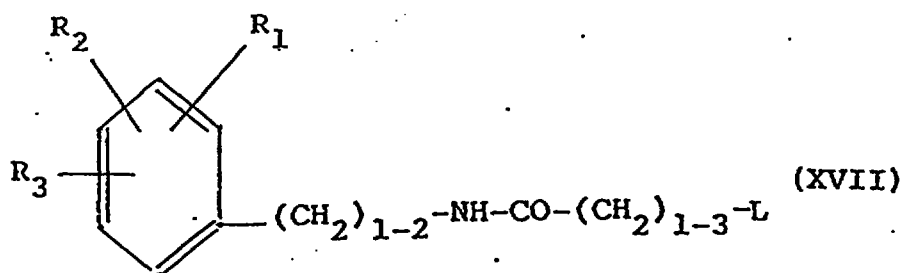
wherein B , R_4 and Z are as hereinbefore defined, with a compound of the formula



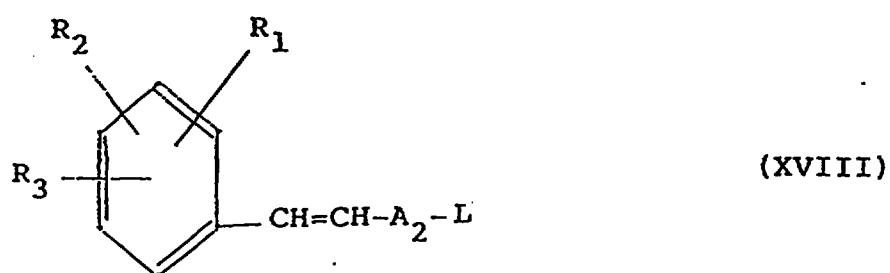
or



or



or

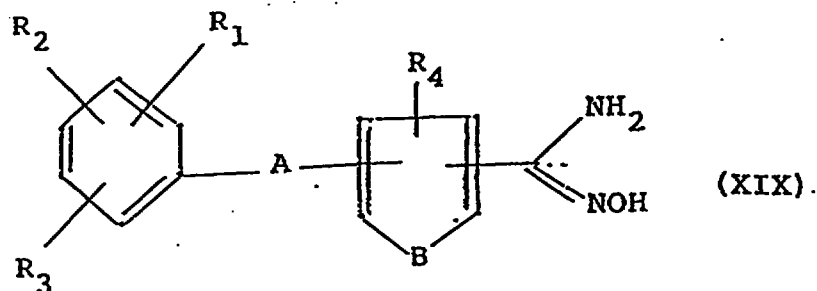


wherein A_1 , A_2 , R_1 , R_2 and R_3 are as hereinbefore defined; and L represents a nucleofugic leaving group.

The reaction is carried out in aprotic solvents such as dimethylsulphoxide, dimethylformamide, acetonitrile or alcohols such as methanol, ethanol or propanol with the addition of a base (metal carbonates, metal hydroxides, metal hydrides) 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. alkali metal salts. Examples of suitable nucleofugic leaving groups include halogens such as Br and Cl.

3. Reduction of an amidoxime of the formula



wherein A, B and R₁ to R₄ are as hereinbefore defined.

For the reduction of XIX it is appropriate to use catalytic hydrogenation, particularly with Raney nickel in a lower alcohol such as methanol. Conveniently, the amidoxime of formula XIX is 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. up to 5 bar, until the uptake of hydrogen has ended.

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 them with HCl via the step of the imide chlorides or directly by reacting them with, for example, C₁₋₆-alcohols or benzyl alcohol in the presence of an acid such as HCl. The reaction of the nitriles with H₂S in solvents such as pyridine or dimethylformamide in the presence of a base such as triethylamine and subsequent alkylation or benzylation result in compounds of formula X. Starting from carboxylic acid amides, which moreover

correspond to the compounds of formula X, compounds of formula X may also be obtained by reaction with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate, in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, preferably at ambient temperature.

The starting materials XIX may also be obtained by reacting corresponding amidoximes instead of amidines analogously to method 1 or 2; by analogous reaction of corresponding nitriles from which the starting materials XIX are finally obtained by the addition of hydroxylamine.

The compounds according to the invention are therapeutically useful, particularly in the light of their LTB₄-antagonistic activity. They are therefore suitable for use, particularly, in those diseases in which inflammatory and/or allergic processes are involved, such as asthma, ulcerative colitis, psoriasis and also for treating gastropathy induced by non-steroidal antiphlogistics. The new compounds may also be used in conjunction with other active substances, e.g. antiallergics, secretolytics, β_2 -adrenergics, steroids for inhalation, antihistamines and/or PAF-antagonists. They may be administered by topical, oral, transdermal, nasal or parenteral route or by inhalation.

The therapeutic or prophylactic dose is dependent on the nature and gravity of the disease, as well as the potency of the individual compounds and the body weight of the patient. For oral administration the dose is between 10 and 250 mg, preferably between 20 and 200 mg. For inhalation, the patient takes between about 2 and 20 mg of active substance. The new compounds may be administered in conventional preparations such as plain or coated tablets, capsules, lozenges, powders,

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granules, solutions, emulsions, syrups, aerosols for inhalation, ointments and suppositories.

The Examples which follow illustrate some possible formulations for the preparations.

Formulation Examples

1. Tablets

Composition:

Active substance according to the invention	20 parts by weight
Stearic acid	6 parts by weight
Dextrose	474 parts by weight

The constituents 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 dextrose reduced or increased accordingly.

2. Suppositories

Composition:

Active substance according to the invention	100 parts by weight
Powdered lactose	45 parts by weight
Cocoa butter	1555 parts by weight

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

3. Powder for inhalation

Micronised powdered active substance (compound of formula I; particle size about 0.5 to 7 μm) is packed into hard gelatine capsules in a quantity of 5 mg,

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optionally with the addition of micronised lactose. The powder is inhaled using conventional inhalation devices, e.g. according to DE-A 3 345 722.

The compounds according to the invention were tested inter alia for their activity in the tests described below.

a) U937 - Receptor binding test/LTB₄

The binding of ³H-LTB₄ (3nM) to vital U937 cells (differentiated human monocytary cell line with naturally expressed LTB₄ receptors) is inhibited, in dosage dependent manner, by an increasing concentration of the test substance (incubation 2 hours at 0°C). After the unbound ³H-LTB₄ has been separated off by membrane filtration, the radioactivity of the bound LTB₄ receptor/³H-LTB₄ complex is quantified by scintillation measurement. The affinity (inhibition constant K_i) was determined by repeated adaptation of a displacement curve to the measurements (program: "coupled mass equilibria" on Wang computer).

b) Aggregation of neutrophilic granulocytes in the guinea-pig

Indicated by LTB₄ in vitro (increase in light transmission in the aggregometer, recorded in mm; each experiment repeated twice): inhibition 2 minutes after incubation with test substance in polydiol/DMSO.

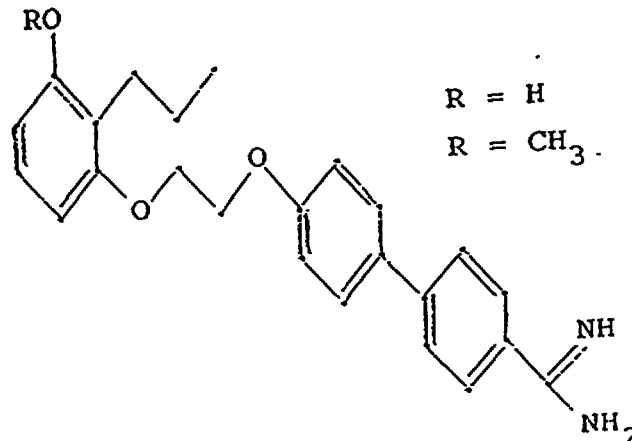
c) Leukotrien-B₄-indicated accumulation of neutrophiles in the mouse ear

Evaluation of the neutrophilic influx by

photometric measurement (mOD/min) of the myeloperoxidase activity (Bradley et al.: J. Invest. Dermatol. 78, 206, 1982) in the skin of the ear. Increase 6 hours after topical treatment of the left ear with LTB₄ (250 ng on each side) compared with the right ear (2 x 5 µl acetone as solvent).

