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EUROPEAN PATENT APPLICATION

N° 91 402269.4

Copy of the English translation of the specification
and claims as originally filed.

PATENT OF INVENTION

3–Amidopyrazole derivatives, process for preparing these and pharmaceutical compositions containing them.

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In the name of: SANOFI

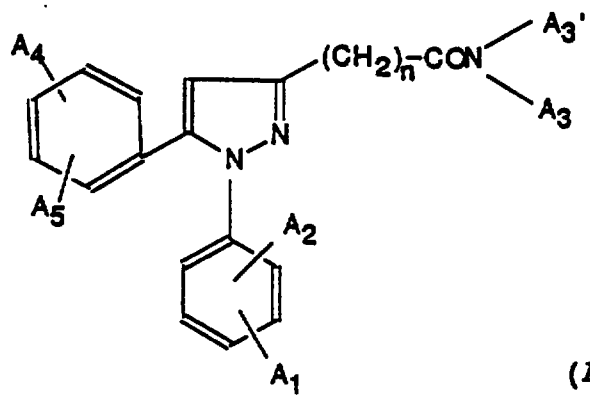
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The present invention relates to new pyrazole derivatives possessing an amide group substituted with an amino acid or one of its derivatives at position 3 and variously substituted in positions 1, 2, 4 or 5 of the pyrazole ring, to a process for preparing these and to pharmaceutical compositions containing the said pyrazole derivatives as an active ingredient.

The compounds according to the invention possess activity with respect to the central nervous system, the cardiovascular system or the gastrointestinal system.

A large number of pyrazole derivatives are described in the literature.

1,5-Diarylpyrazoles substituted at position 3 with an alkyl chain containing from 2 to 16 carbon atoms and variously substituted, in particular with an amide, and corresponding to the formula:

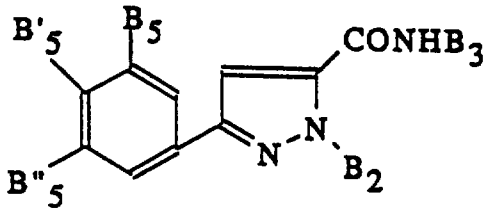


n=2 to 16

(A)

are described in European Patent 0,248,594 as possessing anti-inflammatory activity and activity with respect to the cardiovascular system.

Pyrazole derivatives of formula:

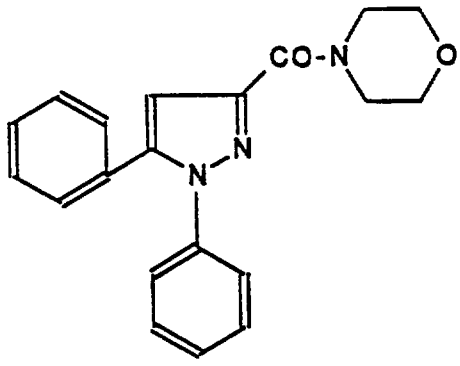


(B)

where B_2 represents either a hydrogen atom or a methyl group, B_3 represents, for example, an alkyl and B_5, B'_5 and $B"_5$ independently represent, for example, hydrogen, a halogen or a C_1-C_3 alkoxy, are described in British Patent

2,130,205 as being capable of use for the purpose of decreasing the blood uric acid level in mammals.

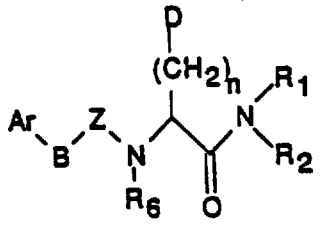
It is, moreover, described in Journal of the Chemical Society, 1973, 2532-2534 that 2-morpholino-5-phenyl-5-phenylazofuran salts rearrange to 1,5-diphenyl-pyrazoles substituted at position 3, of formula:



(C)

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Patent Application WO 89/02,431 describes new N-containing heterocyclic, in particular pyrazolyl, compounds of formula:



(D)

in which, for example:

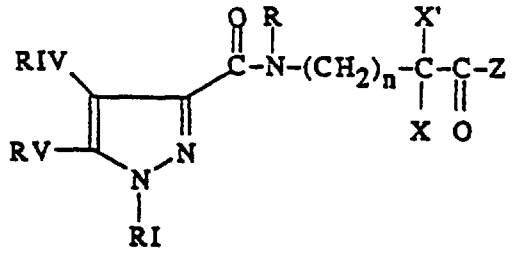
- Ar represents a pyrazolyl,
- B represents $(CH_2)_m$ with m = 0 to 4,
- Z represents -C=O, n = 1 to 3,
- D represents COR_3,
- R_1 and R_2 represent a hydrogen or a C_1-C_8 alkyl or together go to make up a cyclic amine.

These amidopyrazole amide derivatives of acyl-glutamic or -aspartic acid are described as possessing cholecystokinin-inhibiting properties.

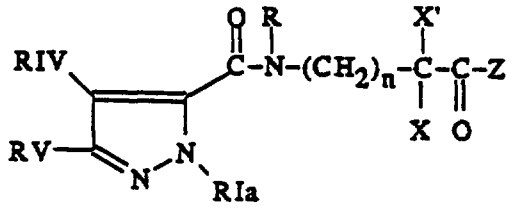
It has now been found that variously substituted derivatives of 3-amidopyrazole possess activity with respect to the central nervous system, and especially with respect to the neuropeptide-regulating systems,

displacing, for example, tritiated or iodinated neurotensin from its receptor.

Thus, the subject of the present invention, according to one of its aspects, is a 3-amidopyrazole of formula (I) or (I'):



(I)

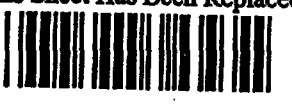


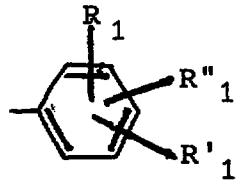
(I')

in which

- R_I represents:

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  - a group 

where R_1, R'_1 and $R"_1$ each independently represent a hydrogen atom, a halogen atom, a hydroxyl, a linear or branched C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a trifluoromethyl group, a trifluoromethoxy group, a nitro group, a carboxyl group or an amino group;

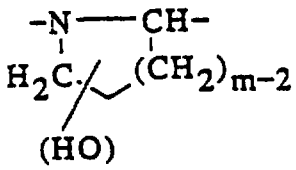
- a carboxyalkyl or alkoxycarbonylalkyl group in which the alkyls are C_1-C_4 groups;
- a cycloalkyl group in which the alkyls are C_3-C_6 groups;
- a tetrahydronaphthyl group;
- a pyridyl group;
- a naphthyl group substituted with R_1, R'_1 and $R"_1$ as defined above;
- a benzyl group substituted with R_1, R'_1 and $R"_1$ as

defined above;

- a cinnamyl group optionally substituted on the aromatic ring with a halogen, a hydroxyl or a C_1-C_4 alkoxy;
- a quinolyl or isoquinolyl group optionally substituted with R_1, R'_1 and R''_1 as defined above;
- a 2-benzothiazolyl group;
- a quinoxalinyldione group;
- a 1-phthalazinyl group;
- a benzothiadiazolyl group;
- a methylene group substituted with a 5- or 6-membered heterocyclic group such as, in particular, a pyridyl and a thienyl;

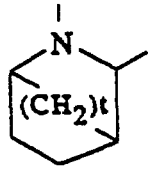
- R_{Ia} represents a benzyl group substituted with R_1, R'_1 and R''_1 as defined above;
- R represents hydrogen or a linear or branched C_1-C_4 alkyl;
- n represents 0, 1, 2 or 3;
- either X represents hydrogen and X' represents hydrogen; a linear or branched C_1-C_6 alkyl; an aryl; a C_1-C_4 aminoalkyl; a C_1-C_4 hydroxyalkyl; a carboxyalkyl in which the alkyl group is a C_1-C_4 group; an acetamidoalkylcysteine in which the alkyl group is a C_1-C_4 group; a guanidinoalkyl in which the alkyl group is a C_1-C_4 group; a nitroguanidinoalkyl in which the alkyl group is a C_1-C_4 group; a C_3-C_7 cycloalkyl; an arylalkyl in which the alkyl is a C_1-C_4 group and in which the aryl is optionally substituted with a halogen or a hydroxyl or with a C_1-C_3 alkyl; a heteroarylalkyl in which the heteroaryl represents an imidazolyl or an indolyl unsubstituted or substituted with a C_1-C_4 alkyl, with a hydroxyl or with a C_1-C_4 alkoxy and in which the alkyl is a C_1-C_4 group;
- or, when n is equal to zero, X represents hydrogen and X' and -N-R considered together form a ring, unsubstituted or substituted with a hydroxyl, of formula:

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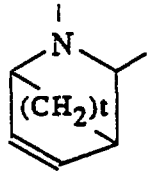
with m = 2,3 or 4

or a ring-system of formula:



with t = 1 or 2

or a ring-system of formula:

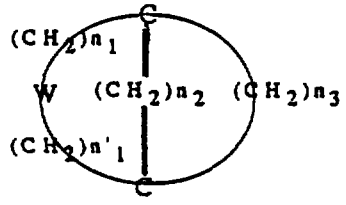


with t = 1 or 2

or an indolinyl, perhydroindole or 4,5,6,7-tetrahydro-thieno[2,3-c]pyrid-6-yl ring-system;

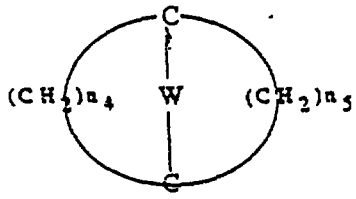
- or X and X' each independently represent a C_1-C_4 alkyl or a C_3-C_6 cycloalkyl; a phenyl;
- or X and X' are linked and form together a cycloalkyl group having 2 to 12 carbon atoms, optionally substituted with a C_1-C_3 alkyl;
- or X, X' and the carbon atom to which they are linked form an adamantyl group; an adamantyl group substituted with one or two methyl groups or with a hydroxyl, a C_1-C_3 alkoxy or a halogen atom; a 1-azaadamantyl group; a quinuclidinyl group; a 4-piperidyl group optionally N-substituted with a benzyl group; a 2,2,6,6-tetramethylpiperidyl group; a tetrahydronaphthyl group; a tetrahydropyran-4-yl or tetrahydrothiopyran-4-yl group; a 2,3-dihydro-4H-benzopyran-4-yl group; a 2,3-dihydro-4H-benzothiopyran-4-yl group; a group of formula a

