The present invention relates to new substituted 1-(1H-imidazol-4-yl)alkyl-benzamides, and their non-toxic pharmaceutically acceptable acid addition salts, as well as to processes for their preparation and to their therapeutic use.

It also relates to pharmaceutical compositions containing these new compounds.

European Patent No. 24,829 describes 4-benzyl-1H-imidazoles, the benzyl group of which contains in the phenyl ring various substituents selected from hydrogen atoms and chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxy and nitro groups. These compounds have antihypertensive, antiulcer, diuretic, sedative, analgesic, anti-inflammatory and tranquillizing properties. European Patent No. 58,047 describes similar 4-(phenylalkyl)-1H-imidazoles but in which the alkyl radical of the phenylalkyl group contains 1-6 carbon atoms; in most of the compounds, the imidazole ring is additionally substituted by an alkyl radical having 1 to 7 carbon atoms, a phenyl group or a substituted or unsubstituted benzyl radical. These compounds possess antithrombotic, antihypertensive, antimicrobial and antifungal properties. European Patent No. 72,615 also describes similar 4-benzyl-1H-imidazoles but in which the benzyl group is substituted in the alpha position by an alkyl radical. The benzyl group contains in the phenyl ring various substituents selected from hydrogen and halogen atoms, methyl, ethyl, hydroxy and methoxy radicals and the methylenedioxy bridge between two adjacent carbon atoms. The pharmacological experiments described in this latter patent demonstrate that the compounds have antihypertensive, antithrombotic and diuretic properties.

European Patent application No.269.599, in the name of the applicant, describes substituted 1H-imidazoles, the most representative of which are 2-hydroxy-3-[1-(1H-imidazol-4-yl)-alkyl]-benzenemethanols.

These 1H-imidazoles have cardiac, cerebral and tissular anti-ischaemic properties.

Continuing research work in this field, the applicant has now synthesized new substituted 1H-imidazoles which not only have excellent cardiac, cerebral and tissular anti-ischaemic properties, but also α_2-adrenergic receptor agonist properties.

These new compounds can therefore be used, inter alia, for the prevention and treatment of disorders induced by ischaemias in general. Among these disorders, angina pectoris is the clinical expression of an acute myocardial ischaemia which is the result of a momentary imbalance between the myocardial oxygen demand and the oxygen supply by the coronary circulation, which imbalance can lead, in very severe cases, to myocardial infarction. For this reason, these compounds are especially useful for the treatment of angina pectoris and of myocardial infarction. The anti-ischaemic properties of these compounds at the cerebral level allow them to be used in the prevention and treatment of functional and neurological disorders arising from cerebrovascular accidents of any origin (thrombosis and infarction), without however exhibiting sedative properties.

In addition, various experimental observations such as measurements of the displacement of tritium-labelled clonidine ([^{3}H]clonidine), carried out with preparations of α-adrenergic receptors, and pharmacological experiments on isolated organs, lead to the conclusion that the new compounds possess a strong α_2-adrenergic receptor agonist activity. This activity is inhibited by α-yohimbine which allows the compounds of the invention to be classified among the α_2-adrenergic receptor agonists. These properties are also demonstrated by the correction of the plasmatic or urinary catecholamine level increase which is due to certain pathological situations reproduced in the pharmacological models.

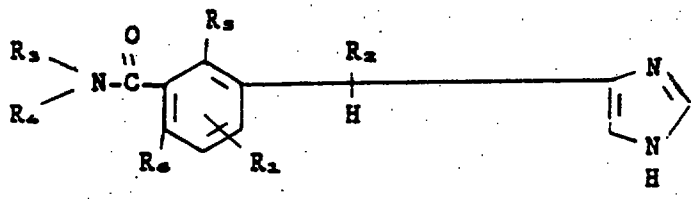
Consequently, the new compounds have beneficial therapeutic effects in the treatment of pathological disorders giving rise to, or resulting from, an abnormal increase in the catecholamine levels, such as pheochromocytoma, cardiac congestion, impaired regulation of the vascular reactivity (Raynaud's disease, migraine or spasm of the coronary

arteries), asthma and other atopic disorders, glaucoma, nasal congestion, headache, tension, stress, anxiety and other psychiatric disorders such as manias, depressions and memory impairments (H.J. MOTULSKY and P.A. INSEL, N.Eng.J.Med.307, (1982), 18-29; A.DENARO et al., Acta Psychiatr.Scand.320, (1985, Suppl.72), 20-25). These same α_2-adrenergic receptor agonist properties enable these compounds to be used in the treatment of disorders associated with gastric and intestinal hypersecretions (J.D. DIJOSEPH et al., Life Sci.35, (1984), 1031-1024), as well as in the treatment of the withdrawal syndromes associated with toxicomanias, whether the latter are of alcoholic origin or whether they result from abuse of tobacco or of opiate substances (G.LAGRUE, Rev. Prat. Médecine générale, 1987, No.9 of 23rd November, 15-17).

Some beneficial effects of the compounds of the invention, linked with these α_2-adrenoceptor agonist properties, may also be expected in the treatment of disorders in the metabolism of lipids and glucosides (M.C.HOUSTON et al., Clin.Res.35, (1987, No.1), 17A).

In addition, it has been found that these compounds possess a not insignificant diuretic, anti-inflammatory and hypotensive activity.

The new compounds according to the present invention are substituted 1-(1H-imidazol-4-yl)alkyl-benzamides having the general formula



(I)

in which

R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkyl radical,

R_3 represents a hydrogen atom, an alkyl or a hydroxyalkyl radical, an amino or hydroxyl group,

R_4 represents a hydrogen atom or an alkyl radical, or

R_3 and R_4 taken together with the nitrogen atom to which they are attached, represent a heterocyclic radical selected from the group consisting of the pyrrolidino, piperidino and morpholino radicals, and

R_5 and R_6 which may be the same or different, each represents a hydrogen atom, a hydroxyl group, an alkyl or alkoxy radical,

at least one of the symbols R_5 and R_6 being other than a hydrogen atom,

all the alkyl and alkoxy radicals having 1 - 4 carbon atoms,

as well as their non-toxic pharmaceutically acceptable acid addition salts.

When the molecule contains an asymmetric carbon atom, the compounds of formula I may be either in the form of a racemic mixture or in the form of one or other enantiomer. These various forms also fall within the scope of the present invention.

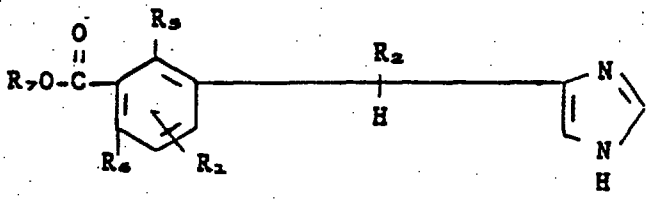
Preferred compounds according to the present invention are :

- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide and its hydrochloride;
- 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide and its hydrochloride;
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide and its hydrochloride;
- 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide and its hydrochloride;
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzamide and its hydrochloride;
- 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzamide;
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzohydrazide;
- (+)-2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide and its hydrochloride;

The present invention also includes the non-toxic pharmaceutically acceptable acid addition salts of the 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I. Examples of pharmaceutically acceptable acids that may be mentioned include inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid etc, and

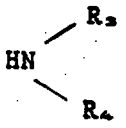
organic acids, such as acetic acid, citric acid, tartaric acid, benzoic acid, salicylic acid and maleic acid etc.

The substituted 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I can be prepared by a general process which consists of reacting an alkyl 1-(1H-imidazol-4-yl)alkyl-benzoate of the formula



(II)

in which R_1, R_2, R_5 and R_6 have the meanings given above and R_7 represents an alkyl radical having 1 to 4 carbon atoms, with a nitrogen compound of the formula

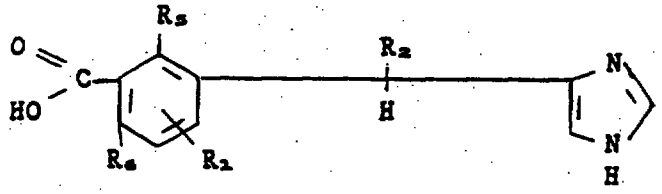


(III)

in which R_3 and R_4 have the meanings given above.

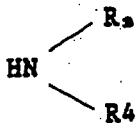
This reaction is generally carried out under normal pressure or under a higher pressure in an autoclave, either in an alcoholic solvent such as, for example, methanol or ethanol, or in a large excess of the nitrogen compound used as starting reagent, at a temperature between ambient temperature and reflux temperature, and if necessary in the presence of sodium methoxide as a catalyst.

According to a particular embodiment, directed to the preparation of the substituted 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I, in which R_5 and R_6 each represents a hydrogen atom, an alkyl or an alkoxy radical having 1 to 4 carbon atoms, at least one of the symbols R_5 and R_6 being other than a hydrogen atom, a 1-(1H-imidazol-4-yl)alkyl-benzoic acid of the formula



(IV)

in which R_1 and R_2 each represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms and R_5 and R_6 have the meanings given above, is reacted with a nitrogen compound of the formula

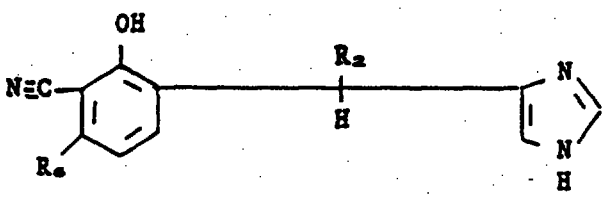


(III)

in which R_3 and R_4 have the meanings given above.

In order to carry out this reaction, the starting acid of formula IV is previously activated, in a known manner, by means of a conventional reagent such as, for example, an alkyl haloformate, preferably ethyl chloroformate. This reaction is generally carried out at a temperature of about 0°C, in an inert solvent such as, for example, dichloromethane or acetonitrile, and in the presence of an auxiliary base such as, for example, triethylamine.

According to yet another embodiment, the substituted 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I in which R_1, R_3 and R_4 are hydrogen atoms, R_5 represents a hydroxyl group and R_6 represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, can also be prepared by hydrolysis in an acid medium of a 2-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitrile of formula



(V)

in which R_2 and R_6 each represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms.

This hydrolysis is generally carried out with an about 80% by volume aqueous sulphuric acid solution, at a temperature of from 60°C to 75°C, for several hours.

As an alternative, this hydrolysis can be carried out in anhydrous methyl alcohol containing a trace of water, through which a stream of hydrogen chloride is passed. The intermediate imidate which is formed in situ is not isolated and is immediately converted to the amide by heating.

The non-toxic, pharmaceutically acceptable acid addition salts can be prepared from the 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I by known methods.

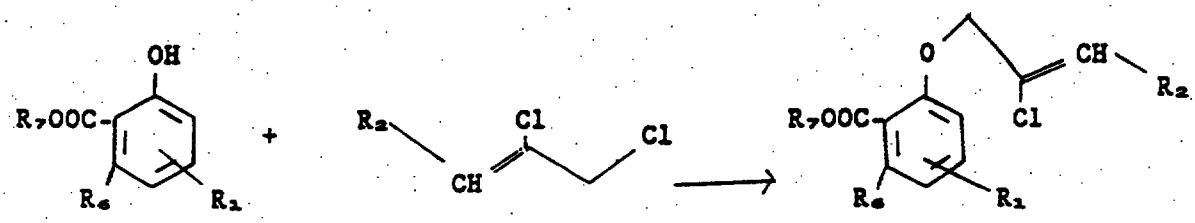
The compounds of formula I in which R_2 is an alkyl radical and which as a result are in the form of a racemic mixture, can be separated into their optical enantiomers by conventional methods, either by fractional crystallization of the diastereoisomeric salts obtained by addition of an optically active acid to the racemic mixture, or by chromatography of the racemic mixture on a chiral support such as, for example, a silica on which a bovine serum albumin (BSA) is covalently grafted or an α-glycoprotein or ß-cyclodextrin containing phase. Several successive passages through the chiral chromatography column may sometimes be necessary to improve the separation of the enantiomers.