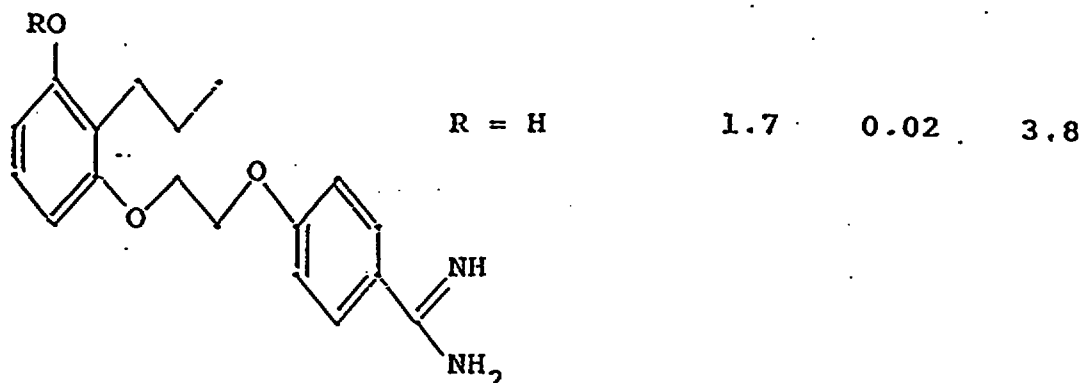
Substance administered by oral route in 1% tylose 300, 30 minutes before the LTB₄ stimulation.

4. Results

	a)*	b)**	c)***
			
R = H	3.8	0.06	1.2
R = CH ₃	6.3	0.31	0.9

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- * Receptor binding U937-8 K_i [nM] (1)
- ** LTB₄-induced neutroph. Aggr. EC₅₀ [μM] (2)
- *** LTB₄-induced neutroph. Accum. p.o. ED₅₀ [mg/kg]

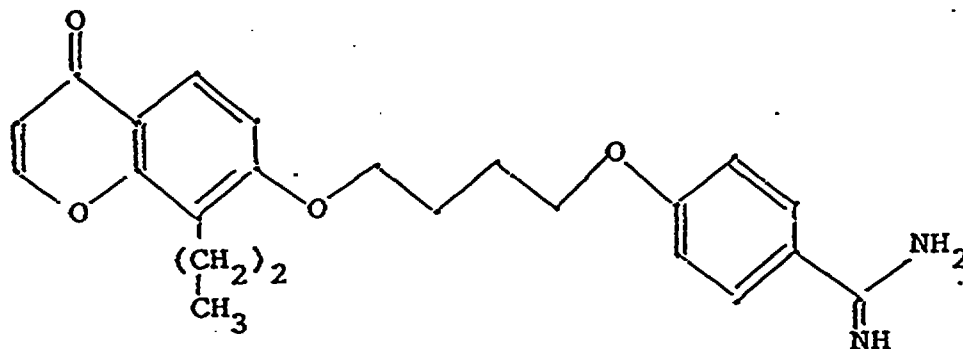
The ³H-LTB₄-receptor binding to guinea-pig spleen cells in the presence of 10% blood plasma yielded K_i -values of, in some cases, far less than 1 μM, more particularly between 0.2 and 0.02. Inhibition of the LTB₄-induced aggregation of neutrophils resulted in EC₅₀-values between about 0.5 and 0.05 μM.

Particular mention should be made of the compounds according to Examples 1 and 4 and Nos. 10, 11, 13, 19, 20, 22 and 23 from Table I, No. 1 from Table II, No. 2 from Table III.

The Examples which follow illustrate the possible methods of preparing the compounds according to the invention.

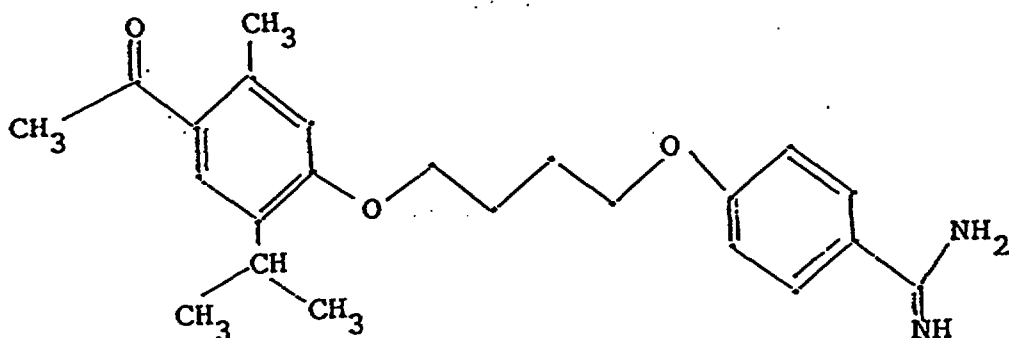
Process 1:

Example 1



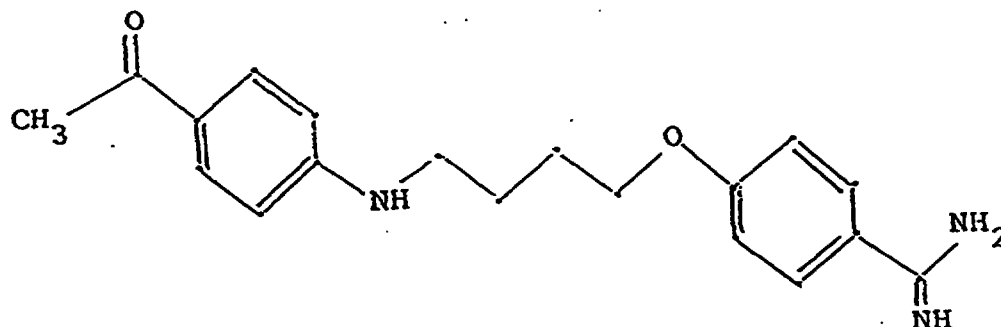
To a solution of 2.0 g of 7-[4-(4-cyano-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one in 50 ml of chloroform and 1.5 ml of ethanol are added 5 ml of a solution of hydrogen chloride in diethylether (17%). The mixture is left to stand for 14 days at ambient temperature and the product is precipitated with diethylether. 1.15 g of 7-[4-(4-imidacaroxyethyl-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained. The imidoester is mixed with 50 ml of ethanolic ammonia solution (5 M) and heated for 3 hours to 70°C. The mixture is evaporated down and the residue is chromatographed (chloroform/methanol 7:3, silica gel). After recrystallisation from dichloromethane/diethylether, 0.6 g of 7-[4-(4-amidino-phenoxy)-E-but(2)-enyloxy]-8-propyl-4H-1-benzopyran-4-one-hydrochloride are obtained (m.p. 144 - 148°C).

Example 2



Hydrogen chloride is introduced at -20°C into a solution of 32.0 g of 4-[(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzonitrile in 350 ml of ethanol and the resulting mixture is stirred for 48 hours. The crystals precipitated are suction filtered and washed with diethylether. 41.0 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzimidooethylester-hydrochloride are obtained (m.p. $100 - 102^{\circ}\text{C}$ decomp.). 15.0 g of the imidoester are added at ambient temperature in several batches to 33 ml of ethanolic ammonia solution (5 M) and 100 ml of ethanol. The mixture is stirred for 36 hours at ambient temperature, evaporated down and the residue is stirred with 50 ml of water. The residue is suction filtered, recrystallised from 30 ml of ethanol and washed with diethylether. 11.5 g of 4-[4-(4-acetyl-2-isopropyl-5-methyl-phenoxy)-butyloxy]-benzamidine-hydrochloride are obtained (m.p. $182 - 183^{\circ}\text{C}$ decomp.).