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a

in which n_1 = 0 or 1, n'_1 = 1 or 2, n_2 = 1, n_3 = 2 or 3 and W represents a carbon atom or an oxygen atom, this group of formula a) being attached to -N(R)- and to -C(O)-Z as defined above through one carbon atom of one or other of the rings, or a group of formula b



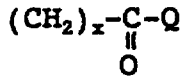
b

in which n_4 = 2, 3 or 4, n_5 = 2 or 3 and W represents a carbon or oxygen atom, this group of formula b) being attached to -N(R)- and to -C(O)-Z as defined above through one carbon atom of one or other of the two rings,

it being possible for the rings of the above groups a and b to be optionally substituted on one and/or other of the rings with one or two C_1-C_4 alkyl groups and it not being possible for the amino acid to be at the alpha-position with respect to W when W represents oxygen; a bicyclo[2.2.1]hept-5-en-2-yl group; an 8-oxabicyclo[3.2.1]oct-6-en-3-yl group; an 8-thiabicyclo-[3.2.1]oct-3-yl group;

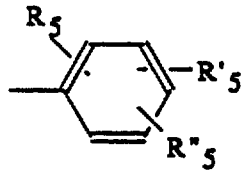
- or X represents hydrogen and X' is an adamantyl group; an adamantyl group substituted with one or two methyls, with a hydroxyl, a C_1-C_3 alkoxy or a halogen atom; a 1-azaadamantyl group; a group of formula a or b as defined above, it not being possible for the bond between these ring-systems and the carbon carrying -COZ and -N-R to be at the alpha-position with respect to W when the latter represents oxygen;
- Z represents a hydroxyl group or a C_1-C_6 alkoxy group; an oxygen atom substituted with a carboxylic acid-protecting group such as a tert-butyl, a

benzyl, a benzyl substituted with a halogen atom, a C_1-C_6 alkyl, a trifluoromethyl, a trifluoromethoxy or a carboxyl group; an amino group; a nitrogen atom substituted with a carboxyalkyl in which the alkyl is a linear or branched C_1-C_6 group, with the limitation that, if Z represents a nitrogen atom substituted as defined above and if n = 0, then, when X = H, X' cannot be a group:



in which x = 1 or 2 and Q is a hydroxyl, a free amino or amino substituted with a C_1-C_6 dialkyl or a C_1-C_6 alkoxy;

- R_{IV} represents a hydrogen atom, a halogen atom or a C_1-C_6 alkyl;
- R_V represents:

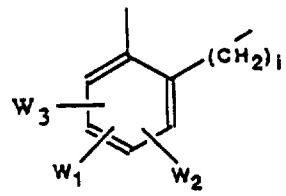
a group 

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where R_5, R'_5 and R''_5 each independently represent a hydrogen atom, a halogen atom, a linear or branched C_1-C_4 alkyl, a hydroxyl, a C_1-C_4 alkoxy, a nitro, a trifluoromethyl, a trifluoromethoxy, a cyano, an amino, a carboxyl, a C_1-C_4 carboxyalkyl or a phenyl;

- a naphthyl group unsubstituted or substituted with a C_1-C_4 alkyl;
- a pyridyl group;
- a styryl group unsubstituted or substituted with a C_1-C_4 alkyl;
- or alternatively R_{IV} and R_V considered together represent:

a group 

in which the phenyl group substitutes the pyrazole at position 5 and the group $-(CH_2)_i-$ in which i = 1

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to 3 substitutes the pyrazole at position 4, W_1, W_2 and W_3 substitute the benzene ring and independently represent hydrogen, a halogen or a hydroxyl group;

or one of its possible salts with organic or inorganic acids or with inorganic or organic bases.

In the present description, "aryl" denotes aromatic rings such as, for example, phenyl.

When the compounds (I) or (I') include an asymmetric carbon, the enantiomers form part of the invention.

When the compounds (I) or (I') contain a group of formula a) or b), the cycloaliphatic amino acids comprise both those for which the amine function is in the endo position with respect to the aliphatic ring system and those for which the amine function is in the exo position with respect to the aliphatic ring system.

The possible salts of the products of formula (I) or (I') according to the present invention comprise both those with inorganic or organic acids which permit an appropriate crystallisation or separation of the compounds of formula (I) or (I'), such as picric acid or oxalic acid, and those which form pharmaceutically acceptable salts such as the hydrochloride, hydrobromide, sulphate, hydrogen sulphate, dihydrogen phosphate, methanesulphonate, methyl sulphate, maleate, fumarate and 2-naphthalenesulphonate.

The possible salts of the products of formula (I) or (I') also comprise the salts with cations, for example the alkali metal or alkaline earth metal salts such as the sodium, potassium and calcium salts, the sodium salt being preferred, when the said product of formula (I) or (I') contains a carboxylic acid group.

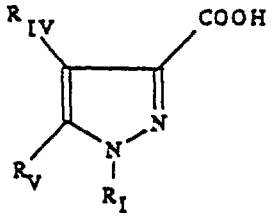
A particular class of the compounds of the invention consists of the compounds of formula (I) in which R_1 is either a naphthyl group or a phenyl group substituted with R_1, R'_1 and R''_1 as defined above, the other substituents being as defined above.

Another preferred group of the compounds of the invention consists of the compounds of formula (I) or (I') in which R_V represents a naphthyl or phenyl group

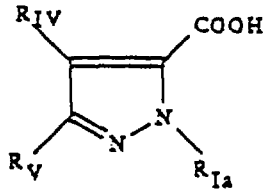
substituted with R_5, R'_5 and R''_5 as defined above, the other substituents being as defined above. Preferably, R_5, R'_5 or R''_5 is hydrogen or a C_1-C_4 alkoxy.

Another preferred group of the compounds of the invention consists of the compounds of formula (I) or (I') in which X, X' and the carbon atom to which they are linked form an adamantyl group, a group of formula a or of formula b as defined above.

According to another of its aspects, the present invention relates to a process for the preparation of the compounds of formula (I) and (I'), characterized in that a functional derivative of formula (II) or (II'):



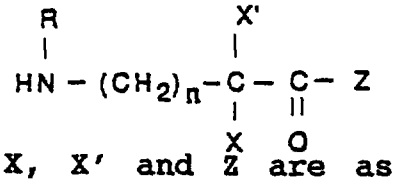
(II)



(II')

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in which R_I, R_{IV}, R_V and R_{Ia} are as defined above, is treated with an amino acid, optionally protected by the protective groups customary in peptide synthesis, of formula:



(V)

in which R, n, X, X' and Z are as defined above or optionally protected.

As a functional derivative of the pyrazolecarboxylic acid of formula (II) or (II'), it is possible to use the acid chloride, the anhydride, a mixed anhydride, an ester, an activated ester, for example the p-nitrophenyl ester, or the free acid judiciously activated, for example, with N,N-dicyclohexylcarbodiimide or with benzotriazolyl-N-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP).

The compounds (I) and (I') thus prepared may then be deprotected, where appropriate, to yield the corresponding free acids.

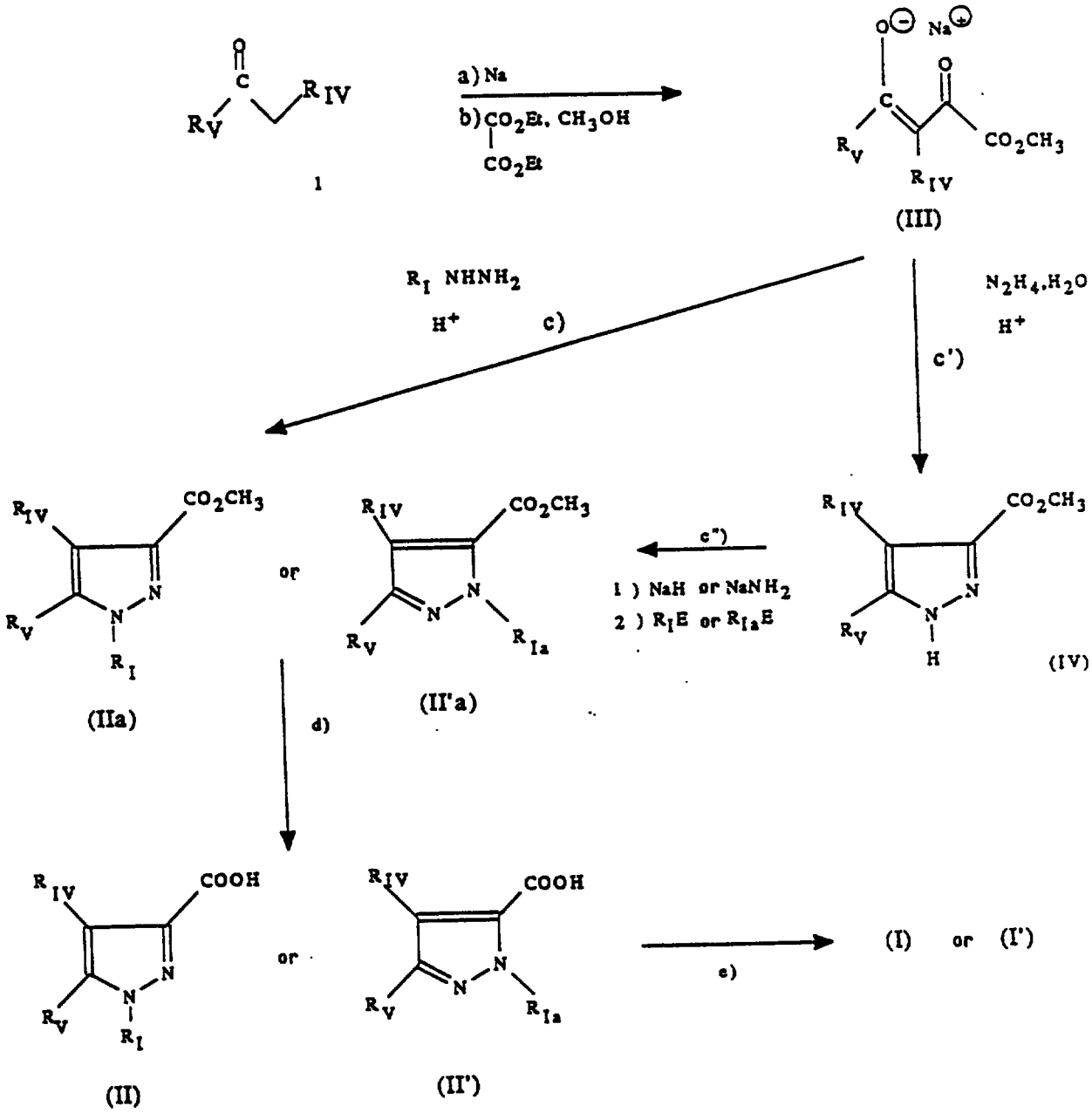
The esters (IIa) and (II'a) which are precursors of the carboxylic acids (II) and (II'), defined above,

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are synthesised by applying the method described in Chem. Pharm. Bull, 1984, 32, 4, 1577.