The starting alkyl 1-(1H-imidazol-4-yl)alkyl-benzoates of formula II may be prepared by one or other of the following methods :

(a) using conventional methods, a 1-(1H-imidazol-4-yl)alkyl-benzoic acid of formula IV, in which R_1, R_2, R_5 and R_6 have the meanings given above, is esterified with an alcohol of formula R_7OH, in which R_7 represents an alkyl radical having 1 to 4 carbon atoms;

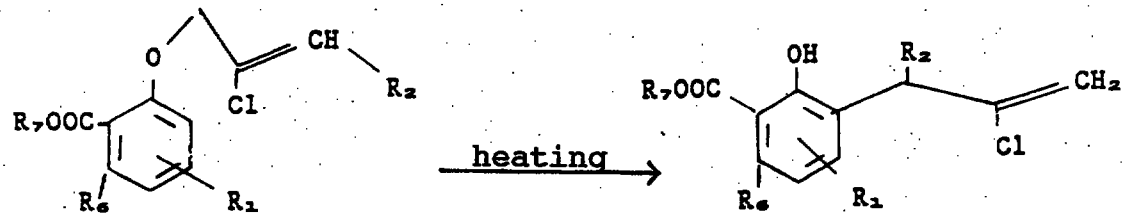
(b) when R_5 represents a C_1-C_4-alkoxy radical, and R_6 a hydrogen atom, a C_1-C_4-alkyl radical or a C_1-C_4-alkoxy radical, a multi-step process can also be used which comprises

(1) reacting in the presence of a base, in acetone under reflux, a suitably substituted alkyl 2-hydroxybenzoate of formula VI, with a 2,3-dichloropropene of formula VII, to give an alkyl 2-(2-chloro-2-propenyloxy)-benzoate of formula VIII, according to the equation



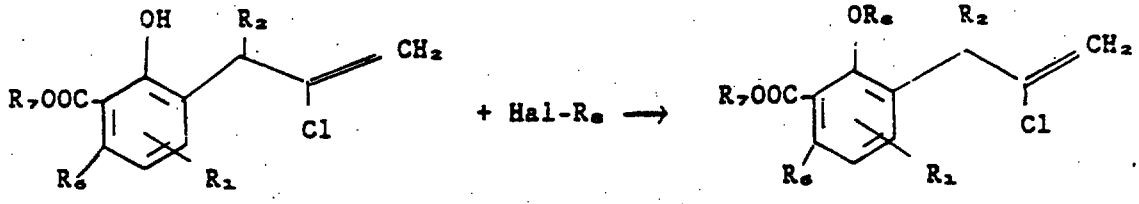
(VI) (VII) (VIII)

(2) heating the alkyl 2-(2-chloro-2-propenyloxy)-benzoate of formula VIII at a temperature of about 260°C, which leads via a Claisen transformation to the alkyl 3-(2-chloro-2-propenyl)-2-hydroxy-benzoate of formula IX, according to the equation



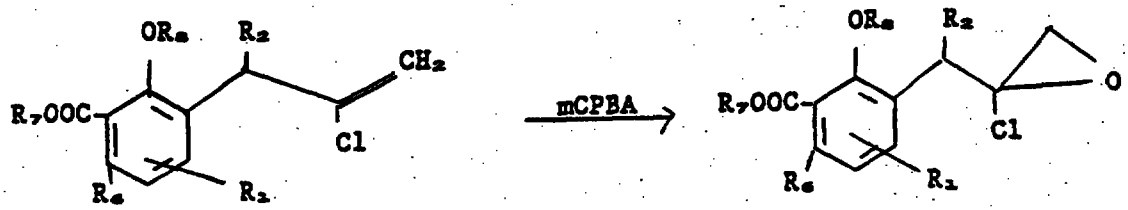
(VIII) (IX)

(3) alkylating the alkyl 3-(2-chloro-2-propenyl)-2-hydroxy-benzoate of formula IX with an R_8 halide according to the equation



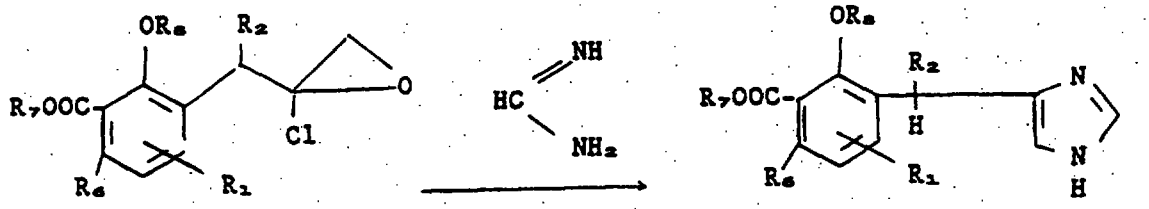
(IX) (X)

(4) oxidizing the alkyl 3-(2-chloro-2-propenyl)-2-(R_8-oxy)-benzoate of formula X with m-chloroperbenzoic acid (mCPBA) in chloroform at reflux temperature for several hours, according to the equation



(X) (XI)

(5) reacting the epoxy ester of formula XI, in the presence of a base and at a temperature of about 60°C, with formamidine acetate, which leads to the alkyl 1-(1H-imidazol-4-yl)alkyl-benzoate of formula II, according to the equation



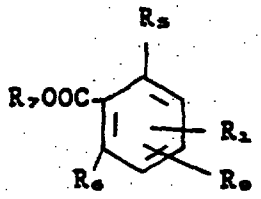
(XI) (II) with $R_5 = OR_8 = C_1$-C_4-alkoxy
R_6 = H, C_1-C_4-alkyl or C_1-C_4-alkoxy

In these formulae, R_1 and R_2 each represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, R_6 has the meaning given above, R_7 represents an alkyl radical having 1 to 4 carbon atoms, preferably the methyl or ethyl radical, R_8 represents an alkyl radical having 1 to 4 carbon atoms and Hal is a halogen atom, preferably a chlorine or bromine atom.

(c) When R_5 represents a hydroxyl group and R_6 a hydrogen atom, a C_1 - C_4 alkyl radical or a C_1 - C_4 alkoxy radical, a variation of method (b) above is followed : in this variation only steps (1) (2) (4) and (5) of method (b) are carried out, the alkylation with an R_8 halide in step (3) being omitted. Thus the compound of formula IX which is obtained from step (2) is subjected directly to oxidation by the m-chloroperbenzoic acid.
These same esters can also be prepared from an alkyl 2-oxo-cyclohexane-carboxylate and a 4-(1-chloroalkyl)-1H-imidazole according to the multistep process described in

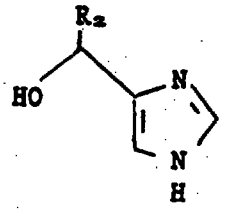
European patent application n°269.599 in the name of the applicant (see Example 4.13 hereinafter).

(d) An alkyl benzoate of formula XII is reacted with a 1H-imidazole-4-methanol of formula XIII, according to the equation

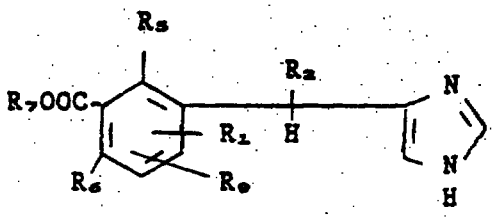


(XII)

+



(XIII)



(II) halogenated if necessary at R_9

In these formulae, R_1, R_2, R_5 and R_6 have the meanings given above, R_7 represents an alkyl radical having 1 - 4 carbon atoms and R_9 represents a hydrogen atom or a halogen atom such as a bromine atom.

This Friedel-Crafts reaction is generally carried out in an inorganic acid such as concentrated sulphuric acid or polyphosphoric acid, or in an organic acid such as formic acid or in a mixture of the aforesaid acids, for several hours at a temperature between 20 and 100°C.

This process does not always result in a single compound. Indeed, a mixture of the position isomers alkyl 3-[1-(1H-imidazol-4-yl)alkyl]-benzoate and 5-[1-(1H-imidazol-4-yl)alkyl]-benzoate is sometimes obtained from which the two isomers can be separated and purified by chromatography.

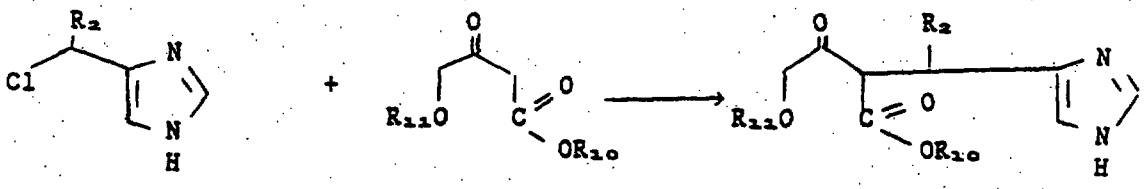
Experience shows, however, that the chromatographic separation is sometimes more easily carried out with acids than with esters. This is why, if necessary, the mixture of the isomeric esters obtained is first subjected to hydrolysis, which results in a mixture of

the corresponding isomeric acids which are then separated by chromatography. These acids are subsequently re-esterified so as to provide the desired esters of formula II.

When in the alkyl 1-[(1H-imidazol-4-yl)alkyl]-benzoates thus obtained, R_9 represents a halogen atom, this halogen atom is eliminated during a supplementary hydrogenolysis step, to give the corresponding compounds of formula II.

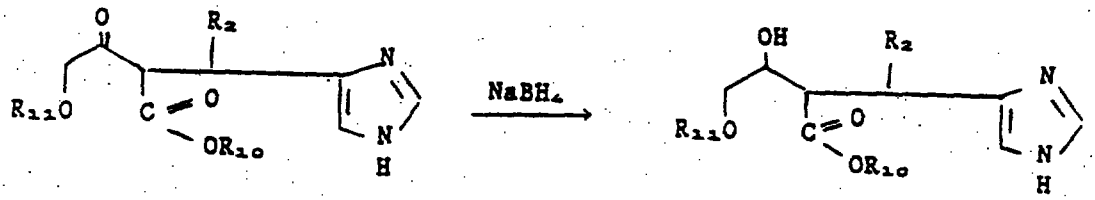
(e) When R_1 represents a hydrogen atom, R_5 a hydroxyl group and R_6 a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, a multistep process can also be used, which includes :

(1) Reacting, in the presence of sodium ethoxide, a 4-(1-chloroalkyl)-1H-imidazole of formula XIV with two equivalents of an alkyl (preferably ethyl) 4-hydroxy-3-oxo-butanoate of formula XV, the hydroxyl function of which is protected, to give an alkyl 4-hydroxy-2-[1-(1H-imidazol-4-yl)alkyl]-3-oxo-butanoate of formula XVI, according to the equation



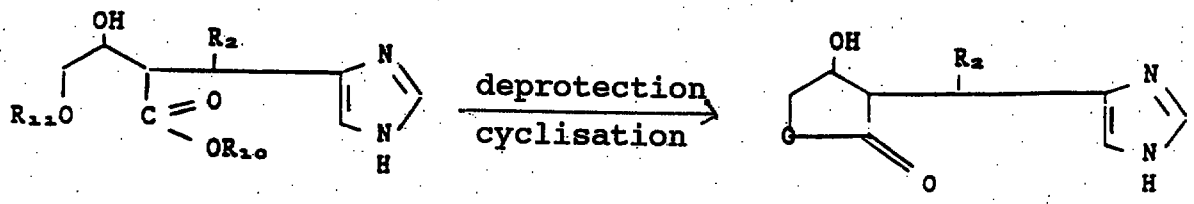
(XIV) (XV) (XVI)

(2) Reducing the beta-ketoester of formula XVI into the beta-hydroxyester of formula XVII with sodium borohydride according to the equation



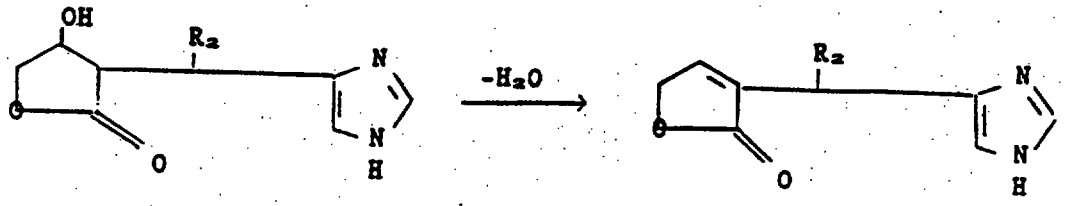
(XVI) (XVII)

(3) Simultaneously deprotecting and cyclizing by means of known methods, the beta hydroxyester of formula XVII to give a 4-hydroxy-3-[1-(1H-imidazol-4-yl)-alkyl]-dihydro-2(3H)-furanone of formula XVIII, according to the equation



(XVII) (XVIII)

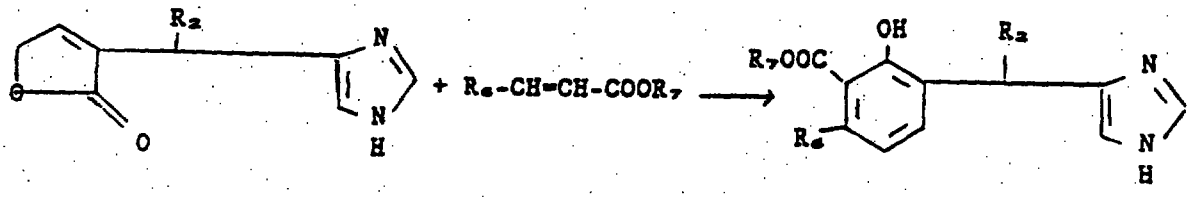
(4) Thermal dehydration of the 4-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-dihydro-2(3H)-furanone of formula XVIII by heating at a high temperature and under reduced pressure to give a 3-[1-(1H-imidazol-4-yl)alkyl]-2(5H)-furanone of formula XIX, according to the equation



(XVIII) (XIX)

This dehydration can also be carried out by heating in a high boiling inert solvent such as, for example, ethylene glycol.

(5) Subjecting to a cycloaddition reaction the 3-[1-(1H-imidazol-4-yl)alkyl]-2(5H)-furanone of formula XIX, with an alkyl acrylate of formula XX, which results in the alkyl 1-(1H-imidazol-4-yl)alkyl-benzoate of formula II, according to the equation



(XIX) (XX) (II) with R_2 = H
R_5 = OH
R_6 = H or
C_1-C_4 alkyl

This Diels-Alter reaction is first of all carried out in the presence of triethylamine and of trimethylchlorosilane whereby the 2-(5H)-furanone of formula XIX is converted into the corresponding 2-trimethylsilyloxyfuran (diene). When the reaction of this silylated intermediate compound with the alkyl acrylate is complete, the primary adduct (an oxanorbornene) is hydrolyzed and aromatized into the hydroxybenzoate of formula II by heating in concentrated hydrochloric or hydrobromic acid for several minutes.

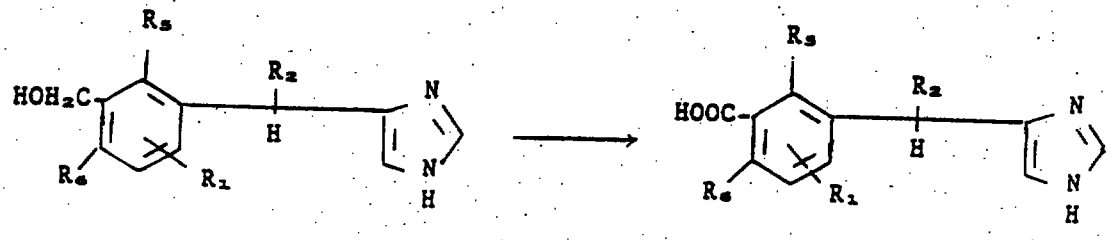
In these formulae, R_2 represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, R_6 has the meaning given above, R_7 and R_{10} each represents an alkyl radical having 1 to 4 carbon atoms, preferably the methyl or ethyl radical, and R_{11} represents a conventional protecting group selected from the methyl, tert-butyl, benzyl and benzoyl radicals, the benzyl radical being preferred.