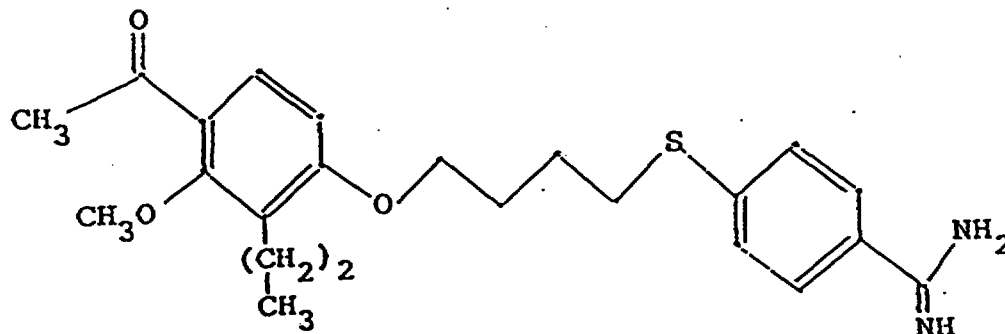
Example 3



Hydrogen chloride is introduced at -20°C into a solution of 3.0 g of 4-[4-(4-cyano-phenoxy)-butylamino]-acetophenone in 40 ml of ethanol, with stirring, for 4 hours and the mixture is left to stand at ambient temperature for 16 hours. The solvent is distilled off in vacuo and the residue is taken up in 50 ml of ethanol. A mixture of 14 ml of ethanolic ammonia solution and 50 ml of ethanol is added dropwise thereto and the mixture is left to stand for 24 hours at ambient temperature. The solvent is evaporated off and the residue is chromatographed (chloroform/methanol 7:3, silica gel 60). 0.3 g of 4-[4-(4-amidino-phenoxy)butylamino]-acetophenone are obtained (m.p. $200 - 202^{\circ}\text{C}$).

Process 2:

Example 4



8.2 g of 4-acetyl-3-methoxy-2-propyl-phenol are dissolved in 80 ml of dimethylformamide and 1.1 g of sodium hydride is added in batches to the solution (as an 80% dispersion in white oil). The mixture is heated to 80°C for 30 minutes and combined with a solution of 5.75 g of 4-(4-bromopropylthio)-benzamidinium (prepared from dibromobutane and 4-cyanobenzothiol by means of 4-(4-bromobutyl-thio)-benzonitrile) in 40 ml of dimethylformamide. After 5 hours at 80°C the mixture is allowed to cool, acidified with ethereal hydrochloric acid and the solvents are distilled off in vacuo. The residue is taken up in ethanol and filtered. The filtrate is concentrated by evaporation. The process is repeated with chloroform and acetonitrile. The residue is stirred with diethylether. After decanting, 5.65 g of a brownish-yellow oil are left. The product is chromatographed (chloroform/methanol 7:3, silica gel). 2.4 g of an oil are obtained which is crystallised from toluene. The product is dissolved in acetonitrile, acidified with ethereal hydrochloric acid. The crystals are suction filtered, washed with cold acetonitrile, dissolved in water and crystallised once more after the addition of 2 N hydrochloric acid. 0.8 g of 4-[4-(4-acetyl-3-methoxy-2-propylphenoxy)-butylthio]-benzamidinium-hydrochloride are obtained (m.p.

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120 - 122°C).

Process 3:

Example 5

a) 4-[4-(4-Acetylphenoxy-butoxy)-benzamido]xime

45.6 g (0.3 mol) of 4-hydroxybenzamido]xime and 81.3 g (0.3 mol) of 4-bromo-butoxy-acetophenone are dissolved in 300 ml of dimethylformamide. After the addition of 55.2 g (0.4 mol) of anhydrous potassium carbonate the mixture is heated to 80°C for 2 hours. The inorganic salts are suction filtered, evaporated down in vacuo and recrystallised from acetonitrile.

Yield: 47.8 g

M.p.: 164.5 - 165.5°C.

b) 4-[4-(4-Acetylphenoxy)butoxy]-benzamidine-methanesulphonate

47.8 g of the compound synthesised according to a) are dissolved in 10 times the quantity of methanol with the addition of the calculated amount of methanesulphonic acid. After the addition of Raney nickel, the mixture is hydrogenated at 5 bar until the uptake of hydrogen has ended. The mixture is suction filtered, the solvent is distilled off in vacuo and the residue is recrystallised from ethanol.

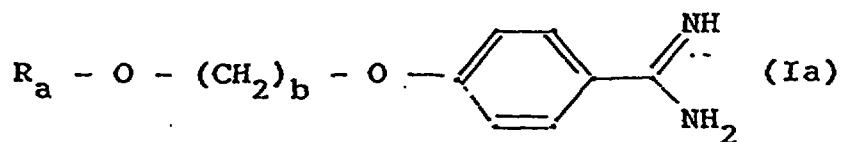
Yield: 45.2 g

M.p.: 204 - 204.5°C.

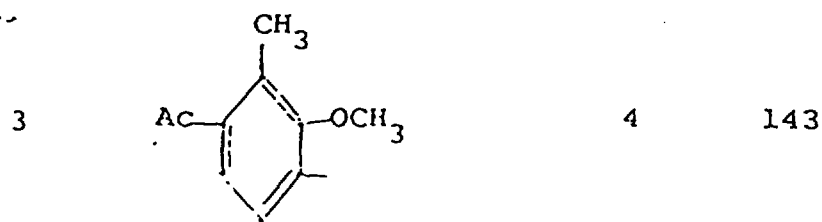
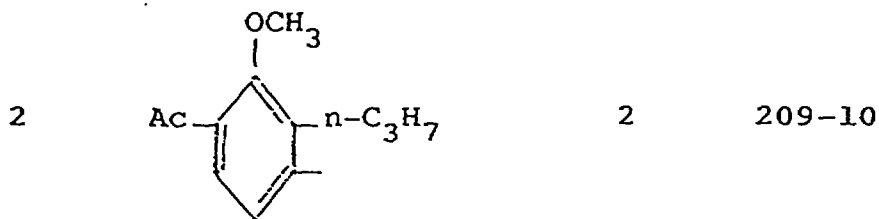
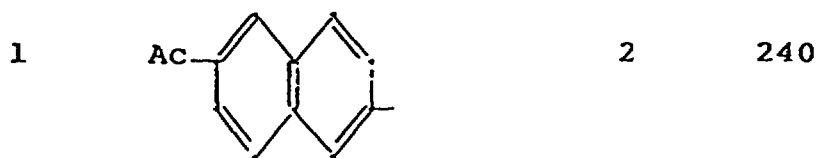
The other compounds of formula I can be obtained according to the processes described above. "Ac" hereinafter denotes CH₃CO-.