The process for preparing the compounds (I) or (I') via the esters (IIa) and (II'a) is represented by the following scheme:

SCHEME 1



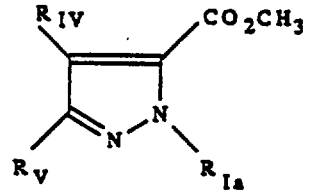
The first step a) consists in the preparation of the sodium enolates of a ketone of formula 1, in which R_V and R_{IV} are as defined above, which are reacted with an equimolar amount of ethyl oxalate (step b)) in an alkanol such as, for example, methanol, according to L. CLAISEN,

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Ber., 1909, 42, 59. After precipitation in ethyl ether, the sodium enolates (III) are separated by filtration.

The sodium enolates (III) thus prepared and an excess of hydrazine or of a hydrazine derivative R_I-$NHNH_2$ are then heated to reflux of acetic acid (step c)).

In the case where R_I represents a substituted or unsubstituted benzyl group R_{Ia}, there is obtained, during the condensation of the benzylhydrazine with the compounds (III), a mixture, in variable proportions depending on the nature and position of the substituents of R_V, of the compounds (IIa) and its isomer (II'a) of formula:



(II'a)

in which R_{Ia}, R_{IV} and R_V are as defined above.

The two isomers (IIa) and (II'a) may then be separated by column chromatography. On saponification of the esters, the pure isomeric acids are obtained, which acids are reacted, for example, with sulphinyl chloride. The acid chlorides are then condensed with the amino acids of formula (V) to yield the compounds (I) and (I') according to the invention (step e)).

A variant of the process, in the case where R_I is a benzyl or cinnamyl group, consists in the condensation of unsubstituted hydrazine with the compound (III) (step c')) to yield the 1H-pyrazole derivative (IV), which is then substituted in the presence of NaH or $NaNH_2$ with a group R_IE or $R_{Ia}E$ (stepc")), where E represents a group which can be eliminated such as a halogen, a p-toluenesulphonyloxy (tosyloxy) or a methanesulphonyloxy (mesyloxy).

The 3-amidopyrazole derivatives (I) and (I') which are subjects of the invention are then prepared from the pyrazole acids ——— by converting the ester derivatives (IIa) and (II'a) to their corresponding acids (II) or (II') by the action of an alkaline agent such as,

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for example, potassium hydroxide, followed by acidification (step d), then the corresponding compounds of formula (I) and (I') are prepared as described above.

If the amino acid contains a hydroxyl group as a substituent, the latter may be protected by an O-protecting group customarily used, and then deprotected according to the usual methods.

When the product of formula (I) or (I') possesses a basic function and is obtained in the form of a free base, the salification is performed by treatment with the chosen acid in an organic solvent. On treatment of the free base, dissolved, for example in an alcohol such as isopropanol, with a solution of the chosen acid in the same solvent, the corresponding salt is obtained, which salt is isolated according to conventional techniques. Thus, for example, the hydrochloride, hydrobromide, sulphate, hydrogen sulphate, dihydrogen phosphate, methanesulphonate, methyl sulphate, oxalate, maleate, fumarate or 2-naphthalenesulphonate is prepared.

When the compound of formula (I) or (I') possesses a basic function and is isolated in the form of one of its salts, for example the hydrochloride or oxalate, the free base may be prepared by neutralisation of the said salt with an inorganic or organic base such as sodium hydroxide or triethylamine, or with an alkali metal carbonate or bicarbonate such as sodium or potassium carbonate or bicarbonate.

When the product of formula (I) or (I') contains an acid group, the compound thereby obtained may be converted to a metal salt, in particular an alkali metal salt such as the sodium salt, or an alkaline earth metal salt such as the calcium salt, according to conventional processes.

The compounds (I) or (I') according to the invention were subjected to biochemical tests.

The same compounds (I) or (I') and their salts displace, at concentrations of less than one micromolar, [Tyr^3-iodinated] neurotensin from its receptor on guinea

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pig brain membranes, according to the method described by SADOUL J.L. et al., Biochemical and Biophysical Research Communications, 1984, 120, 3, 812-819.

The compounds of the present invention are of low toxicity; in particular, their acute toxicity is compatible with their use as a medicinal product. For such a use, an effective amount of a compound of formula (I) or (I') or of one of their pharmaceutically acceptable salts is administered to mammals.

The compounds (I) or (I') according to the invention are the first potential non-peptide synthetic medicinal products capable of binding to the neurotensin receptor and capable of being useful in pathological states associated with a dysfunction of the dopaminergic systems, for example as antipsychotics (D.R. HANDRICH et al., Brain Research, 1982, 231, 216-221 and C.B. NEMEROFF, Biological Psychiatry, 1980, 15-2, 283-302), and in disorders of the cardiovascular or gastrointestinal system.

Thus, the subject of the present invention, according to another of its aspects, is pharmaceutical compositions containing as active principles the compounds of formula (I) or (I') or their possible pharmaceutically acceptable salts.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal or rectal administration, the active principles may be administered, in unit dosage forms, as a mixture or with conventional pharmaceutical carriers, to animals and human beings. The appropriate unit dosage forms comprise forms for oral administration such as tablets, gelatin capsules, powders, granules and oral solutions or suspensions, forms for sublingual and buccal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration.

In order to obtain the desired effect, the dose of active principle can vary between 1 and 1,000 mg per day, and preferably between 2 and 500 mg.

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Each unit dose can contain from 1 to 250 mg of active principle, and preferably from 2 to 125 mg, in combination with a pharmaceutical carrier. This unit dose may be administered 1 to 4 times per day.

When a solid composition is prepared in the form of tablets, the active principle is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. It is possible to coat the tablets with sucrose or with other suitable substances, or they may alternatively be treated in such a way that they have a sustained or delayed activity and release a predetermined amount of active principle in continuous fashion.

A gelatin capsule preparation is obtained by mixing the active principle with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

A preparation in the form of syrup or elixir can contain the active principle together with a sweetener, preferably a zero-calorie sweetener, and methylparaben and propylparaben as antiseptic, as well as an agent imparting flavour and a suitable colouring.

The water-dispersible powders or granules can contain the active principle mixed with dispersing agents or wetting agents, or suspending agents, such as polyvinylpyrrolidone and the like, as well as with sweeteners or flavour correctors.

For rectal administration, suppositories are employed, which are prepared with binders melting at rectal temperature, for example cocoa butter or polyethylene glycols.

For parenteral administration, aqueous suspensions, isotonic saline solutions or sterile and injectable solutions are used, which contain pharmacologically compatible dispersing and/or wetting agents, for example propylene glycol or butylene glycol.

The active principle may also be formulated in the form of microcapsules, optionally with one or more carriers or additives.

The examples which follow illustrate the

invention without, however, limiting it.

The instantaneous melting points (m.p.) of the crystallised products were measured on a Kofler heating bench and are expressed in degrees Celsius. In the tables which follow, the following abbreviations have been used:

CH	cyclohexane
CH_2Cl_2	dichloromethane
EtOH	ethanol
Et_2O	diethyl ether
Hx	hexane
Pn	pentane
iPr_2O	diisopropyl ether
iPrOH	isopropanol
AcOEt	ethyl acetate
MeOH	methanol
C^*	means configuration of the asymmetric carbon.

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The following abbreviations are used in the NMR spectra:

M	multiplet
S	singlet
BS	broad singlet
D	doublet
Har	aromatic H

o : ortho; m : meta

PREPARATION OF THE SYNTHESIS INTERMEDIATES

A. Preparation of the hydrazine derivatives (R_1NHNH_2).

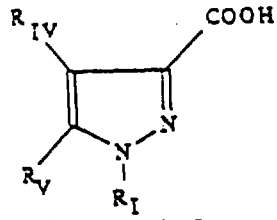
A large number of hydrazine derivatives are commercial products

The others were prepared according to known methods by diazotisation of the corresponding aromatic amine followed by reduction of the diazonium salt. Thus, as an example, the preparation of the following may be mentioned:

- 5,6,7,8-tetrahydro-1-naphthylhydrazine, according to R. FUSCO et al., Gazz. Chim. Ital., 1974, 104, 813-817;
- 8-hydrazinoquinoline, according to A. ALBERT et al., J. Chem. Soc., 1967, 1533-1541;
- 5-hydrazinoquinoline and 5-hydrazinoisoquinoline,

according to M.G. FERLIN et al., Il Farmaco, 1989, 44 (12), 1141-1155.

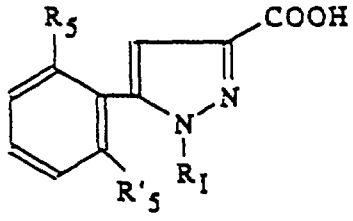
B. Preparation of the pyrazolecarboxylic acids (II):

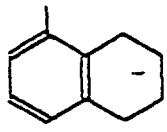
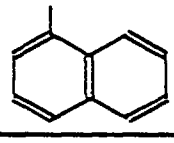
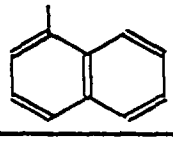
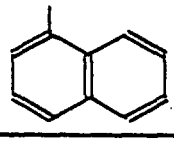
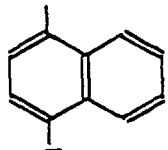


This preparation is carried out according to the above described method.

Table A below shows, as an example and without implied limitation, the characteristics of acids of formula (II).

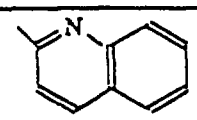
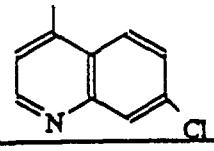
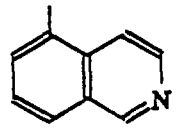
TABLE A



R_I	R_5	R'_5	M.p.; °C
	OCH_3	OCH_3	202
	CH_3	CH_3	>260
	OCH_3	OCH_3	211
	OC_2H_5	OC_2H_5	262
	OCH_3	OCH_3	220

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	OCH_3	OCH_3	241
	OCH_3	OCH_3	> 260
	OCH_3	OCH_3	> 260 (decomposition)

C. **Preparation of the amino acids.**

The non-commercial products are prepared according to the STRECKER synthesis (Ann., 75, 27, 1850) or according to the synthesis of H.T. BUCHERER et al., J. Pract. Chem., 1934, 141, 5, followed by a hydrolysis to yield the amino acids; for example, 2-amino-2-adamantanecarboxylic acid is prepared according to H.T. NASANTA et al., J. Med. Chem., 1973, 16 (7), 823.