The 4-(1-chloroalkyl)-1H-imidazoles of formula XIV can be prepared from the corresponding 1H-imidazole-4-methanols by chlorination according to known methods (J.L.KELLEY et al., J.Med.Chem.20 (1977),721-723).

The alkyl 4-hydroxy-3-oxo-butanoates of formula XV, the hydroxyl function of which is protected by the R_{11} radical, can be prepared from the corresponding ethyl 4-chloro-3-oxo-butanoates according to the method described by T.MEUL et a., Chimia.41,(1987),73-76.

The 1-(1H-imidazol-4-yl)alkyl-benzoic acids of formula IV used as starting materials, either for the preparation of the alkyl 1-(1H-imidazol-4-yl)alkyl-benzoates of formula II by method (a) above, or for the preparation of the compounds of formula I, can be obtained by one or other of the following methods :

(1) Oxidation of the corresponding 1-(1H-imidazol-4-yl)alkyl-benzenemethanols of formula XXI, according to the equation



(XXI) (IV)

In these formulae, R_1. R_2. R_5 and R_6 have the meanings given above.

This oxidation reaction is carried out by heating the starting alcohol at about 170 or 190°C for several hours, in molten potassium hydroxide. The acid is isolated after the reaction mixture has been dissolved in water and after acidification of the aqueous solution of the potassium salt of the acid.

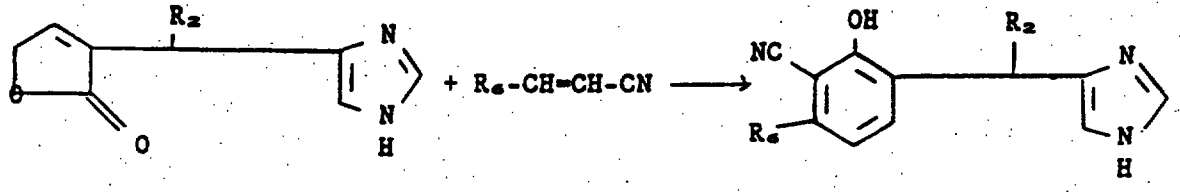
The preparation of the alcohols of formula XXI used as starting materials in this reaction is described in European Patent Application N° 269.599 in the name of the applicant.

(2) Hydrolysis, using conventional methods, of the corresponding esters prepared by one of the methods (b), (c), (d) or (e) described above.

When starting from a mixture of the isomeric esters prepared according to method (d), the mixture of the resulting isomeric acids is subjected to chromatography

so as to separate the individual acids.

The starting 2-hydroxyl-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitriles of formula V can be prepared beginning with steps (1) to (4) of method (e) used in the preparation of the esters of formula II described above, to give the 3-[1-(1H-imidazol-4-yl)alkyl]-2(5H)-furanone of formula XIX, which compound is then further reacted with an acrylonitrile of formula XXII according to the equation



(XIX) (XXII) (V)

This cycloaddition reaction is carried out under the same conditions as those which are described above for step (5) of method (e).

In these formulae, R_2 and R_6 each represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms.

As already mentioned above, the substituted 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I and their non-toxic pharmaceutically acceptable acid addition salts, possess valuable pharmacological properties. In particular, it has been found that they have excellent cardiac and cerebral anti-ischaemic properties, as well as α_2-adrenergic receptor agonist properties.

The pharmaceutical tests described below demonstrate these various properties.

The following compounds according to the present invention have been subjected to pharmacological tests :

- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride (compound A),
- 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride (compound B),
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide hydrochloride (compound C),
- 2-hydroxy-3-[1H-imidazol-4-yl)methyl]-benzohydrazide (compound D)

- 2-hydroxy-N-(2-hydroxyethyl)-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride (compound E)
- 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzamide hydrochloride (compound F),
- 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzamide (compound G),
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N,N-dimethylbenzamide (compound H),
- 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride (compound I),
- 5-tert-butyl-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide (compound J),
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzamide hydrochloride (compound K),
- 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzamide (compound L),
- N,2-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride (compound M),
- 2,6-dihydroxy-3-[1-(1H-imidazol-4-yl)-benzamide hydrochloride (compound N),
- 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzamide hydrochloride (compound O),
- (+)-2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride (compound P).

1. Cardiac anti-ischaemic activity.

   a) Artificially induced acute coronary insufficiency in an awake dog.

   In an awake dog (equipped with a pneumatic occluder around the inferior descending coronary artery and with intracardiac electrodes), an occlusion of the coronary artery is obtained by the pneumatic occluder for a period of six minutes. Because of the reduction in the oxygen supply which results from this, the occlusion produces myocardial ischaemia which is expressed on the electrocardiogram by a reproducible and quantifiable ST-segment elevation. The anti-ischaemic action of a

compound results in a reduction of the magnitude of the ST-segment elevation. (P.P. MAROKO and E.BRAUNWALD, Circulation, 53, (1976, Suppl.I)162-168; S.E. EPSTEIN et al., Circulation,53, (1976, Supp.I),191-197).

Table I shows, for the compounds submitted to the test, the dose (DE_{20} in μmole/kg) which, when administered intravenously to groups of ten animals, produces a mean reduction of at least 20% of the ST-segment elevation on the whole group of animals. As a reference compound, 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol (or propranolol) is used.

Table I.

Test compound	DE_{20} (in μmole/kg)
A	0.03
B	0.02
C	0.3
D	3
E	< 3
F	< 3
G	< 1
I	0.32
K	0.32
propranolol	2

From this table, it is evident that the compounds of the invention display remarkable anti-ischaemic activity.

b) Effort trial on a moving belt.

In this test, a group of at least four dogs is used (equipped with intracardiac electrodes), the dogs having an organic stenosis at the level of a coronary artery. This stenosis causes imbalance between the demand supply of oxygen when the animal is required to make an effort. This imbalance is expressed on the electrocardiogram by an increase in the ST-segment.

In the trial, the dog runs at a speed of 12km/h on a moving belt having a slope of 15°. This maximum effort is required for one minute. During the trial, the

increase in the ST-segment is recorded, together with the natural increase in the pulse rate. The experiment is repeated at least four times, and the mean of the values obtained is taken as a reference (100%) for the group of animals. The animal is then allowed to rest for a minimum of 24 hours before being subjected to a new effort trial under the influence of the compound to be studied.

The compound to be studied is administered slowly (over 1 minute) by intravenous injection 5 minutes before the new effort trial. In the course of the latter, the variations in the same parameters are recorded. Table II shows the mean reduction observed for the ST-segment (in %) at the indicated dose (μmole/kg) and for the pulse rate (in beats per minute), with respect to the reference values obtained in the first trial.

Table II

Maximum effort at 12 km/h for 1 minute

compound	dose (μmole/kg)	reduction in ST-segment (in %)	reduction in pulse rate (in beats/min)
A	0.018	74	3
C	0.32	50	1
propanolol	1.0	74	35

From this table, it can be seen that the compounds of the invention have a good anti-ischaemic activity demonstrated by a high reduction in the ST-segment, which is also found with propranolol, but only at a much higher dose. In addition, unlike the propranolol which causes at the same time a large reduction in cardiac rhythm during the trial, which is not desirable and which is detrimental to the maintenance of the effort, the compounds of the invention are not inimical to the natural increase in pulse rate during the effort. They thus allow the pulse rate to adapt correctly to the effort, while at the same time opposing the ischaemia.

2. Cerebral anti-ischaemic activity.

a) General and permanent cerebral ischaemia in rats.

Male Wistar rats (200 to 250 g) are anaesthetized by inhalation of halothane (1 to 5%) contained in a N_2O-O_2 (70:30) mixture. The two common carotid arteries are ligatured simultaneously close to the passage between the internal carotid and external carotid using the method described by M.LE PONCIN-LAFITTE et al., J.Pharmacol. (Paris),14, (1983),99-102.

The compound to be tested is administered intraperitoneally for a first time 30 minutes before making the ligatures, and subsequently 30 minutes and 270 minutes after making the ligatures.

On the next day, and on the day after the next, the neurological deficit in the surviving animals is evaluated by the method described by C.CAPDEVILLE et al., J.Pharmacol. (Paris),15,(1984),231-237, and by B.KOLB et al., Neurobehav.Toxicol.Teratol.7,(1985),71-78.

The sensorimotor functions taken into consideration during this evaluation are spontaneous motility, grasping reflex, placing reactions both visual and by loss of support, paw-flexion reflex, the righting reflex and the test of tail hanging. The maximum possible score for an animal not having an ischaemia is 17.

Table III gives for compound A. administered intraperitoneally at a dose of 0.76 µg/kg (3.2 nmole), the mean of the neurological scores determined for the whole group of surviving animals of the control group and of the treated group, as recorded two days after the ligatures. The statistical significance (P) of the difference observed between these mean values is evaluated by the Mann-Whitney test.

Table III.

Neurological scores after 2 days

Control (n = 16)	12
A (n = 15)	15
(P)	(0.005)

n = number of surviving animals.

It is seen from this Table that compound A, at a very small dose, significantly reduces the neurological deficit in the treated animals, caused by ischaemia.

b) Unilateral, multifocal cerebral ischaemia in the rat.

In awake, male Sprague-Dawley SPF rats, aged from 8 to 9 weeks, a permanent, unilateral cerebral ischaemia (or embolization) is caused by introduction of 2000 microspheres (provided by 3M, St.Paul, U.S.A.; diameter 58±2 μm) into the right carotid stream (A.M.BRALET et al., Stroke,10,(1979),34-38; M.LE PONCIN-LAFITTE et al., Pathol.Biol.(Paris),30,(1982),289-293) after the permanent ligature of the right pterygopalatine artery (Y.KIYOTA et al., Pharmacol.Biochem.Behav.24 (1986),687-692).

The compound to be studied is administered for the first time 30 minutes before, and for the second time 30 minutes after embolization, whilst the control animals receive only a physiological serum. The animals are then allowed to rest. After 6 days of recovery, the surviving animals are measured for :

1) the residual neurological deficit obtained from the test of posture and gait of the animals (Test A, maximum score: 4 points). This test evaluates :
   a) abnormal positioning of the hind paws (S.IRWIN) Psychopharmacologia (Berlin),13,(1968),222-257);
   b) contralateral inclination of the body during locomotion;
   c) homolateral longitudinal flexion of the body, and
   d) abnormal gait (B.KOLB et al., loc.cit.)
2) The sensorimotor functions (spontaneous motility, grasping reflex, placing reactions both visual and by loss of support (Test B, maximum score : 10 points); (C.CAPDEVILLE et al., loc.cit.).
3) The lateralized sensorimotor response (on the contralateral side) (Test C, maximum score: 3 points). This is evaluated by combining the measurements of visual placing reflex, head orientation reflex towards a lateral sensory

stimulus, and the cutaneous plantar reflex (C.CAPDEVILLE et al., loc.cit.; J.F. MARSHALL et al., Science (Washington),174, (1971),523-525).

4) Tactile extinction on the left side (Test D, maximum score: 300 points). By contrast with the other tests mentioned above, for which the deficit is lower when the score is higher, the deficit is here more pronounced when the score approaches 300 (T.SCHALLERT et al., Pharmacol.Biochem.Behav. 16,(1982),455-462).

On the seventh day of recovery, the oedema present in various ipsilateral cerebral structures is also measured (M.LE PONCIN-LAFITTE et al., loc.cit.).

Table IV gives the results obtained in tests A to D for compound A, administered intraperitoneally at the dose of 0.76 µg/kg (3.2 nmole/kg), i.e. the mean of the neurological scores determined for the whole group of surviving animals of the control group and of the treated group after 6 days of recovery. The mean variation (in g) of body weight measured on the 7th day of recovery is also indicated.
The statistical significance (P) of the difference between the mean values calculated for the control animals and for the treated animals is evaluated by the Mann-Whitney test.
This table shows that compound A significantly reduces the neurological and behavioural deficit caused by ischaemia and improves the ponderal evolution of the treated animals.

Table IV

Mean neurological scores 6 days after embolization

group	n(*)	test A	test B	test C	test D	weight variation (in g)
control	18	1.0	7.3	1.0	243	-5.7
treated	17	2.0	8.0	2.0	96	+0.8
(P)		(<0.01)	(<0.05)	(<0.005)	(<0.05)	(<0.05)

(*): n indicates the number of surviving animals in each group.

In Table V, the quantity of water (as an average of the percentages) retained in various ipsilateral cerebral structures in the control animals and in the treated animals surviving at the 7th day after embolization is indicated. The results obtained show that treatment by compound A significantly reduces the ipsilateral oedema in the different cerebral structures studied.

Table V

Quantity of water in various ipsilateral cerebral structures (average %)

group	n(*)	Hippocampus	Corpus striatum	Diencephalon	Cortex
control	18	80.20	81.57	77.04	81.33
treated	17	79.79	80.05	76.32	80.36
(P)		(< 0.05)	(< 0.005)	(< 0.05)	(< 0.01)

(*) : n indicates the number of surviving animals in each group.

3. α_2-adrenergic agonist property.

a) Competitive binding with a radioligand.

The object of competitive binding assays is to measure the affinity of the compounds of the invention for α_2-adrenoceptors. These conventional experiments involve the competition for binding to α_2-andrenergic receptors between the tested compound on the one hand, and on the other hand, a radioligand which, in this particular case of α_2-andrenergic receptors, is the [^{3}H]clonidine which is known to be a selective α_2-andrenergic agonist. The method used is that of D.C. U'PRICHARD et al., Mol.Pharmacol.13, (1977),454-473.