TABLE I

Compounds of formula



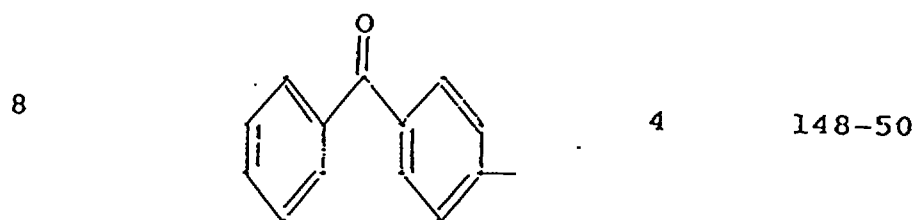
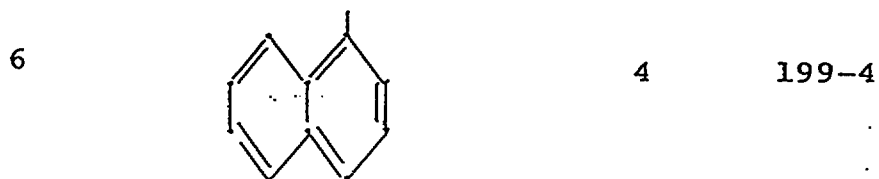
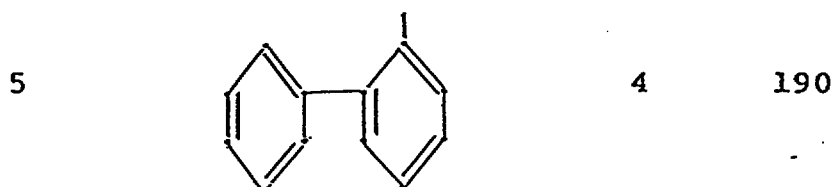
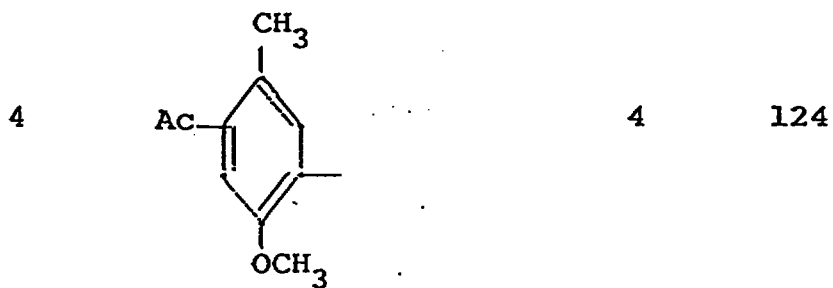
No.	R_a	b	M.p. [°C] (Hydrochloride)
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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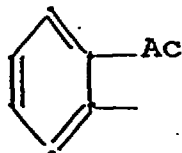


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Date: 01 NOV 1998

No.	R _a	b	M.p. [°C] (Hydrochloride)
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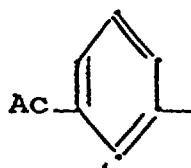
9



4

132-40

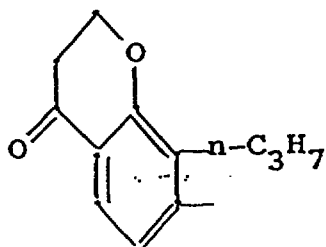
10



4

160-3

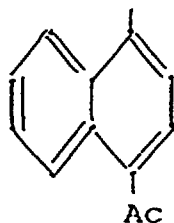
11



4

160-5

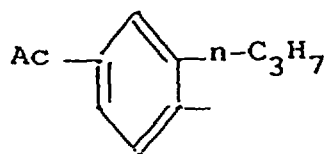
12



4

228-31

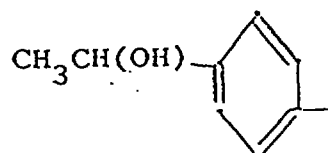
13



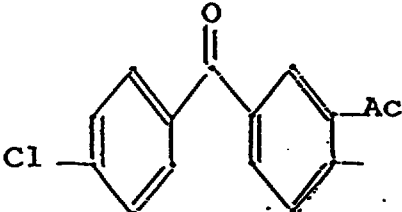
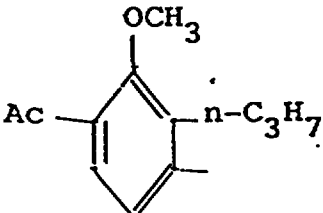
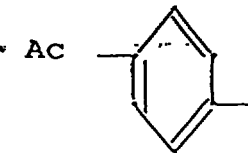
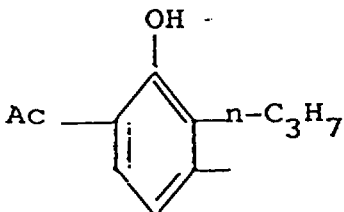
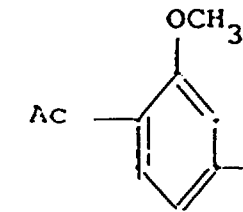
4

140-6

14



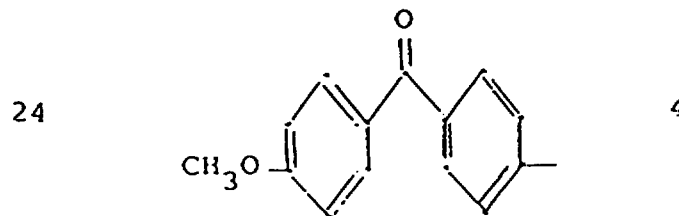
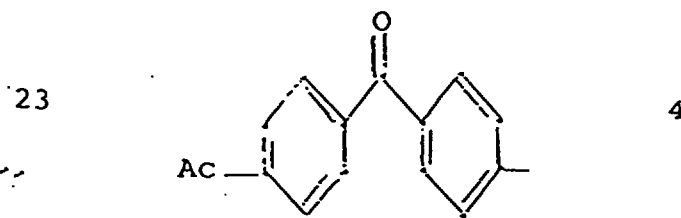
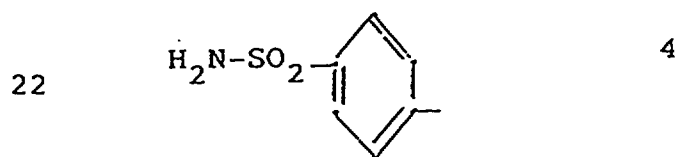
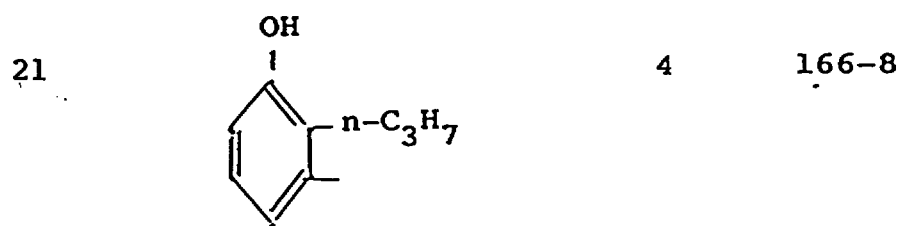
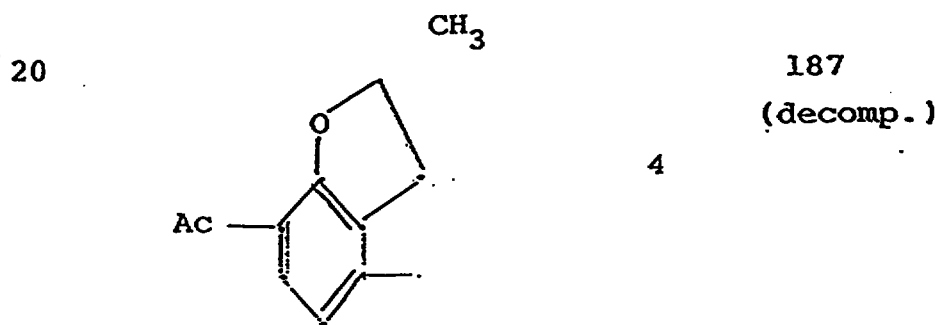
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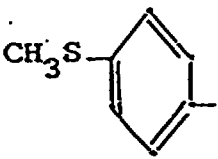
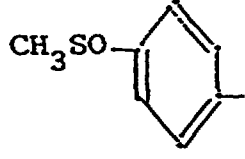
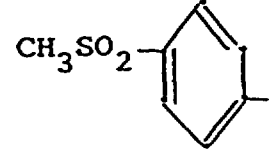
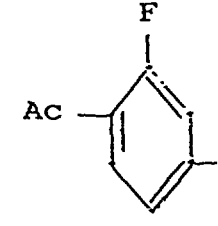
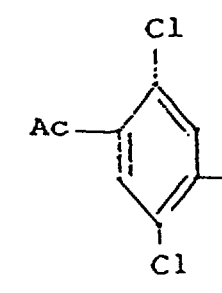
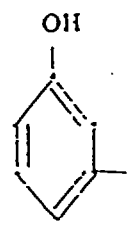
No.	R_a	b	M.p. [°C]
			(Hydrochloride)
15		4	170-2
16		4	149-50
17		4	167 (decomp.)
18		4	179
19		4	168-70 (decomp.)