α-Aminocycloalkanecarboxylic acids are prepared according to J.W. TSANG et al., J. Med. Chem., 1984, 27, 1663.

(R)- and (S)-Cyclopentylglycines are prepared by resolution of benzyloxycarbonylcyclopentylglycine.

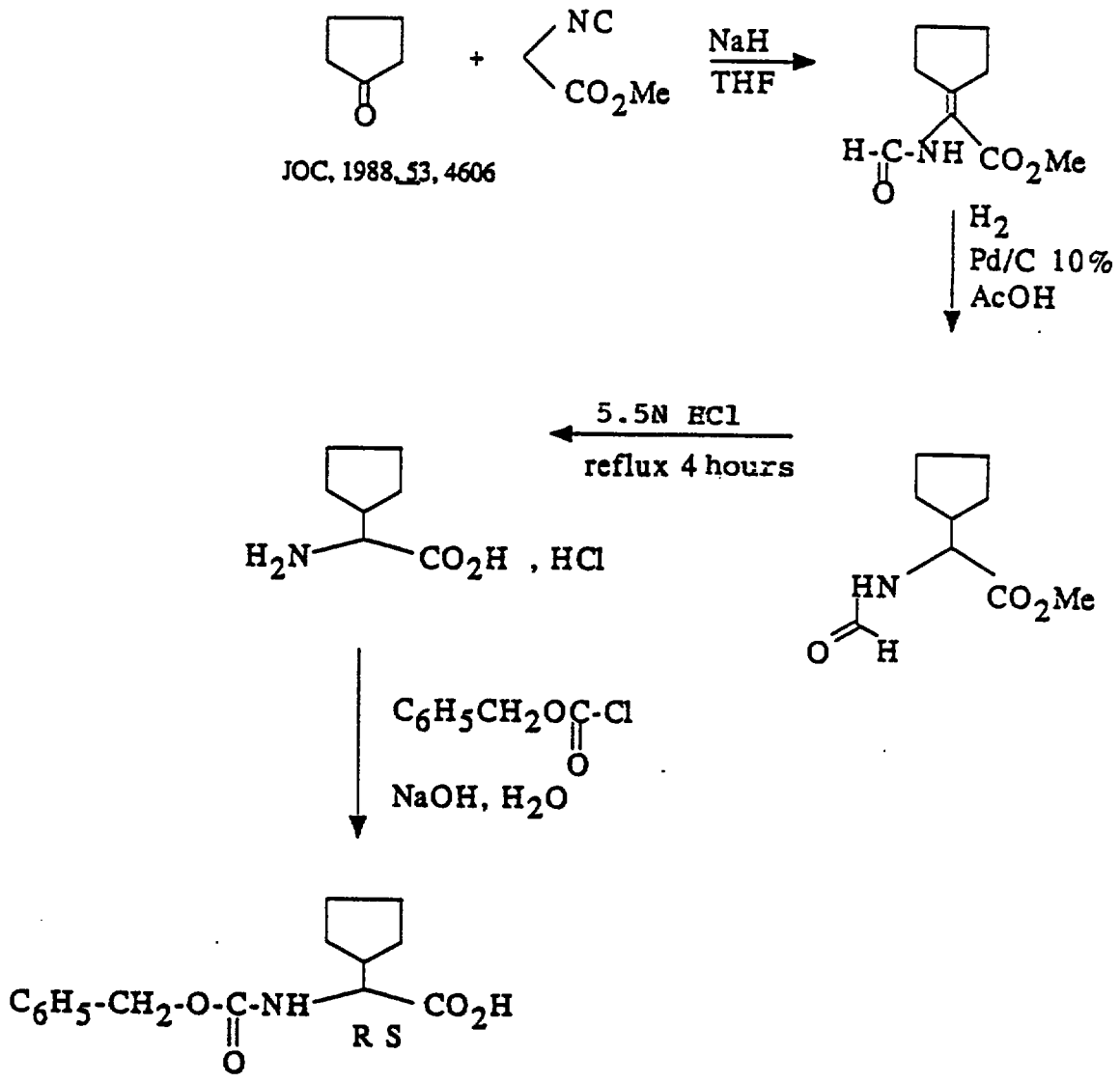
1) Preparation of racemic benzyloxycarbonylcyclopentylglycine

This compound is prepared by the following reaction scheme 2.

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SCHEME 2



2) (RS)-Cyclopentylglycine hydrochloride.

80% NaH (1.8 g) is dissolved in anhydrous THF (50 ml). A mixture of cyclopentanone (4.2 g) and methyl isocyanoacetate (5 g) in THF (50 ml) is added dropwise and with stirring. When the addition is complete, the mixture is left for 2 hours. It is cooled to 5°C and acetic acid in 10% aqueous solution (50 ml) is added slowly. The THF is evaporated off under vacuum. The aqueous residue is extracted with chloroform (3 x 120 ml). The organic phase is dried over Na_2SO_4 and concentrated under vacuum.

The residue is taken up with pentane, filtered

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off and washed with pentane.
The solid (7.6 g) is dissolved in acetic acid (100 ml). Palladium on charcoal (10% Pd) (3 g) is added and the mixture is stirred at atmospheric pressure and room temperature under hydrogen for 24 hours (1 litre of hydrogen is absorbed). The mixture is filtered through Celite, which is washed several times with acetic acid. The filtrate is evaporated under vacuum. The residue is taken up in 5.5 N hydrochloric acid (70 ml). The mixture is heated to reflux for 4 hours. It is concentrated to dryness, and the residue is treated azeotropically with toluene several times and dried under vacuum. The expected product is obtained.
m = 7.2 g
NMR D_2O: 8 H at 1.6 (M, ring $C\underline{H}_2$); 1 H at 2.20 (M, ring $C\underline{H}$); 1 H at 3.80 (D,J=7 $C\underline{H}CO_2H$); 3 H at 8.60 (BS, NH_3^+)

3) Acylation with benzyl chloroformate.
(RS)-Cyclopentylglycine hydrochloride (7.2 g) is dissolved in 2 N sodium hydroxide solution (65 ml). Benzyl chloroformate (8.5 g) in THF (30 ml) is added dropwise, cooling to 5°C. The mixture is left stirring overnight at room temperature. It is cooled in ice. It is acidified with concentrated HCl to pH 2 ($T \leq 5°C$). It is extracted with chloroform and the organic phase is dried and evaporated. The residue is taken up with pentane. (RS)-Benzyloxycarbonylcyclopentyl-glycine is obtained.
M.p. 110°C

4) Resolution of benzyloxycarbonylcyclopentylglycine.
Benzyloxycarbonylcyclopentylglycine (5.54 g) is dissolved in absolute ethanol (65 ml). (-)-(1R,2S,)-1,2-Diphenyl-1-ethanol-2-amine, prepared according to J. WEIJLARD et al., J. Am.

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Chem. Soc. 1951, 73, 1216, is added. The mixture is heated to dissolution. It is left to precipitate overnight and is filtered. 2.8 g of the salt (m.p. 175°C) are obtained. The mother liquors are kept.

The salt obtained is taken up with water (20 ml), HCl (30 ml) and ether (100 ml). The mixture is stirred to dissolution. The organic phase is separated after settling has taken place, dried and evaporated. Benzyloxycarbonylcyclopentylglycine is obtained, which is treated immediately with concentrated HCl (15 ml) and AcOH (15 ml). The mixture is heated to reflux for 3 hours. It is evaporated to dryness. The residue is taken up with dry ether, filtered off and dried. (S)-Cyclopentylglycine hydrochloride is obtained.

$[\alpha]_D^{25}$ = + 10.4° (c = 0.5, N HCl)

m = 0.6 g.

The mother liquors are evaporated to dryness and the residue is taken up with H_2O (50 ml), HCl (60 ml) and Et_2O (300 ml). The mixture is stirred and everything is dissolved. The ether phase is separated after settling has taken place, dried and evaporated. The benzyloxycarbonylcyclopentylglycine (4.3 g) is recovered and is placed in absolute ethanol (50 ml) with (+)-(1S,2R)-1,2-diphenyl-1-ethanol-2-amine (3.30 g). The mixture is heated to dissolution, left standing overnight and filtered. 4.15 g of salt are obtained.

M.p. 175°C

This salt is taken up with water (20 ml), N HCl (40 ml) and ether (200 ml). The mixture is stirred. The ether phase is dried and evaporated and the residue is then treated with concentrated HCl (10 ml) and acetic acid (100 ml). The mixture is heated to reflux for 3 hours and concentrated under vacuum and the residue is taken up with anhydrous ether to obtain (R)-cyclopentylglycine hydrochloride.

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m = 1.2 g

$[\alpha]_D^{25}$ = -10.5 (c = 0.85, N HCl)

Optical purity of the (R)-cyclopentylglycine:

0.10 g of the above hydrochloride are dissolved in absolute methanol. The mixture is cooled to -40°C, 0.5 ml of thionyl chloride is added and the mixture is left for 24 hours at room temperature. It is concentrated under vacuum, the residue is taken up in anhydrous chloroform (20 ml), and triethylamine (0.2 ml) and (S)-phenylmethyl isocyanate (0.074 ml) are added. The mixture is left for 24 hours and the chloroform is then evaporated off. The residue is chromatographed on silica gel; eluent: ethyl acetate. Concentration of the pure fractions yields 0.1 g of the methyl ester. The NMR spectrum in $CDCl_3$ shows, at around 3.8 ppm, the presence of two signals for $-CO_2CH_3$. Integration shows that the weaker signal represents 4%, the more intense signal 96%.

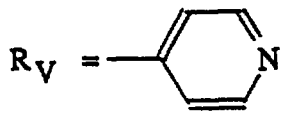
The enantiomeric excess is hence 92%.

It is also possible to prepare the cycloalkyl-α-amino acids of R or S configuration by stereospecific enzymatic hydrolysis of the corresponding racemic N-acetyl derivatives, according to J. HILL et al., J. Org. Chem., 1965, 1321.

EXAMPLE 1

(S)-2-{[1-Phenyl-5-(4-pyridyl)-3-pyrazolyl]carbonyl-amino}-4-methylpentanoic acid methyl ester.