The displacement curves for binding of [^{3}H] clonidine have been determined with nine concentrations of compound A, ranging from 10^{-4} to 10^{-10} mole/l, and with three different preparations of rat brain membranes. The samples were incubated for 30 minutes, and then filtered under reduced pressure using a Whatman GF/B filter. The filters were washed three times with 5 ml of Tris-HCl buffer

(pH 7.5 at 0°C) and then dried for one minute. The radioactivity was measured in an Econofluor (-NEN Corp.) medium. The [^{3}H] clonidine (25.5 Ci/mole) used was provided by Amersham.

The affinity of compound A for the α_2-adrenergic receptors has been calculated from the displacement curves of the [^{3}H] clonidine. It is expressed by the concentration (IC_{50} in mole/l) of compound A that is necessary to obtain a 50% inhibition of the binding of the radioligand to the receptors. The results obtained show that the compound A has a considerable affinity for the α_2-adrenergic receptors :

$$IC_{50} = 8.90 \pm 0.72 \times 10^{-9} \text{ mole/l}$$

b) Stimulation of the isolated guinea-pig atria.

The release of noradrenalin at the level of the nerve endings is mediated by a feedback regulating mechanism through the presynaptic α_2-adrenergic receptors. This mechanism has been demonstrated on the guinea-pig atria by M.J. RAND et al., "Central action drugs in blood pressure regulation", 1975, 94-132, Ed. D.S. DAVIES, J.L. REID, Pitman, London.

Electrical stimulation of the isolated guinea-pig atria induces a release of noradrenalin which results in an increase in the rate of the heart beat (tachycardia). This tachycardia is inhibited by an α_2-agonist such as, for example, clonidine, in a proportion which depends on the dose of the agonist used. The action of the α_2-agonist may be limited in the presence of an α_2-specific antagonist such as α-yohimbine.

The in vitro activity of the compounds of the invention on the presynaptic α_2-adrenergic receptors has been studied on the isolated guinea-pig atria, electrically stimulated according to the method described by I.C. MEDGETT et al., Naunyn-Schmiedeberg's Arch.Pharmacol.304,(1978),215-221.

The compound to be studied is tested in increasing concentrations ranging from 10^{-10} to 10^{-3} mole/l. The concentration (IC_{30} in mole/l) which causes a 30%

reduction in the maximum tachycardia obtained initially during the electrical stimulation of the atria in the absence of the compound to be tested, is determined.

Table VI shows the IC_{30} concentration (in mole/l) obtained for the compounds of the invention as well as for clonidine.

Table VI

Reduction in tachycardia

compound	n(*)	IC_{30} (in mole/l)
A	7	9×10^{-10}
B	6	7.5×10^{-10}
C	3	1.3×10^{-7}
D	5	2.2×10^{-7}
F	8	7×10^{-8}
clonidine	6	3.2×10^{-9}

(*) n = number of tests.

This table shows that the compounds of the invention, in very small concentrations, oppose the tachycardia which is induced by electrical stimulation.

On the other hand, in the presence of a concentration of 10^{-6} mole/l of α-yohimbine, the concentration of compound A necessary to obtain a reduction of 30% in the tachycardia is greater than 10^{-7} mole/l. These results clearly show that the compounds of the invention act through a specific mechanism via an α_2-agonist action.

c) Stimulation of a guinea-pig ileum.

Longitudinal muscles strips attached to an isometric strain gauge are suspended in Tyrode's solution and are stretched under a tension of 1 g (G.M.DREW, Brit.J.Pharmacol.64,(1978),293-300: M.ANDREJAK et al., Naunyn-Schmiedeberg's Arch.Pharmacol.314, (1980),83-87).

Electrical stimulation of the parasympathetic nerves associated with the ileum fragments causes a contraction of the muscle. This contraction is reduced in the presence of a presynaptic α_2-agonist

and the magnitude by which the contraction is reduced depends on the concentration of the agonist used. This effect is antagonized by the simultaneous presence of an α_2-antagonist such as α-yohimbine.

The compounds to be studied have been tested at increasing concentrations ranging from 10^{-10} to 10^{-3} mole/l.

The concentration (IC_{30} in mole/l) that reduces by 50% the intensity of the contraction of the muscle is determined.

Table VII gives the IC_{30} concentrations (in mole/l) obtained for the compounds of the invention. These results show that these compounds are highly active at very low concentration.

Table VII

Inhibition of the contraction of guinea-pig ileum

compound	n(*)	IC_{50} (in mole/l)
A	5	7×10^{-9}
B	6	3×10^{-9}
E	3	6×10^{-5}
F	4	7×10^{-5}
I	7	3×10^{-7}
J	4	3×10^{-5}
L	6	3×10^{-8}
M	5	4×10^{-7}
P	6	2×10^{-9}
clonidine	4	2×10^{-8}

(*) n = number of tests.

In the presence of α-yohimbine at a concentration of 10^{-6} mole/l, the concentration of the compounds A or B for example, that is required for reducing muscle contraction intensity by 50% is higher, and becomes greater than 10^{-6} mole/l, which gives additional confirmation that the compounds of the invention act really at the level of the presynaptic α_2-adrenergic receptors.

4. Diuretic activity.

The diuretic activity of the compounds of the invention has been determined using beagle dogs (6 males and 6 females) by means of a 6-way randomized cross-over study. The compounds to be studied were administered intravenously at increasing doses : 2, 6.5, 20, 65 and 200 μg/kg. During the first three hours following the injection, the volume of urine excreted was measured. Table VIII gives for compound A the mean relative increase in % of the volume of urine excreted with respect to the group of animals which have not received the compound.

The results show that the minimum active dose that causes a statistically significant increase ($P < 0.05$) in urine excretion is ≤ 6.5 μg/kg for males, while for females this dose is ≤ 2 μg/kg.

Table VIII

Mean relative increase in urine secretion (in %)

dose (μg/kg)	males (n=6)	females (n=6)
2	25	74 *
6.5	122 *	291 **
20	383 **	531 **
65	345 **	804 **
200	412 **	988 **

Analysis of the variance : * $P < 0.05$
** $P < 0.01$

n = number of animals

5. Toxicity.

The toxicity of the compounds according to the present invention has been determined in male NMRI mice by means of Irwin's test (S. IRWIN, Psychopharmocologia, 13, (1968), 222-257).

Progressive doses of the test compound were administered intraperitoneally to groups of three mice until the lethal dose was reached (dose causing the death of two out of three animals within 48 hours).

Table IX below gives the lethal dose found for the compounds of the invention. It is seen from this table that the compounds of the invention are not very toxic.

Table IX

Toxicity

compound	lethal dose (in mg/kg)
A	760
B	267
C	267
D	232
E	893
F	802
G	651
H	245
I	>270
K	>268
L	231
M	>288
N	284
O	>268
P	294

The pharmaceutical compositions containing the compounds according to the present invention may be administered orally, parenterally or rectally.

The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example in the form of tablets (coated or uncoated), pills, dragees, gelatine capsules, solutions, syrups, and the like. Similarly, the compositions which can be used for parenteral administration are the pharmaceutical compositions known for this mode of administration, for example aqueous or oily solutions, suspensions or emulsions. For rectal administration, the compositions containing the compounds of the invention are generally used in the form of suppositories.

The pharmaceutical forms such as injectable solutions, injectable suspensions, tablets, drops, suppositories and the like are prepared by the methods currently used by pharmacists.

The compounds of the invention are mixed with a solid or liquid, non-toxic, pharmaceutically acceptable carrier, and optionally with a dispersing agent, a disintegrating agent, a stabilizing agent and the like. If desired, sweetening and colouring agents and the like may also be added.

The percentage of active compound in the pharmaceutical compositions may vary within very wide limits, according to the patient and the mode of administration, and in particular according to the frequency of administration. As far as the daily posology is concerned, it may vary within a very wide range of dosage units, for example from 3 to 350 µg of active compound once or twice a day by intravenous injection, or again from 50 µg to 5 mg of active compound once or twice a day by oral administration.

Non-limiting examples of a composition containing a compound of the invention are given below

a) an example of a sterile solution for intravenous injection :

Active compound		250 µg
Sodium acetate		19.15 mg
Acetic acid		3.59 mg
Sodium chloride		81 mg
Sterile water	ad	10 ml

(to be kept in a 10 ml brown ampoule, after sterile filtration of the solution).

b) an example of a formula for a tablet :

Active compound	0.5 mg
Maize starch	38 mg
Lactose	63 mg
Magnesium stearate	1.2 mg
Polyvinylpyrrolidone	2.5 mg

The following non-limiting examples are given for the purpose of illustrating the preparation of the substituted 1-(1H-imidazol-4-yl)alkyl-benzamides according to the invention as well as the preparation of their intermediates. In these examples, the nuclear magnetic resonance spectra (NMR) were determined with a Bruker apparatus at 250 MHz, using tetramethylsilane as internal reference. The chemical shifts are indicated in delta (ppm). The letters s, d, dd, t, q and m indicate respectively a singlet, a doublet, a double doublet, a triplet, a quartet and a multiplet.

Example 1. Preparation of the starting alkyl 1-(1H-imidazol-4-yl)alkyl-benzoates of formula II

A. By esterification of the corresponding acids (method (a)).

1. Ethyl 2 hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoate hydrochloride.

A suspension of 3.1 g (12.2 mmole) of 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoic acid hydrochloride (prepared as described hereinafter in 2.C.) in 150 ml of absolute ethanol is saturated at 0°C with a current of gaseous hydrochloric acid. This is then slowly heated to reflux temperature which is maintained for 10 hours. Subsequently, the solvent is evaporated until the ester precipitates. The latter is filtered, washed with diethyl ether, and then dried. 2.3 g of ethyl 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoate hydrochloride are obtained.

Yield : 68% M.Pt.: 195-198°C.

NMR (DMSO) spectrum : delta 1.34(3H,t), 4.03(2H,s), 4.37(2H,q), 6.95(1H,d), 7.40(1H,s), 7.49(1H,dd), 8.70(1H,d), 9.12(1H,s), 10.6(1H,s).

2. Ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoate.

This compound is prepared as described in 1. above, but starting from 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoic acid (prepared as described hereinafter in Example 2.A.2.). When the reaction is complete, the reaction medium is neutralized by the addition of a concentrated ammonia solution, the

mineral salts are filtered off and the filtrate is evaporated under reduced pressure. The residue obtained is purified by chromatography on silica gel (eluent 8:2 v/v dichloromethane-methanol). Ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoate is obtained with a 35% yield. The corresponding hydrochloride melts at 168°C (ethanol-ether).

Analysis for $C_{14}H_{16}N_2O_3.HCl$ in %:

calculated:	C 56.66	H 5.40	N 9.44
found :	56.58	5.50	9.21

3. Ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzoate.

1.18 g (3.8 mmole) of 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzoic acid hydrochloride (prepared as described hereinafter in Example 2.A.3.) dissolved in 15 ml of triethyl orthoformate, in the presence of 1.2 g of anhydrous montmorillonite K10, is heated under reflux for 9 hours. The mixture is then filtered and evaporated under reduced pressure. The residue obtained is purified by chromatography on 150 g of silica (eluent: 95:5:0:5 v/v/v dichloromethane-methanol-ammonia). 0.213 g of ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzoate is obtained.

NMR (DMSO) spectrum : delta 0.81(3H,t), 1.0 to 1.29(2H,m), 1.34(3H,t), 1.77 to 2.0(2H,m), 4.31 to 4.41(3H,t+q), 6.77(1H,s), 6.86(1H,t), 7.46 to 7.50(2H,d+s), 7.63(1H,d).

The product obtained is used as such, without further purification, to prepare the corresponding benzamide (Example 4.15).

4. Methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate.

This compound is prepared as described in 2. above, but starting from 2-hydroxy-3-[(1H-imidazol-4-yl) methyl]-benzoic acid hydrochloride (prepared as described hereinafter in Example 2.A.1.) and from methanol. M.Pt.: 153-154°C.

NMR (DMSO) spectrum : delta 3.87(2H,m), 3.91(3H,s), 6.77(1H,s), 6.87(1H,t), 7.45(1H,dd), 7.58(1H,s), 7.69(1H,dd), 10(1H,s).

B. via the Claisen transformation (methods (b) and (c)).

1. Methyl 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoate.

1.a. Methyl 2-(2-chloro-2-propenyloxy)-benzoate.

A suspension of 304 g (2 mole) of methyl 2-hydroxybenzylbenzoate, 25 g of potassium iodide, 69 g (0.5 mole) of potassium carbonate, and 69 g (0.625 mole) of 2,3-dichloropropene in 3 litres of dry acetone is heated under reflux for 10 hours. After two and a half hours, five hours and seven and a half hours of reaction time, 69 g of potassium carbonate and 69 g of 2,3-dichloropropene are added each time. The suspension is then filtered off and the filtrate is evaporated under reduced pressure. The residue is taken up in ethyl acetate, and the solution is washed successively with a saturated aqueous solution of sodium thiosulphate, with water, and finally with a saturated aqueous solution of sodium chloride. The organic phase is dried over sodium sulphate, and is distilled under reduced pressure. 394 g of methyl 2-(2-chloro-2-propenyloxy)-benzoate are obtained.

Yield : 87% B.Pt.: 119°C/1.3 mbar.

1.b. Methyl 3-(2-chloro-2-propenyl)-2-hydroxybenzoate.

274.1 g (1.21 mole) of methyl 2-(2-chloro-2-propenyloxy)-benzoate, placed in a 2 litre round bottomed flask, are carefully degassed with argon. They are then heated as rapidly as possible to 260°C. At this temperature, an exothermic reaction takes place suddenly : the temperature increases to 293°C by itself and reflux and blackening of the reaction mixture

takes place. After cooling to ambient temperature, the product is distilled under reduced pressure. 241.1 g of methyl 3-(2-chloro-2-propenyl)-2-hydroxybenzoate are obtained.

Yield : 88%. B.Pt. : 109-110°C/1.3 mbar.