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No.	R _a	b	M.p. [°C] (Hydrochloride)
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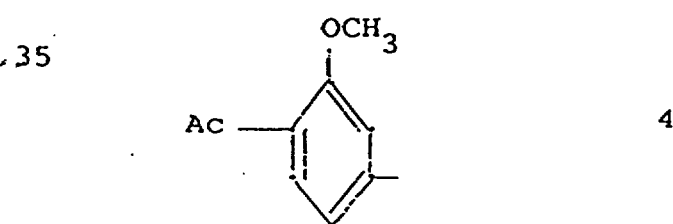
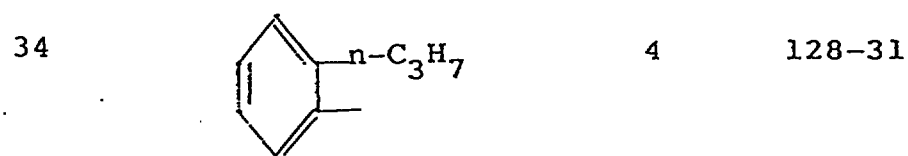
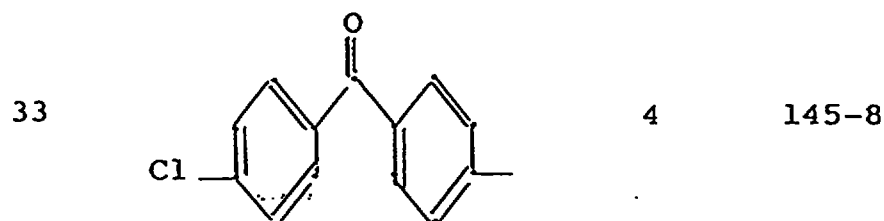
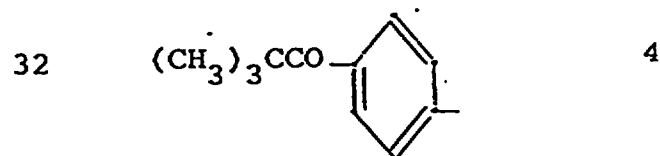


No.	R_a	b	M.p. [°C] (Hydrochloride)
25		4	
26		4	
27		4	174-5
28		4	155-60
29		4	194-60
30		4	214-23

This is the replacement sheet

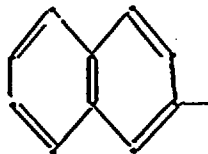
Date: 01 NOV 1998

No.	R _a	b	M.p. [°C] (Hydrochloride)
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No.	R _a	b	M.p. [°C] (Hydrochloride)
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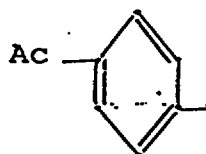
36



4

194

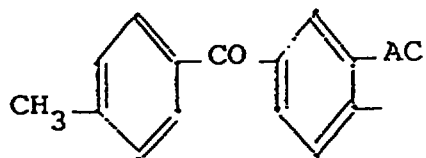
37



6

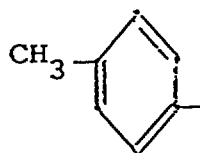
132

38



4

39



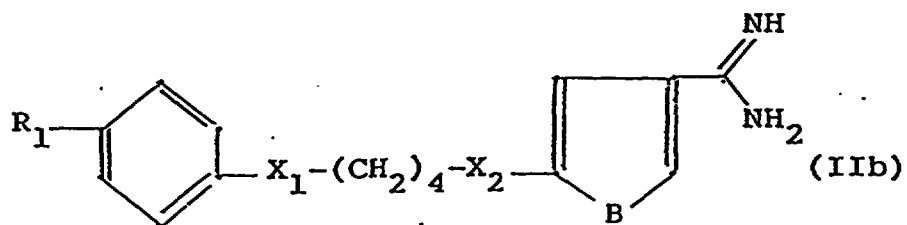
4

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Date: 01 NOV 1998

TABLE II

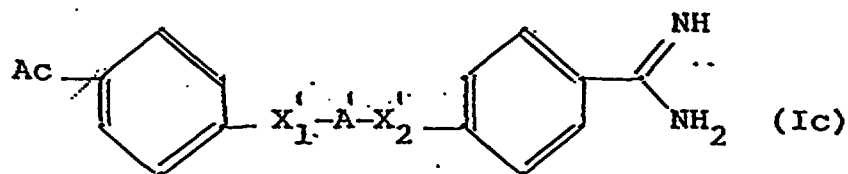
Compounds of formula



No.	B	R ₁	X ₁	X ₂	M.p. [°C] (Hydrochloride)
1	CH=CH	Ac	O	S	
2	CH=CH	Ac	O	SO	
3	CH=CH	Ac	O	SO ₂	160-2 (Base)
4	CH=CH	Ac	S	S	
5	N=CH	Ac	O	S	152-60
6	CH=CH	Ac	O	NH	200-2
7	CH=CH	Ac	S	O	196-7
8	CH=CH	Ac	SO	O	
9	CH=CH	Ac	SO ₂	O	208

TABLE III

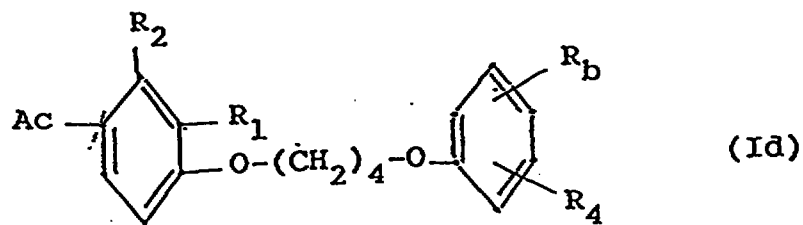
Compounds of formula



No.	A'	X' ₁	X' ₂	M.p. [°C] (Hydrochloride)
1	CH ₂ -CH=CH-CH ₂	O	O	215-8
2		O	O	196-202
3		O	O	205-9
4		O	O	183

TABLE IV

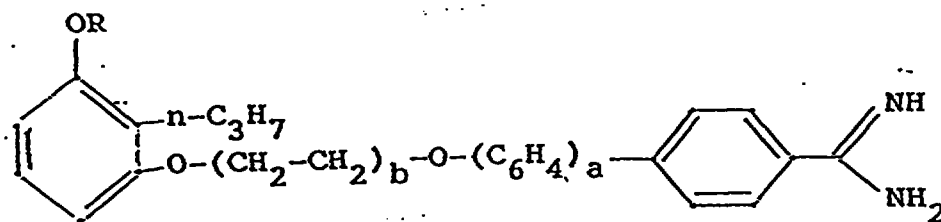
Compounds of formula



No.	R _b	R ₁	R ₂	R ₄	M.p. [°C] (Hydrochloride)
1	$\begin{array}{c} \text{NH} \\ \parallel \\ 2-\text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	H	H	H	
2	$\begin{array}{c} \text{NH} \\ \parallel \\ 3-\text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	H	H	H	174-6
3	$\begin{array}{c} \text{NH} \\ \parallel \\ 4-\text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	n-C ₃ H ₇	OCH ₃	2-OCH ₃	124-7

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Date: 01 NOV 1998

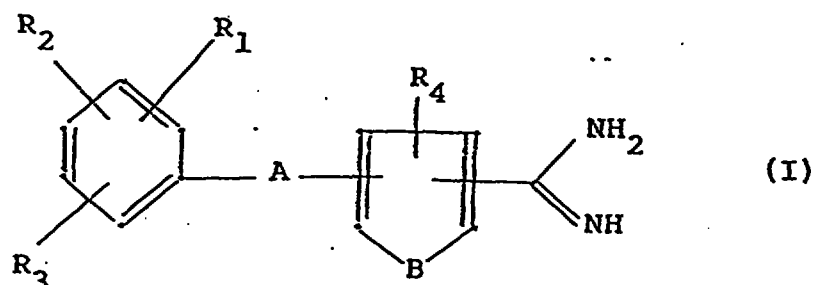


No.	R	a	b	M.p. [°C]
1	H	O	1	178-80 (Hydrochloride)
2	H	1	1	248-51 (Hydrochloride)
3	H	1	2	
4	CH ₃	1	1	236-40 (Methanesulphonate)
5	n-C ₃ H ₇	1	1	
6	i-C ₃ H ₇	1	1	