(I): R=H; n=0; X'=H; $X=-CH_2-CH-(CH_3)_2$; $Z=OCH_3$; $R_I=C_6H_5$; R_{IV}=H;

R_V = 

0.35 g of 1-phenyl-5-(4-pyridyl)-3-pyrazolecarboxylic acid is dissolved in 5 ml of dimethylformamide in the presence of 0.45 ml of diisopropylethylamie (DIPEA) and 0.59 g of benzotriazolyl-N-oxytris(dimethylamino)-

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phosphonium hexafluorophosphate (BOP). 0.23 g (1 equivalent) of (S)-leucine methyl ester hydrochloride, dissolved in 0.4 ml of DIPEA, is then added and the reaction mixture is left overnight at room temperature. The solvents are concentrated under vacuum, the residual oil is extracted with dichloromethane and this solution is washed with water, then with sodium bicarbonate solution and again with water. The organic phase is dried over sodium sulphate and then concentrated under vacuum. The residue is chromatographed on silica gel; eluent: ethyl acetate.

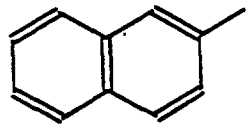
m = 0.18 g

H NMR spectrum of the compound 1: 3H at 8.82 (M, Har o to N and CONH); 5H at 7.50 (M, Phe Har); 3H at 7.27 (Har m to N and pyrazole H_4); 1H at 4.60 (M, α-Leu H); 3H at 3.77 (S, CO_2CH_3); 1H at 2.00 (M, γ-Leu H); 2H at 1.70 (M, β-Leu H); 6H at 1.00 (2D, Leu CH_3).

EXAMPLE 2

(S)-2-{[1-Phenyl-5-(2-naphthyl)-3-pyrazolyl]-carbonylamino}-3-phenylpropanoic acid.

(I): R=H; n=0; X'=H; X=$-CH_2-C_6H_5$; Z=OH; $R_I=C_6H_5$; R_{IV}=H;

R_V = 

Preparation of 5-(2-naphthyl)-1-phenyl-3-pyrazolecarboxylic acid chloride.

5 g of 5-(2-naphthyl)-1-phenyl-3-pyrazolecarboxylic acid are dissolved in 56 ml of toluene, and 3.5 ml of sulphinyl chloride are added dropwise to this solution. The mixture is heated to 90° for 2 1/2 h, then concentrated under vacuum. The residual oil is taken up twice in toluene and concentrated under vacuum.

m = 5 g

Preparation of the compound 2.

4.9 g of (S)-phenylalanine are added to 60 ml of 2N sodium hydroxide solution, and a solution of 4 g of the acid chloride prepared above, dissolved in 65 ml of tetrahydrofuran, is then added dropwise. The reaction mixture is left overnight at room temperature and then

concentrated under vacuum. The residue is taken up in water and the pH is adjusted to 1 by adding hydrochloric acid. The solution is extracted with dichloromethane and the organic phase is washed with water and with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated under vacuum. The residue is recrystallised from pentane.

m = 2 g

M.p. 226°C

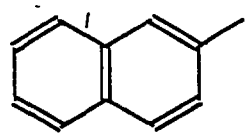
EXAMPLE 3

(S)-N,N-Diethyl-2-{[1-phenyl-5-(2-naphthyl)-3-pyrazol]-carbonylamino}-3-phenylpropanamide

(I): R=H; n=0; X'=H; X=$-CH_2-C_6H_5$; Z=$-N-(C_2H_5)_2$;

$R_1=C_6H_5$; R_{IV}=H;

R_V =



2 g of the product obtained according to Example 2, 0.88 g of dicyclohexylcarbodiimide (DCCI) and 1.14 g of 1-hydroxybenzotriazole (HOBT) are dissolved in 68 ml of tetrahydrofuran and the mixture is stirred for 3/4 hour at room temperature. 0.4 g of diethylamine is then added and the reaction mixture is left at room temperature for 24 hours.

The dicyclohexylurea is separated by filtration and the mother liquors are concentrated under vacuum. The residue is chromatographed on silica gel; eluent: ethyl acetate. The fractions of pure product are concentrated under vacuum and the residue is recrystallised from pentane.

m = 1.46 g

M.p. 70°C

EXAMPLE 4

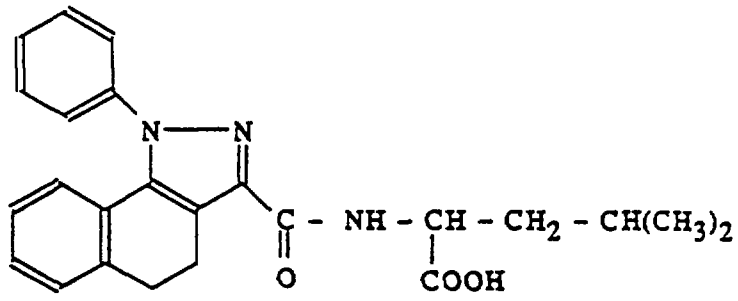
(S)-2-{(1-Phenyl-4,5-dihydrobenz[g]indazol-3-yl)carbonyl-amino}-4-methylpentanoic acid.

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(I):



A) β-Ketocarbethoxy-α-tetralone sodium salt.

This intermediate is prepared according to the method described by D. RAMESH et al. Indian Journal of Chemistry, 1989, 28B, 76-78.

B) 1-Phenyl-4,5-dihydrobenz[g]indazole-3-carboxylic acid ethyl ester.

8.04 g of the sodium salt obtained above are dissolved in 100 ml of acetic acid. 3.3 ml of phenylhydrazine are added and the reaction mixture is heated to reflux for 8 hours. The cooled mixture is poured into ice-cold water; a precipitate is separated by filtration and washed with water and then with pentane.

m = 10.5 g

C) 1-Phenyl-4,5-dihydrobenz[g]indazole-3-carboxylic acid.

9.5 g of the product obtained above are dissolved in 100 ml of methanol and 100 ml of water. 4.2 g of potassium hydroxide are added and the reaction mixture is heated to reflux for 5 hours. The mixture is poured into ice-cold water and the resulting mixture is then washed with ethyl acetate. The aqueous phase is acidified to pH 2 by adding hydrochloric acid, and a precipitate is separated by filtration and washed with water and then with pentane.

m = 7.3 g

D) 1-Phenyl-4,5-dihydrobenz[g]indazole-3-carboxylic acid chloride

2.8 g of the acid obtained above are dissolved in 100 ml of toluene, 2.2 ml of sulphinyl chloride are then added and the mixture is heated to 100°C for 5 hours. The

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solution is concentrated under vacuum, 20 ml of toluene are added and the mixture is concentrated under vacuum. The same operation is repeated twice.

E) Compound 4

0.88 g of (S)-leucine is dissolved in a solution of 1.33 g of sodium hydroxide in 20 ml of water. This solution is cooled, 0.99 g of the acid chloride prepared above, dissolved in 16 ml of tetrahydrofuran, is then added and the reaction mixture is left stirring at room temperature for 18 hours. The solution is concentrated under vaccum, and the residue is taken up in ice and acidified to pH 2 by adding hydrochloric acid and then extracted with ethyl acetate. The organic phase is dried over sodium sulphate, filtered and concentrated under vacuum. The residue is recrystallised from isopropyl ether.

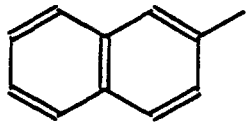
m = 1 g

M.p. 100°C

EXAMPLE 5

(S)-2-{[1-Benzyl-3-(2-naphthyl)-5-pyrazolyl]carbonyl-amino}-3-phenylpropanoic acid.

(I'): R=H; n=0; X'=H; X=$-CH_2-C_6H_5$; Z=OH; R_{Ia}=$-CH_2-C_6H_5$; R_{IV}=H;

R_V = 

A) The reaction of methyl 2-naphthoylpyruvate with benzylhydrazine hydrochloride yields a mixture of the following esters: 1-benzyl-5-(2-naphthyl)-3-pyrazolecarboxylic acid methyl ester and 1-benzyl-3-(2-naphthyl)-5-pyrazolecarboxylic acid methyl ester.

Chromatography on silica gel enables the two isomers to be separated. 1-Benzyl-5-(2-naphthyl)-3-pyrazolecarboxylic acid methyl ester is eluted first with a 50:50 (v/v) ethyl acetate/hexane mixture. 1-Benzyl-3-(2-naphthyl)-5-pyrazolecarboxylic acid methyl ester is eluted as a second fraction.

B) 1-Benzyl-3-(2-naphthyl)-5-pyrazolecarboxylic acid.

The acid was prepared by saponification of the ester obtained above.

C) 1-Benzyl-3-(2-naphthyl)-5-pyrazolecarboxylic acid chloride.

The acid chloride is prepared by the action of sulphinyl chloride on the above acid, and is not isolated.

D) Compound 5.

0.28 g of (S)-phenylalanine are dissolved in a cooled sodium hydroxide solution. A solution of 0.3 g of the acid chloride prepared above in 5 ml of THF is then added and the reaction mixture is left at room temperature for 24 hours. The THF is concentrated under vacuum, and the residue is taken up in water and neutralised by adding concentrated hydrochloric acid. The product is extracted with ethyl acetate and the organic phase is dried over sodium sulphate and concentrated under vacuum. The residue is recrystallised from cyclohexane.

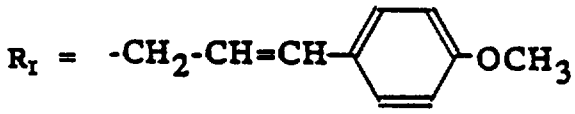
m = 1 g

M.p. 100°C

EXAMPLE 6

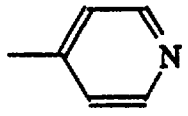
(S)-2-{[1-(4'-Methoxycinnamyl)-5-(4-pyridyl)-3-pyrazolyl]carbonylamino}-4-methylpentanoic acid methyl ester.

(I): R=H; n=0; X'=H; X=$-CH_2-CH-(CH_3)_2$; Z = OCH_3;

R_I =  ; R_{IV}=H;

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R_V = 

A) 1-(4'-Methoxycinnamyl)-5-(4-pyridyl)-3-pyrazolecarboxylic acid methyl ester.