NMR ($CDCl_3$) spectrum : delta 3.71(2H,s), 3.95(3H,s), 5.17(1H,m), 5.28(1H,m) 6.90(1H,t), 7.48(1H,dd), 7.85(1H,dd), 11.22 (1H,s).

1.c. Methyl 3-(2-chloro-2-propenyl)-2-methoxybenzoate.

Without exceeding a temperature of 10°C, 8.81 g (306 mmole) of sodium hydride are added in portions to a solution of 57.7 g (255 mmole) of methyl 3-(2-chloro-2-propenyl)-2-hydroxybenzoate in 500 ml of anhydrous dimethylformamide. The mixture is heated at 40°C for 15 minutes. A solution of 43.45 g (306 mmole) in 50 ml of toluene is then added and the temperature of the mixture is maintained at 40°C for 3 hours. The reaction mixture is carefully poured into five litres of water, and is extracted several times with ethyl acetate. The organic phase is concentrated to a volume of 500 ml and is then washed successively with water and with a saturated aqueous solution of sodium chloride. The solution is dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent : 50:50 v/v dichloromethane-hexane). 49.2 g methyl 3-(2-chloro-2-propenyl)-2-methoxybenzoate are obtained.

Yield : 60% B.Pt. : 107-110°C/0.5 mbar (oil)

NMR ($CDCl_3$) spectrum : delta 3.73 (2H,s), 3.82(3H,s), 3.92(3H,s), 5.14(1H,m), 5.32(1H,m), 7.15(1H,t), 7.47(1H,dd), 7.81(1H,dd).

1.d. Methyl 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoate.

A solution of 45.5 g (189 mmole) of methyl 3-(2-chloro-2-propenyl)-2-methoxybenzoate and of 81.5 g (378 mmole) of m-chloroperbenzoic acid in 300 ml of dry chloroform is heated at reflux temperature for 150 minutes. It is cooled to 0°C and the precipitate thus formed is removed by filtration. The filtrate is successively washed with a saturated aqueous solution of sodium thiosulphate and with a saturated aqueous solution of sodium bicarbonate. The solution is dried over sodium sulphate and the solvent is evaporated under reduced pressure without exceeding 30°C.

The residue obtained is suspended in 300 ml of anhydrous methanol, and mixed with 111.3 g (1.32 mole) of finely ground sodium bicarbonate. The mixture is heated to reflux temperature. 137.6 g (1.32 mole) of formamidine acetate are added in portions, hourly, to the mixture. After five and a half hours of heating at reflux temperature, methanol is removed under reduced pressure. The residue is taken up in 500 ml of water and extracted with ethyl acetate. The organic phase is dried over sodium sulphate and is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent : 92.3:7:0.7 v/v/v dichloromethane-ethanol-ammonia). 13.8 g of methyl 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoate are obtained.

Yield : 30%

NMR (DMSO) spectrum : delta 3.73(3H,s), 3.83(3H,s), 3.89(2H,s), 6.78(1H,s), 7.11(1H,t), 7.24 to 7.73(3H,m).

The product thus obtained is used as such, without further purification, to prepare the corresponding acid (Example 2.B.1.).

The following compounds have been prepared according to the method described in B.1. above.

2. Methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate.
This compound is prepared from methyl 3-(2-chloro-2-propenyl)-2-hydroxybenzoate with a yield of 35.4%, but of course omitting the methylation with methyl iodide described in 1.c.
M.Pt. : 153-154°C
The compound is identical to that prepared in Example 1.A.4.

3. Methyl 3-[(1H-imidazol-4-yl)methyl]-2-n-propoxybenzoate.
Yield : 20% (oil).
The product, obtained in the raw state, is used as such for preparing the corresponding acid (Example 2.B.2.).

C. By Friedel-Crafts reaction (method (d)).

1. Methyl 5-tert-butyl-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]benzoate hydrochloride.
50 g of 1H-imidazole-4-methanol hydrochloride are reacted with 60 g of methyl 5-tert-butyl-2-hydroxybenzoate in 150 ml of concentrated sulphuric acid at 20°C for 21 hours. The reaction mixture is then cautiously decomposed on ice.
The solid product is filtered off, purified by chromatography and then converted into its hydrochloride.
1.1. g of Methyl 5-tert-butyl-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]benzoate hydrochloride are obtained.

Yield : 2.8% M.Pt. : 185-186°C
NMR (DMSO) spectrum : delta 1.3(9H,s), 3.45(3H,s), 4.1(2H,s), 7.3(1H,s), 7.75(2H,m), 9.0(1H,s), 10.5 to 13.0 (3H).

2. Methyl 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]benzoate.
95.84 g (0.57 mole) of methyl 2,6,-dihydroxybenzoate, 190 ml of formic acid and 51.14 g (0.38 mole) of 1H-imidazole-4-methanol hydrochloride are mixed together. The mixture is heated under reflux and the formic acid-water azeotrope is distilled off for 15 minutes. The reflux temperature is then maintained for 17 hours. The reaction mixture is poured into water. Excess methyl 2,6-dihydroxybenzoate is extracted with toluene and the aqueous phase is then neutralized to pH 7-8 by the addition of a saturated aqueous solution of sodium hydroxide. It is then extracted with dichloromethane, the organic phases are dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent : 94:6:0.6 v/v/v dichloromethane-methanol-ammonia). 14.8 g of methyl 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]benzoate are obtained, contaminated by traces of residual solvents.
Yield 13%.
NMR (DMSO) spectrum : delta 3.72 (2H,s), 3.81(3H,s), 6.33(1H,d), 6.86(1H,s), 7.06(1H,d), 7.73(1H,s), 9.5 to 10.2(3H).
In view of its instability, the product thus obtained is used as such, without further purification, to prepare the corresponding benzamide (Example 4.9.).

The following compounds are prepared according to the method described in C.2. above.

3. Methyl 2,6-dihydroxy-3-[1-(1H-imidazol-4-yl)ethyl]benzoate.
This compound is prepared from α-methyl-1H-imidazole-4-methanol hydrochloride. Reflux temperature is maintained for 19 hours. The residue which is finally obtained is purified by chromatography on silica gel (eluent : 95:5:0.5 v/v/v dichloromethane-methanol-ammonia).
Yield : 43%.
NMR ($CDCl_3$) spectrum : delta 1.52(3H,d), 4.0(3H,s), 4,48(1H,q), 6.40(1H,d), 6.79(1H,s), 7.14(1H,d), 7.47(1H,s), 10.0(3H).
The product obtained is used as such, without further purification, to prepare the corresponding benzamide (Example 4.10.).

4. Ethyl 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzoate and ethyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzoate.
These two compounds are simultaneously prepared from a mixture of 80.8 g (0.448 mole) of ethyl 2-hydroxy-6-methylbenzoate, 225 ml of formic acid and 51.5 (0.382 mole) of 1H-imidazole-4-methanol hydrochloride heated at reflux temperature for 53 hours. The products obtained are separated and purified by chromatography on silica gel (eluent : 94:6:0.5 v/v/v dichloromethane-methanol-ammonia)
7.2 g of ethyl 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzoate are thus obtained.
Yield : 7.2% M.Pt : 42-45°C.
NMR ($CDCl_3$) spectrum : delta 1.36 (3H,t), 2.34(3H,s), 3.83(2H,s), 4.37(2H,q), 6.52(1H,s), 6.70(1H,d), 7.08(1H,d), 7.45(1H,s), 10.0(2H).
2.8 g of ethyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzoate are obtained at the same time. Yield : 2.8% M.Pt. : 101-103°C.
NMR ($CDCl_3$) spectrum : delta 1.40(3H,t), 2.47(3H,s), 3.88(2H,s), 4.39(2H,q), 6.62(1H,d), 6.76(1H,s), 7.12(1H,d), 7.43(1H,s), 10.0(2H).

5. Methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate hydrobromide.

5.a. methyl 5-bromo-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate.

95.6 g (0.71 mole) of 1H-imidazole-4-methanol hydrochloride are added in portions, at ambient temperature, to a solution of 87 g (0.355 mole) of methyl 5-bromo-2-hydroxy-4-methylbenzoate (T.M. CRESP et al. J.Chem.Soc. Perkin I, (1973),340) in 900 ml of concentrated sulphuric acid. Stirring is maintained for 234 hours. The reaction mixture is then poured cautiously onto ice and the aqueous phase is neutralized to pH 8 by the addition of a saturated aqueous solution of sodium hydroxide. It is extracted with ethyl acetate. The organic layer is evaporated under reduced pressure and the residue is purified by chromatography on 1.4 kg of silica (eluent, 9:1 v/v dichloromethane-methanol). The product obtained is chromatographed a second time on 400 g of silica (eluent : 95:5:0.5 v/v/v dichloromethane-methanol-ammonia). 2.4 g of methyl 5-bromo-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate are obtained, which are sufficiently pure to be used as such in the following step.

NMR (DMSO) spectrum : delta 2.43(3H,s), 3.90(3H,s), 3.96(2H,s), 6.62(1H,s), 7.51(1H,s), 7.87(1H,s).

5.b. methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate hydrobromide

2.38 g (7.2 mmole) of methyl 5-bromo-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate dissolved in 70 ml of methanol, are subjected to hydrogenolysis at ambient temperature, in the presence of 0.7 g of 10% palladium on carbon, under a hydrogen pressure of 4.2 bar. The catalyst is filtered off and

the solvent evaporated under reduced pressure. 1.83 g of methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate hydrobromide are obtained. Yield : 76%.
NMR (DMSO) spectrum : delta 2.34(3H,s), 3.91(3H,s), 4.02(2H,s), 6.87(1H,s), 7.13(1H,s), 7.68(1H,d), 8.86(1H,s).
The product thus obtained is used as such, without further purification, to prepare the corresponding benzamide (Example 4.14.).

Example 2. Preparation of the starting 1-(1H-imidazol-4-yl)alkyl benzoic acids of Formula IV.

A. By oxidation of the corresponding 1-(1H-imidazol-4-yl)alkyl-benzenemethanols.

1. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoic acid (hydrochloride).
1 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzenemethanol (prepared according to the method described in European Patent Application n° 269.599 in the name of the applicant) is heated at 180°C for two and a half hours with thorough stirring, in the presence of 7.5 g of potassium hydroxide. The reaction mixture is then cooled and dissolved in 10 ml of water. The aqueous solution is acidified to pH 3-4 by addition of concentrated hydrochloric acid. The precipitate which separates is filtered off and dried, and is then extracted with boiling isopropyl alcohol. The isopropyl alcohol is then removed under reduced pressure, and the crystalline residue obtained is recrystallized from 5 ml of a 1N aqueous solution of hydrochloric acid. 0.74 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoic acid hydrochloride are obtained.
Yield : 58%. M.Pt. 257°C (decomposition).
NMR (DMSO) spectrum : delta 4.08(2H,s), 6.09(1H,t), 7.37(1H,d), 7.52(1H,dd), 7.79(1H,dd), 9.05(1H,d).

Analysis for $C_{11}H_{10}N_2O_3$.HCl in %

calculated :	C 51.87	H 4.32	N 11.0
found	51.68	4.03	10.61

This compound is used as a starting material in Example 1.A.4.

The following compound was prepared in the same way.

2. 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoic acid.

This compound, used as a starting compound in 1.A.2., is prepared from 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzenemethanol with a yield of 50%.

The free acid is obtained by neutralization of the hydrochloride and recrystallization from water.

M.Pt. 278-280°C.

Analysis for $C_{12}H_{12}N_2O_3$ in %

calc :	C 62.06	H 5.17	N 12.07
found :	62.05	5.37	11.72

The 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzenemethanol used as the starting material is prepared according to the method described in Example 6.5. of European Patent Application n° 269.599 in the name of the applicant.

3. 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzoic acid (hydrochloride).

3.86 g (14.8 mmole) of 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzenemethanol (prepared according to the method described in Example 6.6. of European Patent Application n° 269.599 in the name of the applicant) are heated at 170°C for 5 hours in the presence of 22 g of potassium hydroxide. The reaction medium is then cooled and dissolved in 100 ml of water. The insoluble material is filtered off and the filtrate acidified to pH 10 by addition of concentrated hydrochloric acid. The salts which separate are removed by filtration and the filtrate

is finally acidified to pH 1. The 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzoic acid hydrochloride precipitates. It is recrystallized from 100 ml of isopropyl alcohol. 1.44 g of the product is obtained.

M.Pt. : 239-251°C.

NMR (DMSO) spectrum : delta 0.83(3H,t), 1.17 to 1.32(4H,m), 1.94 to 2.07(2H,m), 4.43(1H,t), 6.79(1H,t), 7.33(1H,d), 7.47(1H,s), 7.69(1H,d), 8.84(1H,s).

This compound is used as the starting material in Example 1.A.3.

B. By hydrolysis of the corresponding esters by the Claisen transformation.

1. 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoic acid.

4.3 g (17.5 mmole) of methyl 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoate (prepared in example 1.B.1.) dissolved in 20 ml of methanol and 21 ml of a 1N aqueous solution of sodium hydroxide are heated under reflux for 3 hours. The methanol is evaporated under reduced pressure and the aqueous solution is acidified to pH 5 by the addition of 21 ml of a 1N aqueous solution of hydrochloric acid. The precipitate formed is filtered off, the filtrate is concentrated to half its volume and the new precipitate which appears is also filtered off. The two crops are washed with hexane and dried under reduced pressure. 3.16 g of practically pure 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzoic acid are obtained.

Yield : 78%

NMR (DMSO + CF_3COOH) spectrum : delta 3.78(3H,s), 4.07(2H,s), 6.96 to 7.82(4H,m), 8.91(1H,s).

The product obtained is used as such to prepare the corresponding benzamide (Example 5.1.).

The following compound has been prepared in the same way.

2. 3-[(1H-imidazol-4-yl)methyl]-2-n-propoxybenzoic acid.
It is obtained from methyl 3-[(1H-imidazol-4-yl)methyl]-2-n-propoxybenzoate (prepared in example 1.B.3.).
The product obtained is used as such to prepare the corresponding benzamide (Example 5.2.).