Claims

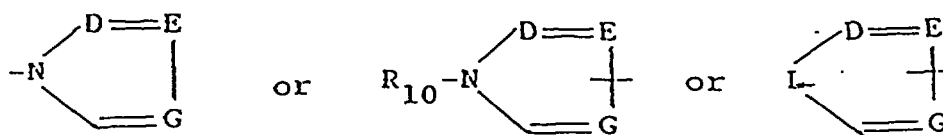
1. Compounds of the formula



wherein

R_1 and R_2 , which may be identical or different, denote CF_3 , halogen, R_5 , OR_5 , COR_6 , SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $C(OH)R_5R_7$ or together may also denote the double-bonded groups $-CR_8=CR_9-CH=CH-$, $-CH=CR_8-CR_9=CH-$, $-CR_8=CH-CR_9=CH-$, $-O-CHR_{10}-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-NH-CO-O-$, $-NH-CO-CH_2-O-$, $-CO-CH_2-O-$ or $-CO-CH_2CH_2-O-$, linked with adjacent carbon atoms of the benzene ring, whilst these groups may in turn be substituted by C_{1-4} -alkyl,

R_3 denotes halogen, OH, CF_3 , R_5 , OR_6 , COR_6 , $CONH_5R_7$, CH_2OH , $CH_2-O-(C_{1-4}-alkyl)$, SR_6 , SOR_6 , SO_2R_6 , $SO_2NR_5R_7$, $NH-CO-(C_{1-4}-alkyl)$, $NH-SO_2-(C_{1-4}-alkyl)$, NR_5R_7 or $C(OH)R_5R_7$ (whilst if R_3 is the same as R_5 , R_5 can only denote H if at least one of the substituents R_1 and R_2 does not denote H), a heterocyclic 5-membered ring having 1 to 3 heteroatoms and of the formula





(wherein D, E and G, which may be identical or different, denote CH, N, C-(C₁₋₄-alkyl) or C-phenyl and L denotes O or S),

R₄ denotes hydrogen, halogen, NH₂, NH-(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, OH, C₁₋₄-alkoxy,

R₅ denotes H, C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl, or phenyl-(C₁₋₄-alkyl),

R₆ denotes C₁₋₁₂-alkyl, phenyl, or phenyl optionally substituted by halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₇ denotes H or C₁₋₁₂-alkyl,

R₈, R₉ (which may be identical or different) denote H, OH, C₁₋₄-alkyl, C₁₋₄-alkoxy or C₂₋₅-acyl,

R₁₀ denotes H or C₁₋₄-alkyl,

R₁₁, R₁₂, which may be identical or different, denote H, OH, halogen, CF₃, C₁₋₄-alkyl or C₁₋₄-alkoxy,

A denotes one of the groups

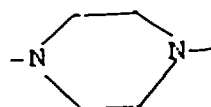
X₁-A₁-X₂ (II)

X₂-A₂-X₃ (III)

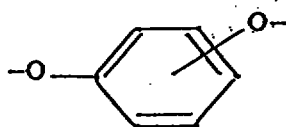
X₄-A₂-X₂ (IV)

(CH₂)₁₋₂-NH-CO-(CH₂)₁₋₃-X₂ (V)

-CH=CH-A₂-X₂ (VI)

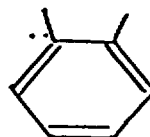


(VII)

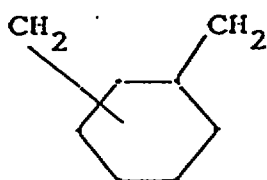


(VIII)

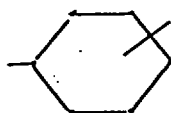
B denotes CH=CH, CH=N, S or



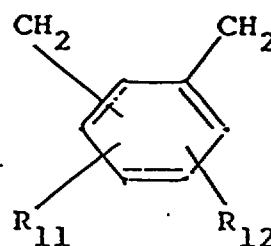
A₁ denotes C₂₋₄-alkylene, cis- or trans-CH₂-CH=CH-CH₂, CH₂-C=C-CH₂ or



(IX)



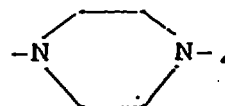
(IXa)



(IXb)

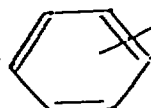
A₂ denotes C₁₋₅-alkylene,

X₁ denotes O, NH, S, SO, SO₂, CO, CH₂ or

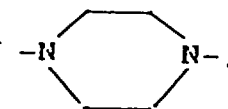


X₂,

denotes O, NH, S or



X₃ denotes NH-CO, CO-NH, SO₂-NH or



X₄ denotes NH-CO, CO-NH, NH-SO₂, SO₂-NH or NH-CO-NH,

as racemates, in enantiomerically pure or concentrated form, possibly as pairs of diastereomers and in cis- or trans-form and as free bases or as salts, preferably with physiologically acceptable acids,

This is the replacement sheet

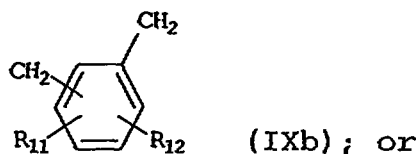
Date: 01 NOV 1998



With the proviso that when

B denotes $-\text{CH}=\text{CH}-$ and A denotes the group $\text{X}_1-\text{A}_1-\text{X}_2$, wherein X_1 denotes O or S, X_2 denotes O or S and A_1 is as defined above,

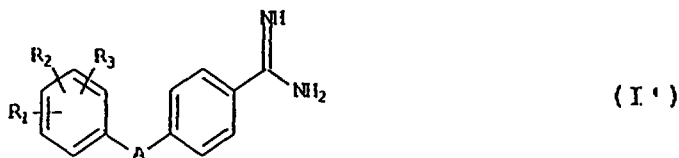
- then if any one of R_1 , R_2 or R_3 denotes $\text{O}-\text{C}_{1-12}$ -alkyl or $\text{O}-(\text{C}_{1-4}$ -alkyl)-phenyl then at least one of the remaining substituents R_1 , R_2 and R_3 is not H, halogen, OH, CF_3 , C_{1-12} -alkyl, phenyl- C_{1-4} -alkyl, $\text{O}-\text{C}_{1-12}$ -alkyl or $\text{O}-(\text{C}_{1-4}$ -alkyl)-phenyl;
- and if R_3 denotes CONR_5R_7 , wherein R_5 denotes C_{1-12} -alkyl, phenyl, phenyl optionally substituted by halogen, C_{1-4} -alkyl or C_{1-4} -alkoxy, or phenyl- $(\text{C}_{1-4}$ -alkyl), and R_7 is as defined above, then A_1 does not denote C_{2-4} alkylene or



B denotes $-\text{CH}=\text{CH}-$, R_4 denotes hydrogen, X_1 and X_2 denote oxygen, A_1 denotes a C_3 or C_4 -alkylene and the amidino group is in the meta position to the group A,

- then R_1 , R_2 or R_3 do not denote NH_2 , chlorine, methoxy or CF_3 .