4.6 g of 5-(4-pyridyl)-1H-pyrazole-3-carboxylic acid methyl ester are dissolved in 60 ml of dimethylformamide, 0.63 g of sodium hydride in 80% suspension in oil is then added and the reaction mixture is heated to 40°C for 1 hour. A solution of 5.2 g of

4'-methoxy-1-cinnamyl bromide, dissolved in 60 ml of dimethylformamide, is then added to the cooled mixture and the reaction mixture is left at room temperature for 12 hours. The dimethylformamide is concentrated under vacuum, the residue is taken up in water and extracted with ethyl acetate and the organic phase is dried over sodium sulphate, filtered and concentrated under vacuum. The residual oil is chromatographed on silica gel; eluent: 50:50 (v/v) ethyl acetate/cyclohexane. The fractions of pure product are concentrated under vacuum.

m = 2.6 g

M.p. 118°C

B) Compound 6

0.4 g of the acid obtained above is dissolved in 12 ml of dimethylformamide in the presence of 0.63 ml of DIPEA and 0.53 g of BOP. 0.22 g of (S)-leucine methyl ester hydrochloride, dissolved in 0.63 ml of DIPEA, is then added and the reaction mixture is left overnight at room temperature. The dimethylformamide is concentrated under vacuum and the residue is taken up in water. The product is extracted with ethyl acetate and the organic phase is dried over sodium sulphate, filtered and concentrated under vacuum. The residue is solidified in diisopropyl ether.

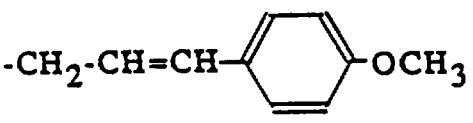
m = 0.15 g

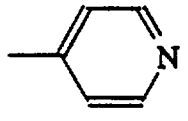
M.p. 172°C

EXAMPLE 7

(S)-2-{[1-(4'-Methoxycinnamyl)-5-(4-pyridyl)-3-pyrazolyl]carbonylamino}-3-phenylpropanoic acid sodium salt.

(I): R=H; n=0; X'=H; X=$-CH_2-C_6H_5$; Z=O^- Na^+

R_I =  ; R_{IV}=H;

R_V = 

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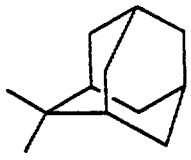


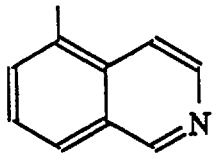
Using the procedure described in Example 6, and replacing (S)-leucine methyl ester hydrochloride by (S)-phenylalanine methyl ester hydrochloride, the methyl ester is obtained, which ester is hydrolysed to a sodium salt with 0.9 equivalent of sodium hydroxide in 10 ml of 96° strength ethanol. The mixture is left overnight at room temperature and concentrated under vacuum and the residue is washed with ether. After filtration, the compound 7 is obtained.

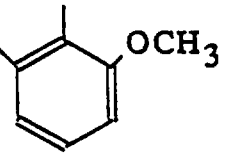
M.p. 137°C

EXAMPLE 8

2-{[1-(5-Isoquinolyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]carbonylamino}-2-adamantanecarboxylic acid.

(I): R=H ; n=0 ; $X-\overset{|}{\underset{|}{C}}-X'$ =  ;

Z = OH ; R_I =  ; R_{IV} = H ;

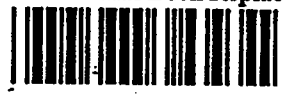
R_V = 

0.75 g of 2-amino-2-adamantanecarboxylic acid is dissolved in 20 ml of pyridine. 1.4 g of 1-(5-isoquinolyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolecarboxylic acid chloride, dissolved in 20 ml of dichloromethane, are added and the reaction mixture is left overnight at room temperature. It is concentrated under vacuum, the residue is taken up with pH 2 buffer, the precipitate is filtered off and rinsed with diisopropyl ether.

m = 0.4 g

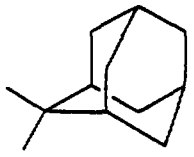
M.p. > 260°C

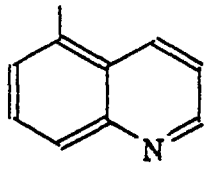
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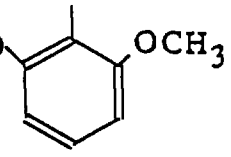


EXAMPLE 9

2-{[1-(5-Quinolyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]-carbonylamino}-2-adamantanecarboxylic acid.

(I): R=H ; n=0 ; $X-\overset{|}{\underset{|}{C}}-X'$ =  ;

Z = OH ; R_I =  ; R_{IV} = H ;

R_V = 

0.23 g of 2-amino-2-adamantanecarboxylic acid, 0.5 g of 1-(5-quinolyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolecarboxylic acid chloride and 0.7 g of potassium hydroxide are dissolved in 25 ml of dichloromethane in the presence of 0.1 g of Aliquat 336®.

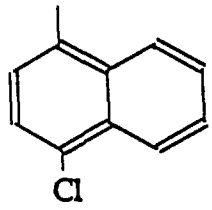
The reaction mixture is stirred overnight at room temperature, 0.7 g of potassium hydroxide is added and the mixture is stirred for 4 hours. It is filtered and 0.2 g of the expected product is obtained.

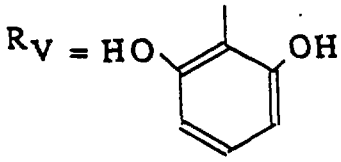
M.p. > 260°C

EXAMPLE 10

(S)-2-{[1-(4-Chloro-1-naphthyl)-5-(2,6-dihydroxyphenyl)-3-pyrazolyl]carbonylamino}hexanoic acid.

(I): R=H ; n=0 ; X' = H ; X = $(CH_2)_3-CH_3$

Z = OH ; R_I =  ; R_{IV} = H ;

R_V = 

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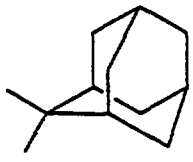
0.3 g of 2-{[1-(4-chloro-1-naphthyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]carbonylamino}hexanoic acid is dissolved in 6.7 ml of dichloromethane and the mixture is cooled to -70°C. 5.7 ml of boron tribromide, dissolved in 20 ml of dichloromethane, are added dropwise and the reaction mixture is left for 2 hours at -70°C. It is allowed to return to room temperature, and 12 ml of water are then added while cooling. Concentrated NaOH is added to pH 14. The aqueous phase is washed with ether and brought to pH 2, the product is extracted with ethyl acetate and the organic phase is dried over sodium sulphate, filtered and evaporated. The residue is crystallised from diisopropyl ether.

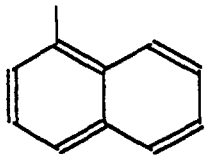
m = 0.13 g

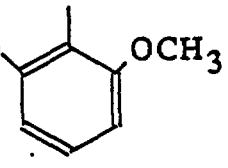
M.p. > 260°C

EXAMPLE 11

2-{[1-(1-Naphthyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]-carbonylamino}-2-adamantanecarboxylic acid.

(I) : R=H ; n = 0 ; $X-\overset{|}{C}-X'$ =  ;

Z = OH ; R_I =  ; R_{IV} = H ;

R_V = 

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0.107 g of sodium hydroxide in 1.36 ml of water and 0.51 ml of tetrahydrofuran are cooled to 0°C. 0.52 g of 2-amino-2-adamantanecarboxylic acid is added in a single portion, and 0.53 g of 1-(1-naphthyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolecarboxylic acid chloride, dissolved in 3 ml of tetrahydrofuran, is then added dropwise. The mixture is left for 10 minutes, and the same amount of

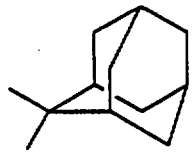
the above acid chloride, in 3 ml of tetrahydrofuran, is added again; simultaneously, 1.32 ml of 2N sodium hydroxide are added. The reaction mixture is left for 4 days at room temperature; successively, ice-cold water is added and concentrated hydrochloric acid is added to pH 1, and the precipitate is filtered off. The crystals are washed with diisopropyl ether.

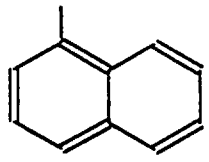
m = 0.48 g

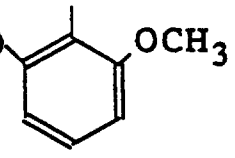
M.p. > 260°C

EXAMPLE 12

Methyl 2-{[1-(1-naphthyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]carbonylamino}-2-adamantanecarboxylate.

(I) : R=H ; n=0 ; $X-\overset{|}{\underset{|}{C}}-X'$ =  ;

$Z = OCH_3$; R_I =  ; $R_{IV} = H$;

R_V = 

0.5 g of the compound prepared in Example 11 is dissolved in 34.6 ml of anhydrous tetrahydrofuran and 4 ml of dimethylformamide. 3.5 ml of water and 0.208 g of caesium carbonate are added and the reaction mixture is left at room temperature for 1 hour. It is concentrated under vacuum and treated azeotropically with toluene. The residue is taken up in 5 ml of tetrahydrofuran. 0.6 ml of methyl iodide is added and the reaction mixture is left for 1 hour at room temperature. It is concentrated under vacuum, the residue is taken up in water, the mixture is stirred and the precipitate is separated by filtration. The precipitate is washed with water and with pentane.

m = 0.38 g

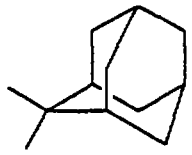
M.p. 242-244°C

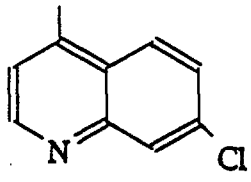
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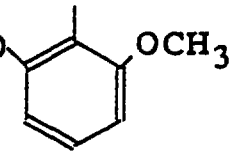


EXAMPLE 13

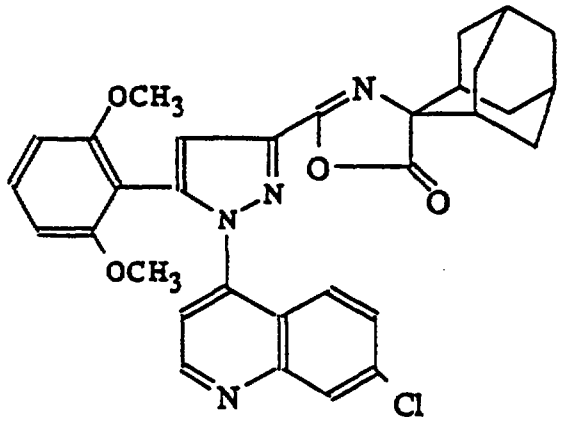
2-{[1-(7-Chloro-4-quinolyl)-5-(2,6-dimethoxyphenyl)-3-pyrazolyl]carbonylamino}-2-adamantanecarboxylic acid.