C. By hydrolysis of the corresponding esters obtained by the Friedel-Crafts reaction.
2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoic acid and 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoic acid (hydrochloride).
181 g (1.35 mole) of 1H-imidazole-4-methanol hydrochloride are added in portions to a mixture of 156 ml (1.2 mole) of methyl 2-hydroxybenzoate and 675 g of polyphosphoric acid heated to 80°C.
The reaction mixture is maintained at this temperature for 288 hours with good stirring. The mixture is then decomposed on ice, and extracted twice with toluene. The aqueous phase is adjusted to pH 9.5 by the addition of 790 ml of saturated aqueous solution of sodium hydroxide. The mineral salts which precipitate are removed by filtration and washed with methanol. This methanolic washing solution is added again to the aqueous phase and the resulting mixture is concentrated with partial elimination of the methanol. The solution is then adjusted to pH 10.3 by addition of a 10N aqueous solution of sodium hydroxide, and is heated at 100°C for one and a half hours so as to saponify the esters. The aqueous solution is neutralized to pH 7.5 by addition of 10N hydrochloric acid, filtered on Norit and the filtrate is evaporated under reduced pressure. The residue is taken up three times in succession in a toluene-ethanol mixture and dried by azeotropic distillation. It is then partially dissolved in hot methanol and the insoluble mineral salts are removed by filtration. The filtrate is

evaporated under reduced pressure, the residue is redissolved in a minimum of water and purification is then carried out by passing through a column of Amberlite IR93 (height of the column: 60 cm; diameter: 8 cm; equivalence: 2.64 mole). Excess 1H-imidazole-4-methanol, together with its polymers, are eluted with water (the pH of the eluate varies from 11.2 to 7.3). Elution is then continued with a 4% aqueous solution of hydrochloric acid. The acid eluate (9 litres) is adjusted to pH 7.7 by addition of a saturated aqueous solution of sodium hydroxide and is then evaporated under reduced pressure. The residue thus obtained is once again dried by azeotropic distillation with a toluene-ethanol mixture and is then taken up in 1.6 litres of acetonitrile. It is then filtered. The residue on the filter (129 g) is chromatographed on silica (800 g, 15 μm) after having been previously deposited on 300 g of silica (0.2 to 0.5 mm) (eluent : 75:25 v/v ethyl acetate-ethanol). 5.99 g of 2-hydroxy-3-[1H-imidazol-4-yl)methyl]-benzoic acid are thus obtained. M.Pt.: 245-252°C (water).

Analysis for $C_{11}H_{10}N_2O_3$ in %

calc.:	C 60.56	H 4.59	N 12.04
found :	60.32	4.69	12.41

At the same time, 31 g of 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoic acid are obtained. Its hydrochloride, used as starting material in Example 1.A.1., melts at 254-258°C (methanol-diethyl ether).

Analysis for $C_{11}H_{10}N_2O_3.HCl$ in %:

calculated:	C 51.87	H 4.32	N 11.0	Cl 13.40
found :	51.65	4.24	10.45	13.73

Example 3. Preparation of the starting 2-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitriles of formula V.

1. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzonitrile.

1.a. Ethyl 4-benzyloxy-2-[(1H-imidazol-4-yl)methyl]-3-oxo-butanoate.

182 g (0.77 mole) of ethyl 4-benzyloxy-3-oxo-butanoate are added at once, at a temperature of

10°C, to a solution of 16.9 g (0.735 mole of sodium in 590 ml of absolute ethanol.
The mixture is stirred for 45 minutes at ambient temperature, it is then cooled to -45°C and a solution of 53.6 g of (0.35 mole) of 4-chloromethyl-1H-imidazole hydrochloride in 300 ml of absolute ethanol is added thereto, at once. The mixture is allowed to return to ambient temperature and is stirred for 1 hour. Subsequently the suspension is evaporated to dryness. The residue is taken up in a solution of 35 ml of concentrated hydrochloric acid in 900 ml of water, and is then extracted several times with diethyl ether. The aqueous phase is neutralized with a solution of 18 g of sodium hydroxide in 200 ml of water and is then extracted several times with ethyl acetate. The organic phases are washed successively with cold water and with a saturated aqueous solution of sodium chloride. It is dried over sodium sulphate and evaporated under reduced pressure. 107 g of practically pure ethyl 4-benzyloxy-2-[(1H-imidazol-4-yl)methyl]-3-oxo-butanoate are obtained.
Yield :97%.
NMR (DMSO) spectrum : delta 1.11(3H,t), 2.98(2H,m), 4.05(2H,q), 4.08(1H,m), 4.25(2H,dd), 4,47(2H,s), 6.75(1H,s), 7.25 to 7.39(5H,m), 7.47(1H,d).

1.b. Ethyl 4-benzyloxy-3-hydroxy-2-[(1H-imidazol-4-yl)methyl]-butanoate.
An ice cold solution of 6.03 g (0.16 mole) of sodium borohydride in 25 ml of water, is added at once to a solution of 101.2 g (0.32 mole) of ethyl 4-benzyloxy-2-[(1H-imidazol-4-yl)methyl]-3-oxo-butanoate in 600 ml of ethanol cooled to -20°C. The mixture is allowed to return to ambient temperature and is stirred for one hour. Subsequently, 25 ml of acetone are added. The solution is evaporated to dryness and the residue is taken up in 500 ml of water. It is extracted several times with ethyl acetate. The organic phases are washed with water

and with a saturated aqueous solution of sodium chloride. They are dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent: 93.5:6:0.5 v/v/v dichloromethane-methanol-ammonia). 95.8 g of ethyl 4-benzyloxy-3-hydroxy-2-[(1H-imidazol-4-yl)methyl]-butanoate are obtained (mixture of diastereoisomers). Yield: 94%. NMR ($CDCl_3$) spectrum : delta 1.15 and 1.16(3H,2t), 2.90 to 3.05(3H,m), 3.51 to 3.58(2H,m), 3.96 to 4.11(3H,2q+1m), 4.51 and 4.53(2H,2s), 6.73 and 6.75(1H,2s), 7.25 to 7.36(5H,m).

1.c 4-hydroxy-3-[(1H-imidazol-4-yl)methyl]-dihydro-2(3H)-furanone hydrochloride.
93.9 g (0.295 mole) of ethyl 4-benzyloxy-3-hydroxy-2-[(1H-imidazol-4-yl)methyl]-butanoate dissolved in 500 ml of absolute ethanol and 65 ml of a 6.8N ethanolic solution of hydrochloric acid, are subjected to hydrogenolysis in the presence of 5 g of 10% palladium on carbon under a hydrogen pressure of 3.5 bars. The catalyst is then filtered off and the solvent is removed at 65°C under reduced pressure. 67.1 g of 4-hydroxy-3-[(1H-imidazol-4-yl)methyl]-dihydro-2(3H)-furanone hydrochloride are obtained (mixture of diastereoisomers). The yield is practically quantitative.
The product obtained is used as such in the following step.

1.d. 3-[(1H-imidazol-4-yl)methyl]-2(5H)-furanone.
67.1 g (0.295 mole) of 4-hydroxy-3-[(1H-imidazol-4-yl)methyl]-dihydro-2(3H)-furanone hydrochloride are heated at 160°C for 75 minutes under a pressure of 0.0013 mbar, then cooled and taken up in 125 ml of absolute ethanol. It is neutralized by addition of 70 ml of a 5N ethanolic solution of ammonia. The suspension is filtered off and the solvent is removed under reduced pressure. The residue is

purified by chromatography on silica gel (eluent 91.5:8:0.5 v/v/v dichloromethane-methanol-ammonia). After recrystallization from acetonitrile, 27.5 g of 3-[(1H-imidazol-4-yl)methyl]-2(5H)-furanone are obtained. Yield : 53% (calculated on steps 1c and 1d together). M.Pt. : 123°C.

NMR ($CDCl_3$) spectrum : delta 3.63(2H,q), 4.79(2H,q), 6.90(1H,d), 7.25(1H,quintuplet), 7.52(1H,d).

1.e. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzonitrile.

63 ml (0.45 mole) of anhydrous triethylamine and 57 ml (0.45 mole) of trimethylchlorosilane are successively added to a suspension of 24.6 g (0.15 mole) of 3-[1H-imidazol-4-yl)methyl]-2(5H)-furanone in 225 ml of anhydrous acrylonitrile. The mixture is heated under reflux (72 to 74°C) for 4 hours. It is then evaporated under reduced pressure. The residue is treated at once with 75 ml of concentrated hydrobromic acid and is maintained at 80°C for 2 minutes. The solution is then poured onto ice, diluted by addition of 300 ml of ethyl acetate and 300 ml of water and then neutralized with solid sodium bicarbonate. It is filtered on Celite and the filtrate is extracted several times with ethyl acetate. The organic phases are washed with water and with a saturated aqueous solution of sodium chloride, then dried over sodium sulphate and evaporated under reduced pressure. The residue obtained is triturated in diethyl ether. 22.8 g of 2-hydroxy-3-[(1H-imidazol-4-yl(methyl]-benzonitrile are obtained. Yield: 76%.

NMR (DMSO) spectrum : delta 3.90(2H,s), 6.88(1H,t), 7.06(1H,s), 7.41(1H,dd), 7.47(1H,dd), 7.99(1H,d).

Its hydrochloride melts at 245°C.

2. 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzonitrile.

2.a. Ethyl 4-benzyloxy-2-[1-(1H-imidazol-4-yl)ethyl]-3-oxo-butanoate.

This compound is prepared as described in 1.a. above starting from ethyl 4-benzyloxy-3-oxo-butanoate and from 4-(1-chloroethyl)-1H-imidazole. Yield: 68% (mixture of diastereoisomers).

NMR ($CDCl_3$) spectrum : delta 1.10 and 1.22(3H,2t), 1.33 and 1.36(3H,2d), 3.60 to 3.72(1H,m), 3.93 to 4.20(3H,m), 4.47 and 4.55(1H,2s), 6.70 and 6.74(1H,2s), 7.26 to 7.35(5H,m), 7.41 and 7.45(1H,s+d).

2.b. Ethyl 4-benzyloxy-3-hydroxy-2-[1-(1H-imidazol-4-yl)ethyl]-butanoate.

This compound is prepared as described above, by reduction of ethyl 4-benzyloxy-2-[1-(1H-imidazol-4-yl)ethyl]-3-oxo-butanoate. Yield: 91% (mixture of diastereoisomers).

Mass spectrum : 332(M+), 314, 287, 211, 181, 135, 95, 91.

2.c. 4-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-dihydro-2(3H)-furanone hydrochloride.

This compound is prepared as described in 1.c. above, by hydrogenolysis of ethyl 4-benzyloxy-3-hydroxy-2-[1-(1H-imidazol-4-yl)ethyl]-butanoate. The yield is practically quantitative. A mixture of diastereoisomers is obtained and is used as such in the following step.

2.d. 3-[1-(1H-imidazol-4-yl)ethyl]-2(5H)-furanone.

75.1 g (0.32 mole) of 4-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-dihydro-2(3H)-furanone hydrochloride in 30 ml of ethylene glycol are heated at 170°C for one hour under a pressure of 13.3 mbar. The solvent is then removed under a pressure of 0.0013 mbar. The residue is taken up in 300 ml of absolute ethanol and is neutralized by addition of 63.2 ml of a 5N ethanolic solution of ammonia. The suspension is filtered off and the solvent is evaporated under reduced pressure. The residue is purified by

chromatography on silica gel (eluent: 91.5:8:0.5 v/v/v dichloromethane-methanol-ammonia). After recrystallization from acetonitrile, 41.9 g of 3-[1-(1H-imidazol-4-yl)ethyl]-2(5H)-furanone are obtained. Yield:74% (calculated on steps 2.c and 2.d. together). M.Pt.: 127-129°C.
NMR (DMSO) spectrum : delta 1.40(3H,d), 3.72(1H,q). 4.84(2H,t), 6.80(1H,t), 7.35(1H,q), 7.51(1H,s).

2.e 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzonitrile.
56 ml (0.4 mole) of anhydrous triethylamine and 50.7 ml (0,4 mole) of trimethylchlorosilane are successively added to a suspension of 17.8 g (0.1 mole) of 3-[1-(1H-imidazol-4-yl)ethyl]-2(5H)-furanone in 150 ml of anhydrous acrylonitrile. The mixture is heated under reflux for 3 and a half hours. The reaction mixture is then evaporated under reduced pressure. The residue is treated at once with 50 ml of concentrated hydrochloric acid and is maintained at 80°C for 2 minutes. The solution is then poured onto ice, neutralized with a saturated aqueous solution of sodium bicarbonate and extracted several times with ethyl acetate. The organic phases are washed with water and with a saturated aqueous solution of sodium chloride, then dried over sodium sulphate and evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent: 93.5:6:0.5 v/v/v dichloromethane-methanol-ammonia. 17.6 g of practically pure 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzonitrile are obtained. Yield: 83%. M.Pt.: 172°C.
NMR (DMSO): delta 1.52(3H,d), 4.21(1H,q), 6.86(1H,t), 7.02(1H,s), 7.41(1H,dd), 7.44(1H,dd), 7.85(1H,s).

Example 4. Preparation of the 1-(1H-imidazol-4-yl)alkyl benzamides of Formula I by reaction of the esters of Formula II with a nitrogen compound of Formula III.

1. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride.

A stream of ammonia gas, dried over potassium hydroxide, is passed into a solution of 18.1 g (78 mmole) of methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate (prepared in Example 1.B.2. and Example 1.A.4.) in 400 ml of anhydrous methanol for one night. It is then heated under reflux for 2 hours. The reaction mixture is then evaporated under reduced pressure and the residue is purified by chromatography on silica gel (eluent : 89.5:10:0.5 v/v/v dichloromethane-methanol-ammonia). 16.6 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide are obtained.