2. Compounds of the formula



wherein

R_1 , R_2 , which may be identical or different, denote R_7 , OR_7 , COR_6 , halogen or together denote the double bonded groups $-\text{CR}_8=\text{R}_9-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CR}_8-\text{CR}_9=\text{CH}-$,

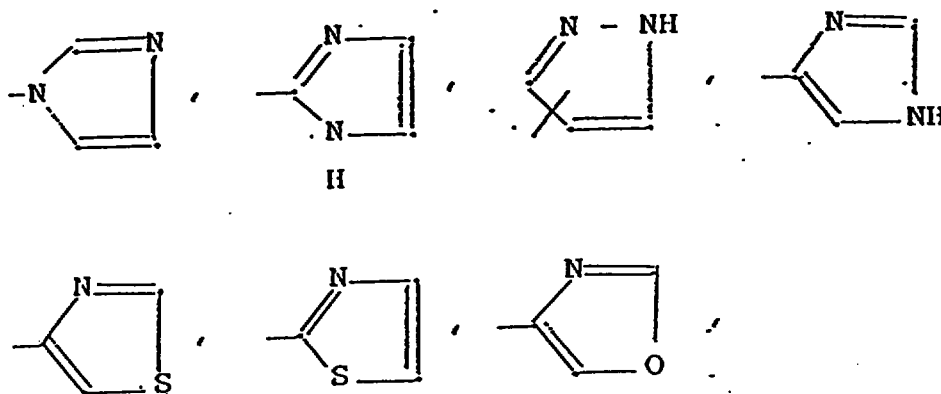
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-O-CHR₁₀-CH₂- or -CO-CH₂-CH₂-O-, linked with adjacent carbon atoms of the benzene ring,

R₃ denotes halogen, CF₃, R₇, OR₇, CO-(C₁₋₄-alkyl), NH-CO-(C₁₋₄-alkyl), NHSO₂-(C₁₋₄-alkyl) or N(R₁₀)₂ (whilst R₇ can only denote H if at least one of the substituents R₁ and R₂ does not denote H) or a heterocyclic five-membered ring such as



R₆ and R₇ are as defined in claim 1,

and

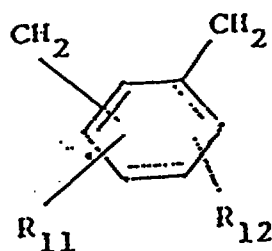
A denotes the group II, wherein the group II is as defined in claim 1;

with the proviso that when B denotes -CH=CH- and A denotes the group X₁-A₁-X₂, wherein X₁ denotes O or S, X₂ denotes O or S and A₁ is as defined above,

- then if any one of R₁, R₂ or R₃ denotes O-C₁₋₁₂-alkyl or O-(C₁₋₄-alkyl)-phenyl then at least one of the remaining substituents R₁, R₂ and R₃ is not H, halogen, OH, CF₃, C₁₋₁₂-alkyl, phenyl-C₁₋₄-alkyl, O-C₁₋₁₂-alkyl or O-(C₁₋₄-alkyl)-phenyl;
- and if R₃ denotes CONR₅R₇, wherein R₅ denotes C₁₋₁₂-alkyl, phenyl, phenyl optionally substituted by



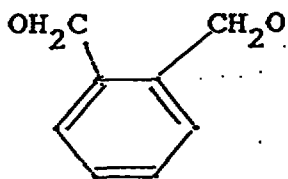
halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy, or phenyl-(C₁₋₄-alkyl), and R₇ is as defined above, then A₁ does not denote C₂₋₄ alkylene, CH₂-CH=CH-CH₂, CH₂-C= or



(IXb)

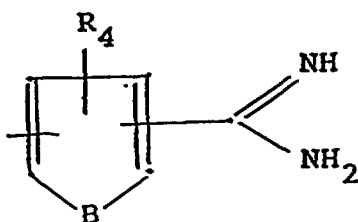
3. Compounds according to claim 1 or 2, wherein
R₁/R₂/R₃ have the meanings C₂₋₅-acyl/H/H;
C₆H₅CO/H/H; C₁₋₄-alkyl/OH/H;
C₂₋₅-acyl/C₁₋₄-alkyl/H;
C₂₋₅-acyl/OH/C₁₋₄-alkyl;
OH/C₂₋₅-acyl/C₁₋₄-alkyl.
4. Compounds according to claim 1, 2 and 3,
characterised in that A denotes

O-(CH₂)₂-O, O-(CH₂)₄-O or

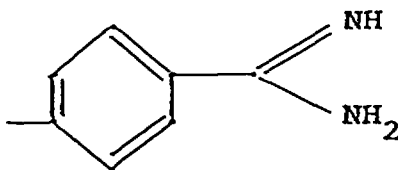


5. Compounds according to claim 1, 2, 3 or 4, wherein at least one of the groups R_1 , R_2 and R_3 is acyl.

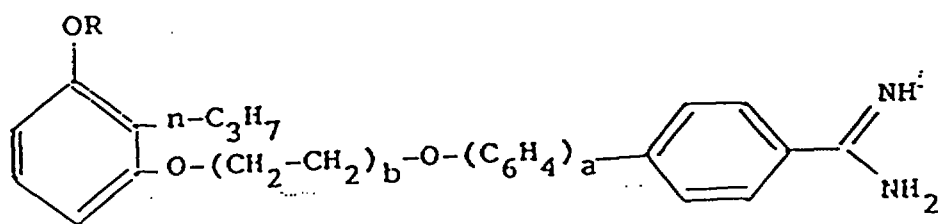
6. Compounds according to claim 1, 2, 3, 4 or 5, characterised in that the group



represents



7. Compounds of the formula



wherein

a denotes 0, b denotes 1 and R denotes H,
or a denotes 1, b denotes 1 or 2, and
R denotes C_{1-4} -alkyl, and if $b = 2$ it may also denote hydrogen,
in the form of free bases or acid addition salts.

8. Compounds according to claim 7, wherein $a = 0$ or 1 and $b = 1$ or $a = 0$ and $b = 2$ as free bases or as acid addition salts.

9. Compounds according to claim 8, wherein R denotes H, CH_3 or C_2H_5 , a denotes 0 or 1 and b denotes 1, as free bases or as acid addition salts.

10. Compounds as claimed in any one of the preceding claims as herein specifically disclosed in any one of Examples 1 to 5 or the Tables.

11. Pharmaceutical compositions, characterised in that they contain a compound according to claims 1 to 10.

12. A pharmaceutical preparation as claimed in claim 11 substantially as hereinbefore described and with reference to the Pharmaceutical Preparations.

13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 or claim 13 which comprises mixing a compound as claimed in any one of claims 1 to 10 with conventional excipients, diluents and/or carriers.

14. A method of treatment of diseases which are susceptible to LTB_4 - antagonistic therapy which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1-10 or an effective amount of a composition as claimed in claim 11 or claim 12.

15. A method of treatment of diseases in which inflammatory and/or allergic processes are involved, including asthma, ulcerative colitis, psoriasis or of treating gastropathy induced by non-steroidal antiphlogistics, which comprises administering to said

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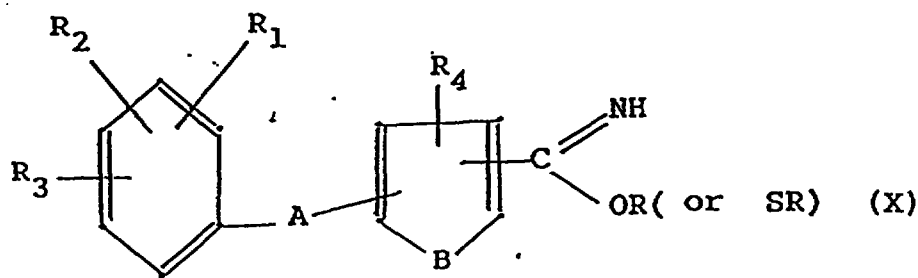
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subject an effective amount of a compound as claimed in any one of claims 1-10 or an effective amount of a composition as claimed in claim 11 or claim 12.