(I) : R=H ; n=0 ; $X-\overset{|}{C}-X'$ =  ;

Z = OH ; R_I =  ; R_{IV} = H ;

$R_V = H_3CO$  OCH_3

Using the procedure employed in Example 8, and replacing the acid chloride by 1-(7-chloro-4-quinolyl)--5-(2,6-dimethoxyphenyl)-3-pyrazolecarboxylic acid chloride, the intermediate compound of formula:



is obtained, the melting point of which is 249°C.

0.1 g of this intermediate is dissolved in 5 ml of dichlormethane; 5 ml of trifluoroacetic acid are added and the mixture is left for half an hour at room temperature. It is concentrated under vacuum to obtain the expected compound.

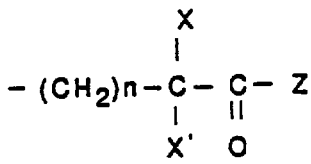
m = 0.080 g

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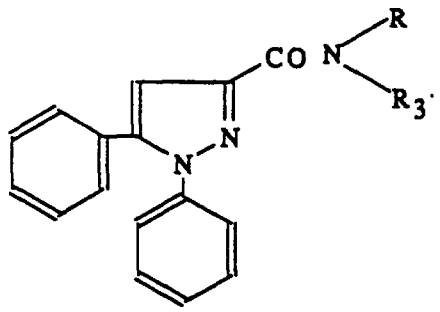
M.p. > 260°C

By repeating any one of the procedures described in Examples 1 to 13, the compounds shown in Tables 1 to 15 below were prepared. In these tables, R_3, when it is used, represents the group:



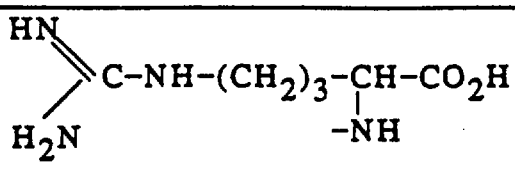
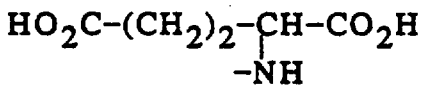
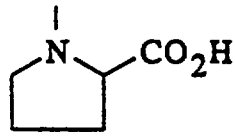
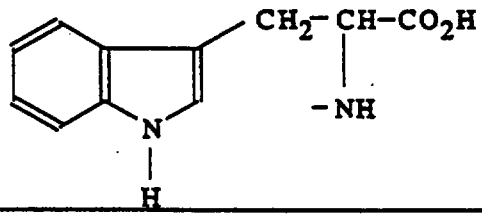
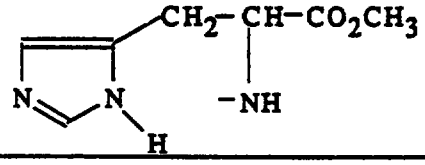
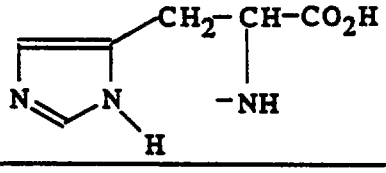
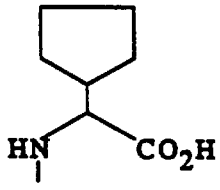
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TABLE 1



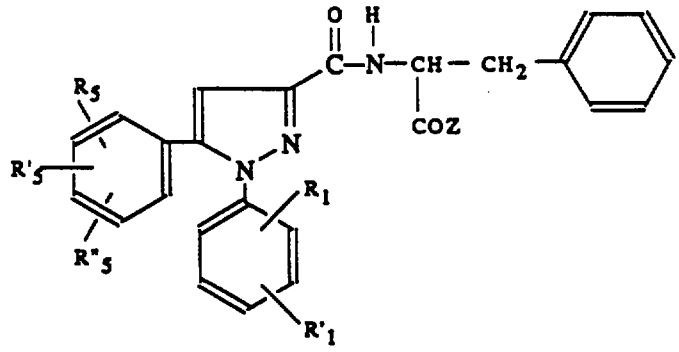
Example n°	$-N(R)(R_3)$	C*	M.p. ; °C crystallisation solvent
14	- NH-CH_2-CO_2 H	-	170 iPr_2O
15	- NH-CH_2-CO_2 Et	-	116 iPr_2O
16	- NH-$(CH_2)_2$-CO_2 H	-	170 iPr_2O
17	$CH_3-(CH_2)_3-CH(NH)-CO_2H$	S	70 CH
18	$(CH_3)_2-CH-CH(NH)-CO_2H$	S	152 iPr_2O
19	$C_6H_5-CH_2-CH(NH)-CO_2H$	S	214 iPr_2O
20	$C_6H_5-(CH_2)_2-CH(NH)-CO_2H$	S	79 CH
21	$HO-CH_2-CH(NH)-CO_2H$	S	242 iPr_2O
22	$NH_2-(CH_2)_4-CH(NH)-CO_2H$	S	150 iPr_2O (HCl)

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23		S	125 CH (HCl)
24		S	100 iPr_2O
25		S	212 iPr_2O
26		S	207 iPr_2O
27		S	90 iPrOH
28		S	220 $EtOH,H_2O$
29		R S	84 Pn,Et_2O

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TABLE 2



Example No.	R_1	R'_1	R_5	R'_5	R''_5	Z	M.p.; °C crystal. solvent
30	H	H	4-CH_3	H	H	ONa	140 EtOH
31	H	H	4-NO_2	H	H	OCH_3	69 Hx
32	H	H	4-C_6H_5	H	H	OH	104 iPr_2O
33	H	H	2-Cl	4-Cl	H	OH	108 iPr_2O
34	H	H	2-CH_3	4-CH_3	6-CH_3	OH	120 iPr_2O
35	H	H	2-OCH_3	6-OCH_3	H	OH	99 iPr_2O
36	4-F	H	2-F	H	H	OH	203 iPr_2O
37	4-F	H	4-Cl	H	H	OH	90 Pn
38	4-F	H	2-CH_3	H	H	OH	208 iPr_2O
39	4-F	H	4-OCH_3	H	H	OH	92 iPr_2O
40	4-Cl	H	4-Cl	H	H	OH	98 Pn

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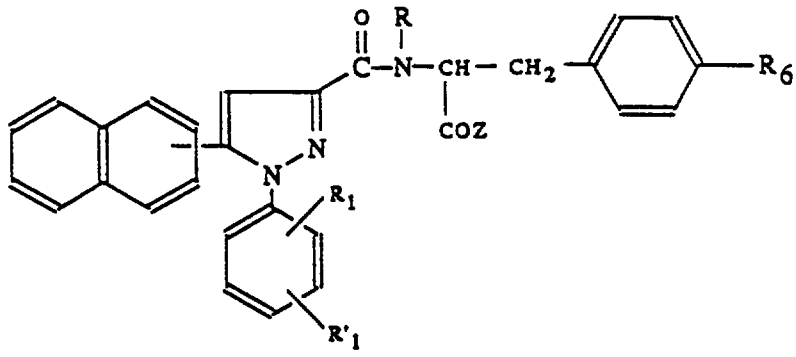
41	4-CH_3	H	4-OCH_3	H	H	OH	94 iPr_2O
42	4-OCH_3	H	4-Cl	H	H	OH	84 Pn
43	4-OCF_3	H	2-F	H	H	OH	86 iPr_2O
44	2-Cl	4-Cl	4-Cl	H	H	OH	110 Pn
45	2-Cl	5-Cl	4-CH_3	H	H	OH	90 Pn
46	2-CH_3	5-F	2-Cl	H	H	OH	100 Pn
47	3-Cl	4-Cl	H	H	H	OH	83 Hx
48	3-Cl	4-Cl	4-CH_3	H	H	OH	100 Pn
49	4-t-Bu	H	H	H	H	OH	88 CH
50	4-NO_2	H	H	H	H	OCH_3	69 Hx
51	4-NH_2	H	H	H	H	OCH_3	97 Hx
52	4-NH_2	H	H	H	H	ONa	155 H_2O

The compounds of Table 2 are all of S configuration.

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TABLE 3

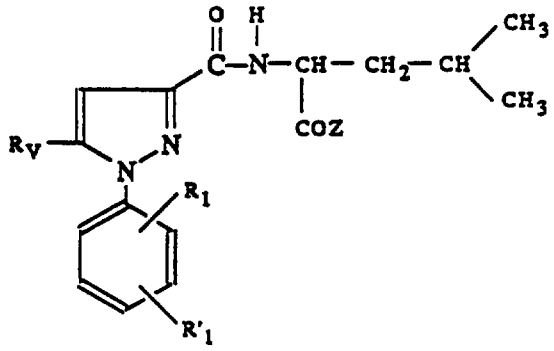


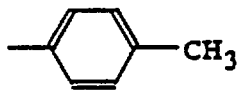
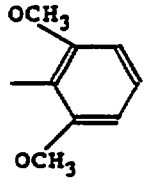
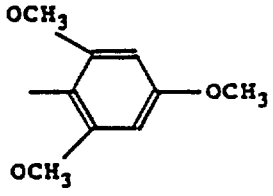
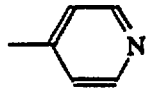
Example No.	R_1	R_1'	R	Z	R_6	Naphthyl position	C*	M.p; °C crystal. solvent
53	H	H	H	OH	H	1	S	221 iPr_2O
54	H	H	H	OH	H	2	R	224 iPr_2O
55	H	H	CH_3	OH	H	2	S	84 Hx
56	H	H	H	OH	Cl	1	R S	212 iPr_2O
57	H	H	H	OH	Cl	2	R S	196 iPr_2O
58	H	H	H	OH	OH	2	S	96 Hx
59	H	H	H	OCH_3	H	2	S	69 Pn
60	2-Cl	5-Cl	H	OH	H	1	S	115 Hx
61	2-Cl	5-Cl	H	OH	H	2	S	105 Hx
62	2-Cl	5-Cl	H	OH	Cl	1	R S	139 Hx
63	2-Cl	5-Cl	H	OH	Cl	2	R S	221 iPr_2O

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64	3-Cl	4-Cl	H	OH	H	1	S	224 $iPrO_2$
65	3-Cl	4-Cl	H	ONa	H	2	S	140 EtOH