Yield : 98%. M.Pt. : 197.6°C

Analysis for $C_{11}H_{11}N_3O_2$ in % :

calculated :	C 60.83	H 5.07	N 19.35
found:	60.91	5.06	19.32

The amide, treated in ethanol with 1.2 equivalent of hydrochloric acid, gives a hydrochloride with a yield of 73%. M.Pt. : 287.8°C.

Analysis for $C_{11}H_{11}N_3O_2.HCl$ in % :

calculated :	C 52.07	H 4.73	N 16.57	Cl^- 14.00
found:	52.04	4.76	16.54	13.94

2. 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzamide.

This compound is prepared as described in 1. above, starting from ethyl 2-hydroxy-5-[(1H-imidazol-4-yl)-methyl]-benzoate hydrochloride (prepared in Example 1.A.1.). The reaction mixture is stirred for three days at ambient temperature. The product of the reaction is purified by chromatography on silica gel (eluent : 85:15 v/v dichloromethane-methanol).

M.Pt. : 180-185°C (isopropyl alcohol).

Analysis for $C_{11}H_{11}N_3O_2$ in % :

calculated:	C 60.83	H 5.07	N 19.35
found:	60.71	5.25	19.01

3. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide hydrochloride.

6.96 g (30 mmole) of methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate (prepared in Example 1.B.2.) and 60 ml of methylamine dissolved in 350 ml of ethanol, are heated in an autoclave at 75°C for 3 hours. The mixture is evaporated under reduced pressure. The residue is taken up in water and extracted three times with ethyl acetate. The organic phase is dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent : 91.5:8.0:0.5 v/v/v dichloromethane-methanol-ammonia).

After the solvents have evaporated, the product thus obtained is crystallized from ethyl acetate. 4.95 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide are obtained. Yield : 71%.

The amide, treated in a mixture of ethanol and ether with 1.2 equivalent of hydrochloric acid, yields 4.7 g of hydrochloride.

Yield : 59%. M.Pt. : 233.9°C.

Analysis for $C_{12}H_{13}N_3O_2.HCl$ in % :

calculated :	C 53.83	H 5.23	N 15.70
found:	53.74	5.17	15.55

4. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzohydrazide

A mixture of 10 g (43.1 mmole) of methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate (prepared in Example 1.B.2.) and 4.31 g (86.2 mmole) of hydrazine hydrate, dissolved in 100 ml of methanol, is heated under reflux for 13 hours. 2.15 g (43.1 mmole) of hydrazine hydrate are added again and heating under reflux is maintained for another 24 hours. The mixture is then evaporated under reduced pressure. The residue is taken up in 100 ml of water (pH = 8). The solution is saturated with sodium chloride and extracted with ethyl acetate. The organic phase is dried over sodium sulphate, and the

solvent is evaporated under reduced pressure. The residue is crystallized from ethanol. 6.1 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzohydrazide, recrystallizable from methanol, are obtained.
Yield : 61%. M.Pt. : 189.7°C
Analysis for $C_{11}H_{12}N_4O_2$ in %

calculated :	C 56.88	H 5.21	N 24.13
found :	56.91	5.24	24.00

5. 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride.
A solution of 2 g of ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoate (prepared in Example 1.A.2.) in 50 ml of methanol, through which a stream of gaseous ammonia is passed, is stirred for 90 hours at ambient temperature and in the presence of a catalytic amount of 20 mg of sodium methoxide. The methanol is then evaporated and the residue is purified by chromatography on silica gel (eluent : 8.5:1:0.5 v/v/v dichloromethane-methanol ammonia). The product obtained is converted into the hydrochloride in a solution of hydrochloric acid in ethanol in the presence of diethyl ether. 1.2 g of 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride are obtained.
Yield : 68%. M.Pt - 240-243°C.
Analysis for $C_{12}H_{13}N_3O_2.HCl$ in % :

calculated :	C 53.85	H 4.86	N 15.70	Cl^- 13.27
found :	54.0	4.88	15.73	13.17

The amide obtained after purification by chromatography on silica gel is resolved into its two enantiomers by chromatography on a chiral phase of α-glycoprotein (eluent: 1:99 v/v isopropyl alcohol-phosphate buffer 0.02M, pH 7). Each of the enantiomers of the amide is then converted into the corresponding hydrochoride according to the method indicated above.
There are thus obtained in almost equal amounts :
a) hydrated (+)-2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride. M.Pt.: 107.8°C (water).
$[\alpha]_D^{25}$ = + 82.04° (c = 1, methanol).

NMR (DMSO) spectrum : delta 1.57(3H,d), 3.30(5H,m), 4.56(1H,q), 6.83(1H,t), 7.23(1H,dd), 7.40(1H,s), 7.82(1H,dd), 7.92(1H,m), 8.51(1H,m), 8.98(1H,d), 13.5 to 14.5(2H,m).

b) hydrated (-)-2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride.

M.Pt.: 107.4°C (water).

$[\alpha]_D^{25}$ = - 79.13° (c = 1, methanol).

The NMR spectrum is identical to that of the other isomer.

6. 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide.

This compound is prepared according to the method described in 3. above, starting from ethyl 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzoate hydrochloride (prepared in Example 1.A.1.) and from methylamine. The base is previously liberated from the hydrochloride by a slight excess (1.2 equivalent) of sodium methoxide. The product obtained after evaporation of the solvent is purified by chromatography on silica gel (eluent : 97.5:12:0.5 v/v/v dichloromethane-ethanol-ammonia).

Yield : 67% (after recrystallization from ethanol).

M.Pt. : 219.5°C.

Analysis for $C_{12}H_{13}N_3O_2$ in % :

calculated :	C 62.32	H 5.67	N 18.17
found :	62.23	5.65	18.06

NMR (DMSO) spectrum : delta 2.80(3H,d), 3.27(1H,s), 3.76(2H,s), 6.67(1H,s), 6.80(1H,d), 7.23(1H,dd), 7.49(1H,s), 7.87(1H,d), 8.80(1H,s), 11.8(1H,s)

7. 1-[2-hydroxy-5-[(1H-imidazol-4-yl)methyl]benzoyl]-pyrrolidone.

A solution of 300 mg of ethyl 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]benzoate hydrochloride (prepared in Example 1.A.1) in 5 ml of pyrrolidone is heated under reflux for 30 minutes. Excess amine is removed under reduced pressure and the residue is purified by chromatography on silica (eluent : 88.5:11:0,5 v/v/v dichloromethane-ethanol-ammonia). 120 mg of 1-[2-hydroxy-5-[(1H-imidazol-4-yl)methyl]benzoyl]-pyrrolidone are obtained.

M.Pt. : 96-98°C. Yield : 36%.

NMR (DMSO) spectrum : delta 1.81(4H,s), 3.35(4H,s), 3.74(2H,s), 6.70(1H,s), 6.78(1H,d), 7.04(1H,d), 7.08(1H,dd), 7.50(1H,s), 9.85(1H,s), 11.8(1H,s).

8. 5-tert-butyl-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide.

This compound is prepared as decribed in 2. above, starting from methyl 5-tert-butyl-2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate hydrochloride (prepared in Example 1.C.1.).

Yield : 22.7%. M.Pt. : 209-211°C (tetrahydrofuran).

Analysis for $C_{15}H_{19}N_3O_2$ in % :

calculated :	C 65.91	H 7.00	N 15.37
found :	65.42	7.06	15.14

9. 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride.

This compound is prepared as in 1. above, starting with methyl 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate (prepared in Example 1.C.2.). A stream of gaseous ammonia is passed for three hours through the solution which is maintained at ambient temperature and this is then evaporated. The residue is recrystallized from dioxane. Yield 81%.

The amide, treated in ethanol with 1.2 equivalent of hydrochloric acid, is converted into the hydrochloride with a yield of 73%. M.Pt. : 290.3°C (decomp).

Analysis for $C_{11}H_{11}N_3O_3.HCl$ in % :

calculated :	C 48.99	H 4.49	N 15.58	Cl^- 13.15
found :	48.79	4.43	15.44	13.16

10. 2,6-dihydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide hydrochloride.

This compound is prepared as described in 9. above, starting from methyl 2,6-dihydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzoate (prepared as in Example 1.C.3.). The residue is recrystallized from toluene. Yield : 85%.

The amide, treated in a mixture of ethanol and diethyl ether with 1.1 equivalent of hydrochloric acid, is converted into the hydrochloride.

Yield : 77% (after recrystallization from water).

M.Pt.: 288.8°C (decomp.)

Analysis for $C_{12}H_{13}N_3O_3$.HCl in % :

calculated :	C 50.80	H 4.97	N 14.81	Cl^- 12.50
found :	50.68	4.92	14.67	12.09

11. 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzamide hydrochloride.

A solution of 6.1 g (23.4 mmole) of ethyl 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzoate (prepared in Example 1.C.4.) in 400 ml of liquid ammonia, is heated in an autoclave at 60°C for 72 hours. The mixture is then evaporated under reduced pressure and the residue is purified by chromatography on silica gel (eluent : 80:20:0.5 v/v/v ethyl acetate-ethanol-ammonia). 3.3 g of 6-hydroxy-3-[(1H-imidazol-4-yl)methyl]-2-methylbenzamide are obtained. Yield : 61%.

The amide, treated in ethanol with 1.1 equivalent of hydrochloric acid, is converted into the hydrochloride. Yield 66% (after recrystallization from water).

M.Pt.: 262.8°C

Analysis for $C_{12}H_{13}N_3O_2$.HCl in % :

calculated :	C 53.84	H 5.27	N 15.70	Cl^- 13.24
found :	54.22	5.29	15.74	13.12

12. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzamide hydrochloride.

This compound is prepared as described in 11. above, starting from 2.0 g (7.68 mmole) of ethyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzoate (prepared in Example 1.C.4.) and from 12 ml of liquid ammonia. The mixture is heated at 60°C for 24 hours and is then evaporated under reduced pressure. The crude amide is treated without purification, with 1.1 equivalent of hydrochloric acid in a mixture of ethanol and diethyl ether. The hydrochloride is recrystallized from tetrahydrofuran. Yield : 49%. M.Pt.: 164.8°C (mixture of amorphous and crystalline products).

Analysis for $C_{12}H_{13}N_3O_2HCl$ in % :

calculated :	C 53.84	H 5.27	N 15.70	Cl^- 13.24
found :	52.55	5.30	15.65	13.92

13. N,2-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride monohydrate.
A solution of 5 g (125 mmole) of sodium hydroxide in 15 ml of water is added dropwise to a mixture of 4.1 g (25 mmole) of hydroxylamine sulphate and 25 g of crushed ice. When the temperature has returned to 0°C, 0.5 g of solid sodium sulphite is added, followed by 6.15 g (25 mmoles) of ethyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate. After solution is complete, the reaction mixture is neutralized with 20.8 ml of a 6N aqueous solution of hydrochloric acid. The white precipitate which separates is filtered off, washed with water and purified by chromatography on silica gel (eluent : 76:20:2:2 v/v/v/v dichloromethane-methanol-acetic acid-water). The acetate obtained after evaporation of the solvents is taken up in 30 ml of water to which are added 5 ml of concentrated hydrochloric acid. The N,2-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride precipitates in the form of the monohydrate. 4.8 g of pure product are obtained.
Yield 55%. M.Pt. : 240°C (decomp.).
Analysis for $C_{11}H_{11}N_3O_3.HCl.H_2O$ in % :

calculated :	C 45.92	H 4.90	N 14.61	Cl^- 12.32
found :	46.33	4.63	14.69	12.57

The ethyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzoate used as starting material, is prepared according to the method described in Example 7 of European Patent Application 269.599 in the name of the applicant.

14. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzamide.
This compound is prepared as indicated in 2. above, starting from methyl 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-4-methylbenzoate hydrobromide (prepared in Example 1.C.5.). The reaction product is purified by chromatography on silica gel (eluent : 95:5:0.5 v/v/v dichloromethane-methanol-ammonia).
Yield : 44%. M.Pt. : 172-178°C (diethyl ether).
Analysis for $C_{12}H_{13}N_3O_2$ in % :

calculated :	C 62.33	H 5.62	N 18.18
found :	62.42	5.61	18.08

15. 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzamide hydrochloride.
This compound is prepared as indicated in 5. above, starting from ethyl 2-hydroxy-3-[1-(1H-imidazol-4-yl)-pentyl]-benzoate (prepared in Example 1.A.3.). The residue obtained after evaporation of the solvent is dissolved in a 2.5N ethanolic solution of hydrochloric acid and the 2-hydroxy-3-[1-(1H-imidazol-4-yl)pentyl]-benzamide hydrochloride precipitates after addition of diethyl ether. Yield : 50%.
NMR (DMSO) spectrum : 0.83(3H,t), 1.08 to 1.34(4H,m), 3.3 to 3.5(2H,m), 4.44(1H,t), 6.82(1H,t), 7.37 to 7.40(2H,s+d), 7.82(1H,d), 8.97(1H,s).

The following compounds have been prepared in the same way :

16. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N,N-dimethylbenzamide.
M.Pt. : 208°C.
Analysis for $C_{13}H_{16}N_3O_2$ in % :

calculated :	C 63.67	H 6.12	N 17.14
found :	63.58	6.06	17.09

17. 2-hydroxy-N-(2-hydroxyethyl)-3-[(1H-imidazol-4-yl)-methyl]-benzamide hydrochloride.
M.Pt. : 200.6°C.
Analysis for $C_{13}H_{15}N_3O_2.HCl$ in % :

calculated :	C 52.44	H 5.38	N 14.12
found :	52.49	5.36	13.98

Example 5. Preparation of the 1-(1H-imidazol-4-yl)alkyl benzamides of Formula I by reaction of the esters of Formula IV with a nitrogen compound of Formula III.