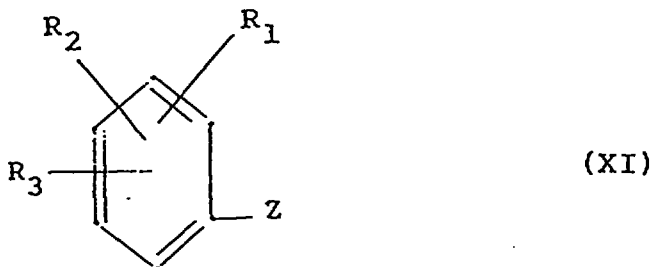
16. Process for preparing compounds according to claims 1 to 10, characterised in that

a) an imidoester of the formula

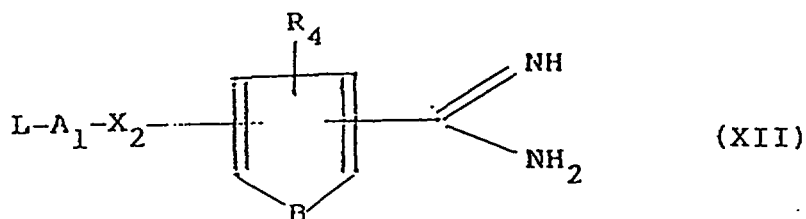


wherein R_1 to R_4 , A and B are as hereinbefore defined and R preferably represents a C_{1-6} -alkyl group or benzyl, is reacted with ammonia, or

b1) a phenol or thiophenol of the formula

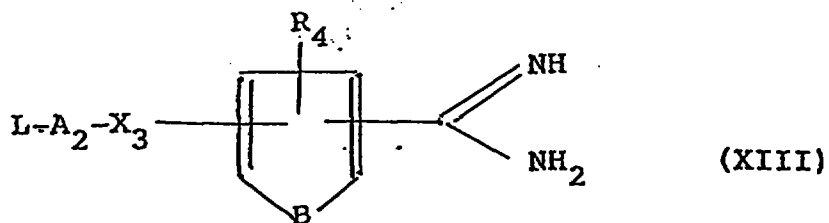


wherein Z denotes OH or SH and R_1 , R_2 and R_3 are as hereinbefore defined, is reacted with a compound of formula



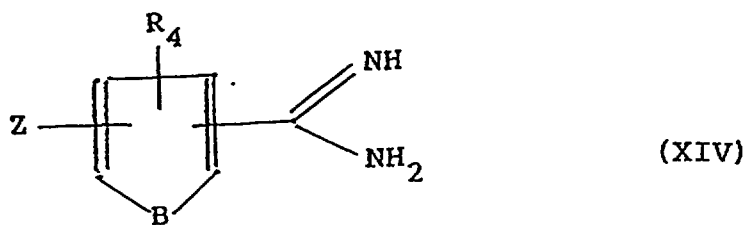


or

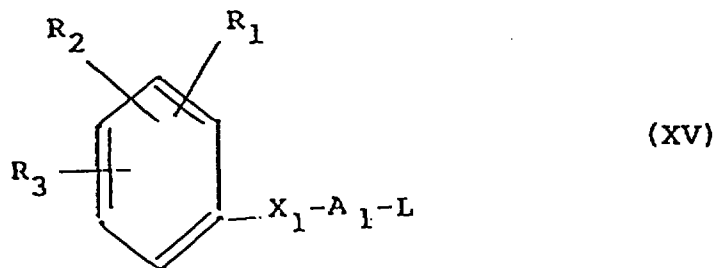


wherein A_1 , A_2 , B , R_4 , X_2 and X_3 are as hereinbefore defined and L denotes a nucleofugic leaving group,
or

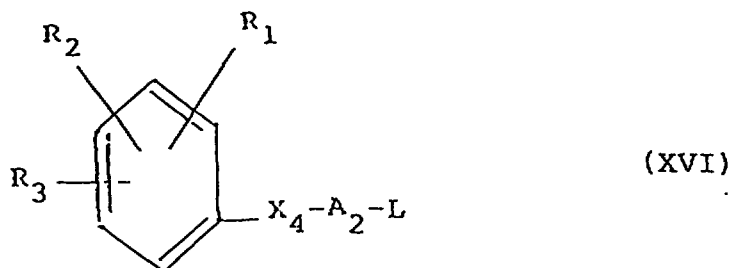
b2) a phenol or thiophenol of formula



wherein B , R_4 and Z are as hereinbefore defined, is reacted with a compound of formula



or

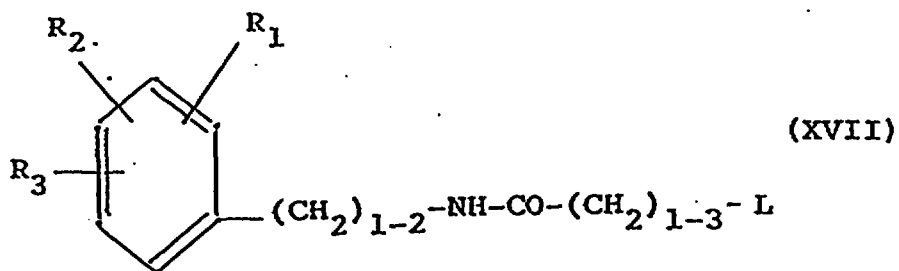


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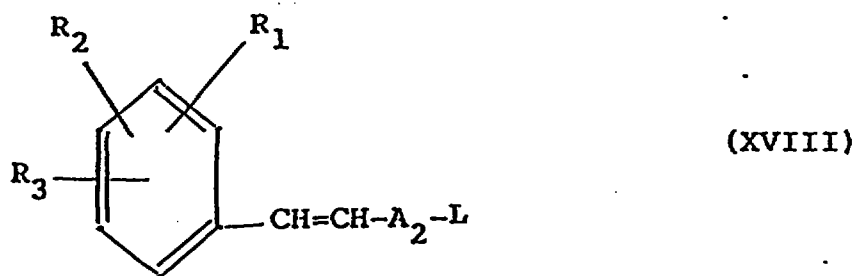
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or

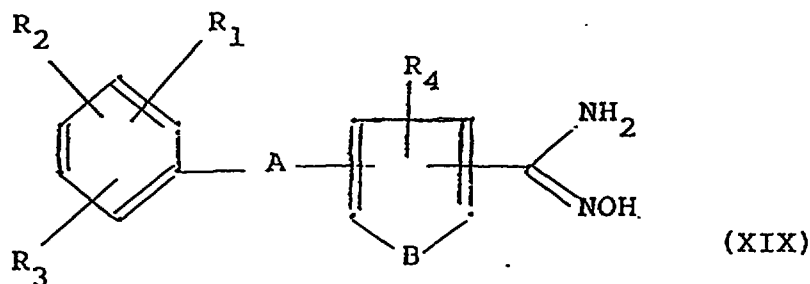


or



wherein A_1 , A_2 , R_1 , R_2 and R_3 are as hereinbefore defined; and L denotes a nucleofugic leaving group; or

c) an amidoxime of the formula



wherein A , B and R_1 to R_4 are as hereinbefore defined, is reduced to form the corresponding amidine.

17. A process as claimed in claim 18 substantially as hereinbefore described.

18. A process as claimed in claim 18 substantially as hereinbefore described and with reference to Examples 1 to 5 and the Tables.

21. Each and every novel compound, composition, method process or use hereinbefore described.

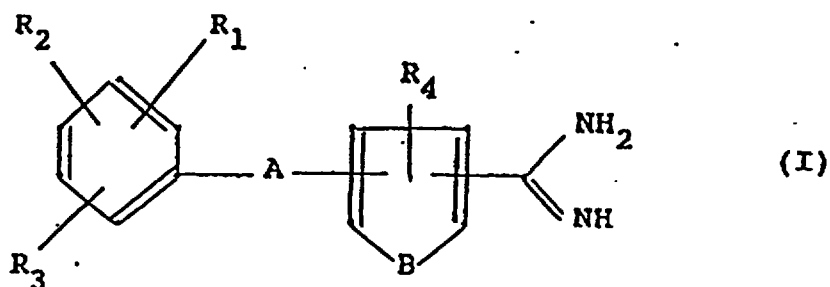
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New amidine derivatives, the preparation and use thereof as pharmaceutical compositions with LTB₄-antagonistic activity

Abstract

Compounds of the formula



which is explained more fully in the specification, may be prepared by conventional methods and used therapeutically in conventional galenic preparations.