1. 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzamide hydrochloride.
A suspension of 3.1 g (13.4 mmoles) of 3-[(1H-imidazol-4 yl)methyl]-2-methoxybenzoic acid (prepared in Example 2.B.1) and 4.06g (40.2 mmoles) of triethylamine, in 30 ml

of dry dichloromethane, is cooled to 0°C. 4.36 g (40.2 mmoles) of ethyl chloroformate in solution in 10 ml of dry dichloromethane are added thereto. After this addition, the mixture is stirred further for half an hour at 0°C, and then for another half an hour at ambient temperature. A stream of gaseous ammonia, dried over potassium hydroxide, is then passed through the reaction mixture for one night. The mixture is then heated under reflux for half an hour, the solvent is evaporated under reduced pressure, and the residue is purified by chromatography on silica gel (eluent : 89:10:1 v/v/v dichloromethane-methanol-ammonia). 2.9 g of 3-[(1H-imidazol-4-yl)methyl]-2-methoxybenzamide, which crystallizes from acetonitrile, are obtained.
Yield : 95%.
The amide, treated with 1.2 equivalent of hydrochloric acid in ethanol, is converted into the hydrochloride.
M.Pt. : 160.5°C (isopropyl alcohol).
Analysis for $C_{12}H_{13}N_3O_2$ in % :

calculated :	C 53.84	H 5.27	N 15.73
found :	53.94	5.30	15.81

The following compound has been prepared in the same way :

2. 3-[(1H-imidazol-4-yl)methyl]-2-n-propoxybenzamide.
This compound is prepared from 3-[(1H-imidazol-4-yl)-methyl]-2-n-propoxybenzoic acid (prepared in Example 2.B.2) with a yield of 52%.
M.Pt. : 161°C.
Analysis for $C_{14}H_{17}N_3O_2$ in % :

calculated :	C 64.86	H 6.56	N 16.22
found :	64.93	6.60	16.14

Example 6. Preparation of the 1-(1H-imidazol-4-yl)alkyl benzamides of Formula I by hydrolysis of the 2-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitriles of Formula V.

1. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide.
13.1 g (66 mmoles) of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzonitrile (prepared in Example 3.1.) are stirred in 50 ml of an 80% by volume aqueous solution

of sulphuric acid, until solution is complete. The mixture is then heated at 65°C for 3 hours. The reaction mixture is poured onto ice and neutralized with sodium bicarbonate. It is then filtered and the filtrate is extracted several times with ethyl acetate. The organic phases are washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated under reduced pressure. The residue is purified by chromatography on silica gel (eluent : 84:15:1 v/v/v dichloromethane-methanol-ammonia). 9.8 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide are obtained, this compound being identical to that obtained in Example 4.1. Yield: 68%.

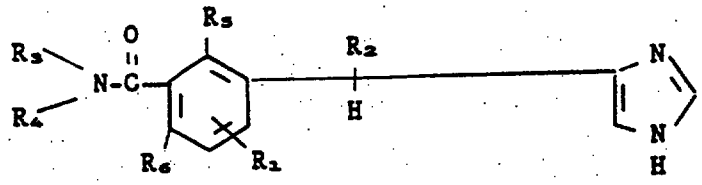
2. 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide.
A suspension of 1.07 g (5 mmoles) of 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzonitrile (prepared in Example 3.2.) in 4 ml of an 80% by volume aqueous solution of sulphuric acid, is stirred at 65°C for 3 hours. The reaction mixture is then poured onto ice, neutralized with sodium bicarbonate and extracted several times with ethyl acetate. The organic phases are dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is taken up in 50 ml of a 6N aqueous solution of hydrochloric acid and then neutralized with a 1N aqueous solution of sodium hydroxide. The precipitate which separates is filtered off, washed with water and with diethyl ether and dried under reduced pressure. 0.7 g of practically pure 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide is obtained. Yield : 70%.
The hydrochloride of the compound obtained is identical to that prepared in Example 4.5.

3. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride.
2 g of 2-hydroxy-3-[1H-imidazol-4-yl)methyl]-benzonitrile (prepared in Example 3.1) are added to 4 ml of water in 40 ml of methanol previously saturated at -10°C with a stream of gaseous hydrogen chloride. The mixture is

stirred at ambient temperature for 24 hours. The solution is then concentrated under reduced pressure and the residue is heated at 75°C for 3 hours. The latter is then recrystallized twice from water. 1.5 g of 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide hydrochloride are obtained, this compound being identical to the compound obtained in Example 4.1. Yield : 59%.

Claims for the Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Substituted 1-(1H-imidazol-4-yl)alkyl-benzamides, their optical isomers and their racemic mixtures, having the general formula



(I)

in which

R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkyl radical,

R_3 represents a hydrogen atom, an alkyl or a hydroxyalkyl radical, an amino or hydroxyl group,

R_4 represents a hydrogen atom or an alkyl radical, or

R_3 and R_4 taken together with the nitrogen atom to which they are attached, represent a heterocyclic radical selected from the group consisting of the pyrrolidino, piperidino and morpholino radicals, and

R_5 and R_6, which may be the same or different, each represents a hydrogen atom, a hydroxyl group, an alkyl or alkoxy radical,

at least one of the symbols R_5 and R_6 being other than a a hydrogen atom, all the alkyl and alkoxy radicals having 1 - 4 carbon atoms,

as well as their non-toxic pharmaceutically acceptable acid addition salts.

2. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.



3. 2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

4. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-N-methylbenzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

5. 2,6-dihydroxy-3-[(1H-imidazol-4-yl)methyl]-benzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

6. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-6-methylbenzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

7. 2-hydroxy-5-[(1H-imidazol-4-yl)methyl]-benzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

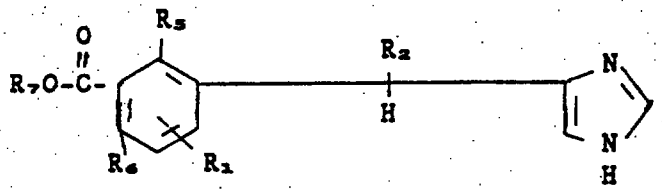
8. 2-hydroxy-3-[(1H-imidazol-4-yl)methyl]-benzohydrazide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

9. (+)-2-hydroxy-3-[1-(1H-imidazol-4-yl)ethyl]-benzamide according to Claim 1 and its non-toxic, pharmaceutically acceptable acid addition salts.

10. Process for the preparation of substituted 1-(1H-imidazol-4-yl)alkyl-benzamides and their salts such as defined in Claim 1, characterized in that :

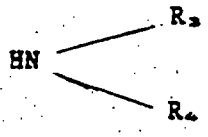
* C L M S *

a) An alkyl 1-(1H-imidazol-4-yl)alkyl-benzoate of the formula



(II)

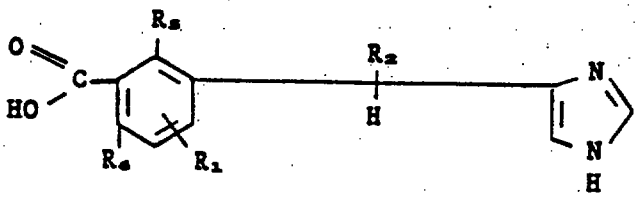
in which R_1, R_2, R_5 and R_6 have the meanings given in Claim 1 and R_7 represents an alkyl radical having 1 to 4 carbon atoms, is reacted with a nitrogen compound of the formula



(III)

in which R_3 and R_4 have the meanings given in Claim 1; or

b) in order to prepare the 1-(1H-imidazol-4-yl)alkyl-benzamides of the general formula I, in which R_5 and R_6 each represents a hydrogen atom, an alkyl or an alkoxy radical having 1 to 4 carbon atoms, at least one of the symbols R_5 and R_6 being other than a hydrogen atom, a 1-(1H-imidazol-4-yl)alkyl-benzoic acid of the formula

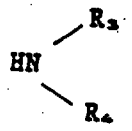


(IV)

in which R_1 and R_2 have the meanings given in Claim 1 and R_5 and R_6 have the meanings given above, is reacted with a

* C L M S *

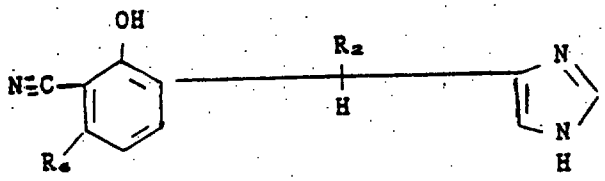
nitrogen compound of the formula



(III)

in which R_3 and R_4 have the meanings given in Claim 1; or

c) in order to prepare the 1-(1H-imidazol-4-yl)alkyl-benzamides having the general formula I in which R_1, R_3 and R_4 are hydrogen atoms, R_5 represents a hydroxyl group and R_6 represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, a 2-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitrile of formula



(V)

in which R_2 has the meaning given in Claim 1 and R_6 has the meaning given above, is hydrolysed in acid medium ; and

d) optionally, the 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I thus obtained are converted into their non-toxic, pharmaceutically acceptable acid addition salts.

11. 1-(1H-imidazol-4-yl)alkyl-benzamides according to any of Claims 1 to 9 or one of their non-toxic, pharmaceutically acceptable acid addition salts for use in therapy as anti-ischaemic agents.

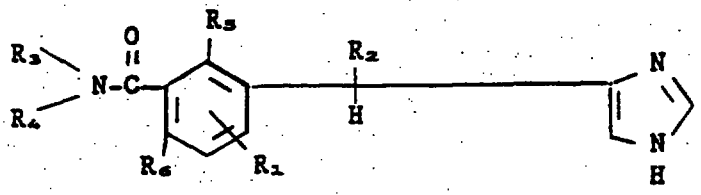
* C L M S *

12. 1-(1H-imidazol-4-yl)alkyl-benzamides according to any of Claims 1 to 9 or one of their non-toxic, pharmaceutically acceptable acid addition salts for use in the treatment or the prevention of disorders associated with an abnormal increase in catecholamine levels.

13. Therapeutic compositions containing a therapeutically effective amount of a 1-(1H-imidazol-4-yl)alkyl-benzamide according to any of Claims 1 to 9 or one of its non-toxic, pharmaceutically acceptable acid addition salts, in association with solid or liquid pharmaceutical excipients.

Claims for the Contracting States : ES, GR

Process for the preparation of substituted 1-(1H-imidazol-4-yl)alkyl-benzamides, their optical isomers and their racemic mixtures, having the general formula



(I)

in which

R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkyl radical,

R_3 represents a hydrogen atom, an alkyl or a hydroxyalkyl radical, an amino or hydroxyl group,

R_4 represents a hydrogen atom or an alkyl radical, or

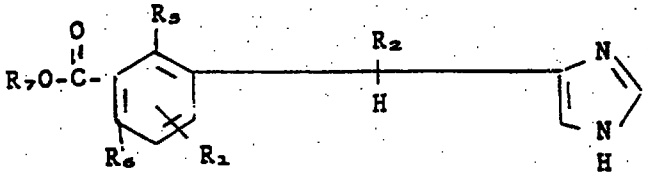
R_3 and R_4 taken together with the nitrogen atom to which they are attached, represent a heterocyclic radical selected from the group consisting of the pyrrolidino, piperidino and morpholino radicals, and

R_5 and R_6, which may be the same or different, each represents a hydrogen atom, a hydroxyl group, an alkyl or alkoxy radical, at least one of the symbols R_5 and R_6 being other than a hydrogen atom, all the alkyl and alkoxy radicals having 1 - 4 carbon atoms,

as well as their non-toxic pharmaceutically acceptable acid addition salts characterized in that:

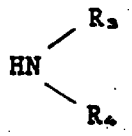
* C L M S *

a) An alkyl 1-(1H-imidazol-4-yl)alkyl-benzoate of the formula



(II)

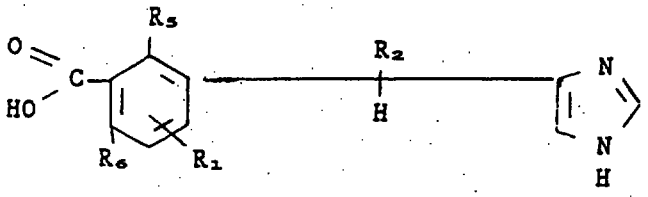
in which R_1, R_2, R_5 and R_6 have the meanings given above and R_7 represents an alkyl radical having 1 to 4 carbon atoms, is reacted with a nitrogen compound of the formula



(III)

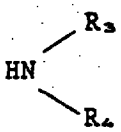
in which R_3 and R_4 have the meanings given above; or

b) in order to prepare the 1-(1H-imidazol-4-yl)alkyl-benzamides of the general formula I, in which R_5 and R_6 each represents a hydrogen atom, an alkyl or an alkoxy radical having 1 to 4 carbon atoms, at least one of the symbols R_5 and R_6 being other than a hydrogen atom, a 1-(1H-imidazol-4-yl)alkyl-benzoic acid of the formula



(IV)

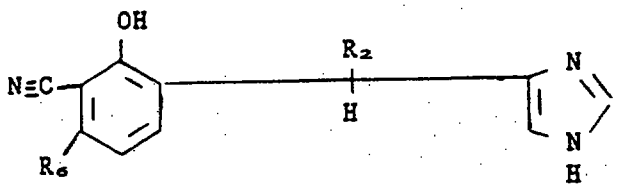
in which R_1, R_2 R_5 and R_6 have the meanings given above, is reacted with a nitrogen compound of the formula



(III)

in which R_3 and R_4 have the meanings given above; or

c) in order to prepare the 1-(1H-imidazol-4-yl)alkyl-benzamides having the general formula I in which R_1, R_3 and R_4 are hydrogen atoms, R_5 represents a hydroxyl group and R_6 represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, a 2-hydroxy-3-[1-(1H-imidazol-4-yl)alkyl]-benzonitrile of formula



(V)

in which R_2 and R_6 have the meanings given above, is hydrolysed in an acid medium; and

d) optionally, the 1-(1H-imidazol-4-yl)alkyl-benzamides of formula I thus obtained are converted into their non-toxic, pharmaceutically acceptable acid addition salts.

* C L M S *