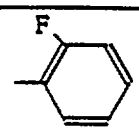
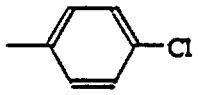
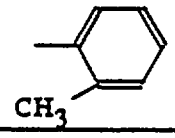
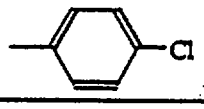
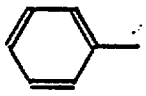
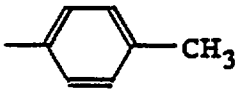
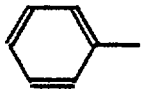
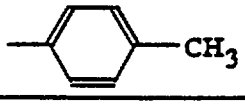
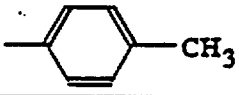
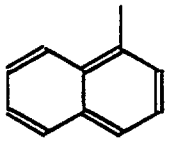
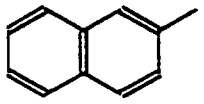
TABLE 4



Example No.	R_1	R'_1	Z	R_V	C*	M.p.; °C crystal. solvent
66	H	H	OH		S	86 Hx
67	H	H	OH		S	107 Hx
68	H	H	OH		S	96 CH
69	H	H	OH		S	165 Hx (HCl)

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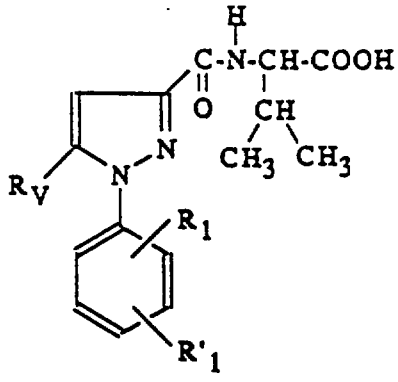


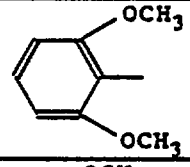
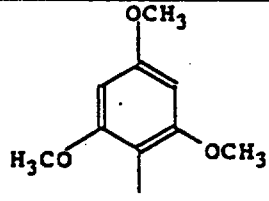
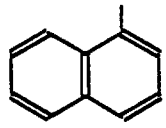
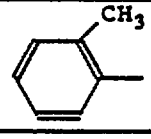
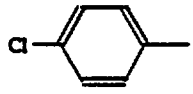
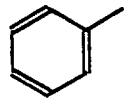
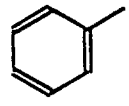
70	4-F	H	OH		S	174 iPr_2O
71	4-F	H	OH		S	92 Hx
72	4-F	H	OH		S	96 Hx
73	4-Cl	H	OH		S	89 Hx
74	4-t-Bu	H	OH		S	88 CH
75	2-Cl	5-Cl	OH		S	225 iPr_2O
76	3-Cl	4-Cl	OH		S	72 Hx
77	3-Cl	4-Cl	OH		R	98 Hx
78	3-Cl	4-Cl	OH		S	94 Pn
79	3-Cl	4-Cl	OH		S	135 Hx
80	2-Cl	5-Cl	OH		S	225 Hx

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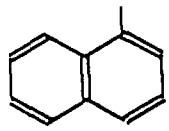
TABLE 5



Example n°	R_1	R'_1	R_V	M.p. ; °C crystallisation solvent
81	H	H		161 iPr_2O
82	H	H		201 AcOEt
83	H	H		190 iPr_2O
84	4-F	H		99 Hx
85	4-Cl	H		100 Hx
86	4-t-Bu	H		88 Hx
87	3-Cl	4-Cl		83 Hx

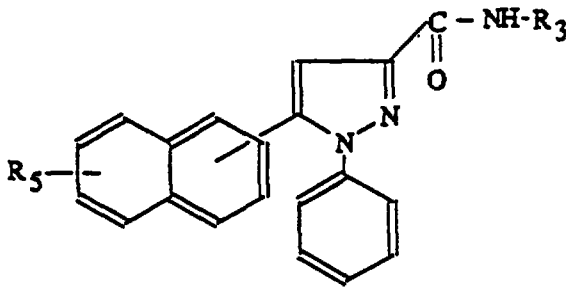
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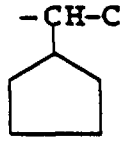


88	3-Cl	4-Cl		90 Hx

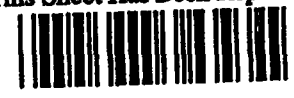
The compounds of Examples 81 to 88 are of S configuration.

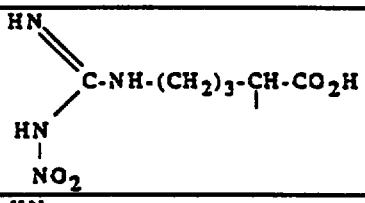
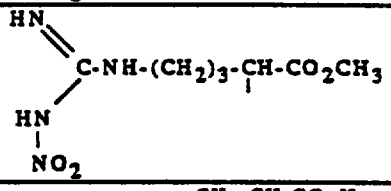
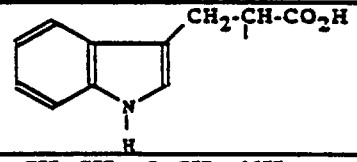
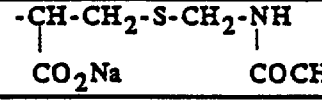
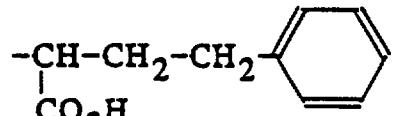
TABLE 6



Example No.	R_3	R_5	Naphthyl position	C*	M.p; °C crystal. solvent
89	$HO\text{-}CH_2\text{-}CH(CO_2H)$	H	2	S	170 AcOEt
90	$(CH_3)_2\text{-}CH\text{-}CH_2\text{-}CH(CO_2H)$	H	1	S	88 Hx
91	$CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}CH(CO_2H)$	H	1	S	206 iPr_2O
92	$CH_3\text{-}(CH_2)_2\text{-}CH(CO_2H)$	H	1	S	198 iPr_2O
93	$CH_3\text{-}(CH_2)_3\text{-}CH(CO_2H)$	H	1	R S	92 CH
94	$CH_3\text{-}(CH_2)_3\text{-}CH(CO_2H)$	H	1	R	190 iPr_2O
95		H	1	R S	226 iPr_2O

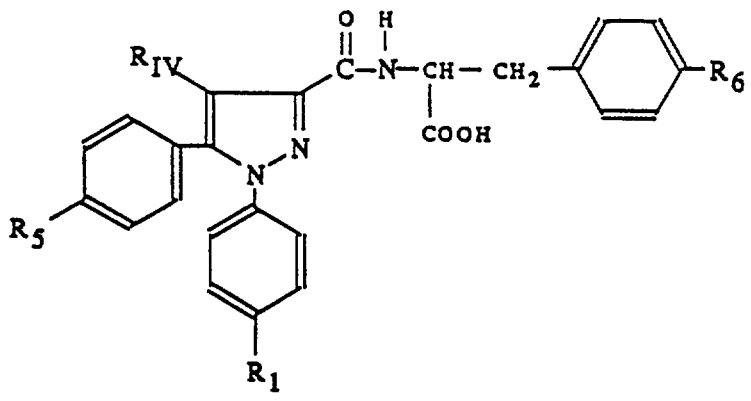
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96	$(CH_3)_3$-C-CH-CO_2H	H	1	S	230 iPr_2O
97	CH_3-$(CH_2)_2$-CH-CO_2H	6-OCH_3	2	S	92 Hx
98	CH_3-$(CH_2)_3$-CH-CO_2H	6-OCH_3	2	S	98 CH
99	$(CH_3)_2$-CH-CH-CO_2H	6-OCH_3	2	S	95 Hx
100	$(CH_3)_2$-CH-CH_2-CH-CO_2H	6-OCH_3	2	S	95 Hx
101	$(CH_3)_2$-CH-CH_2-CH-CO_2H	H	2	S	100 Hx
102	C_6H_5-$(CH_2)_2$-CH-CO_2H	H	2	S	120 CH
103	C_6H_5-CH_2-CH-CO_2H	6-OCH_3	2	S	95 Hx
104		H	2	S	175 AcOEt
105		H	2	S	110 CH
106		H	2	S	200 AcOEt
107		H	2	S	217 EtOH
108		H	1	S	100 Hx

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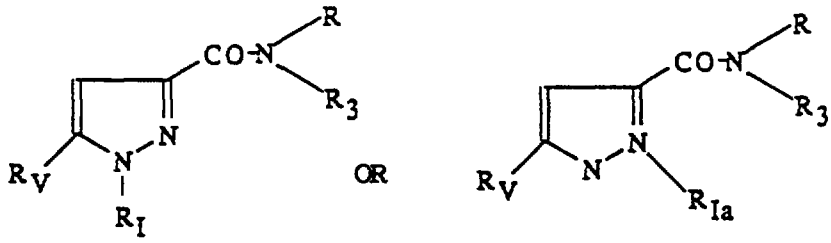
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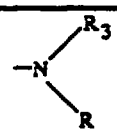
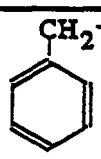
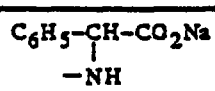
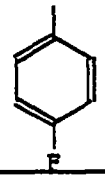
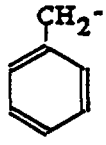
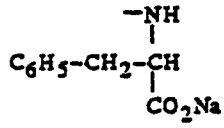
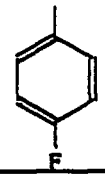
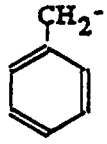
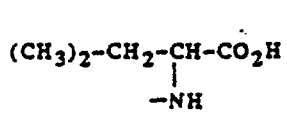
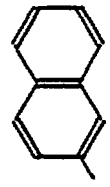
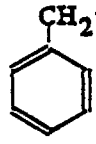
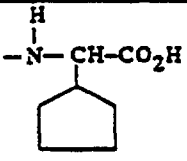
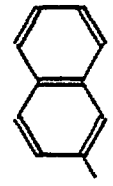
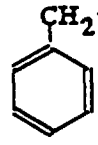
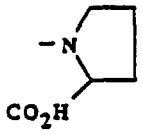
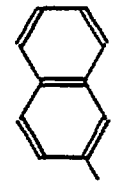
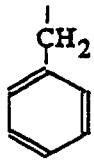
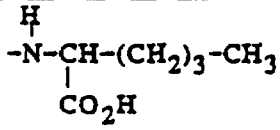
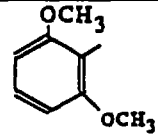


Example n°	R_1	R_6	R_{IV}	R_5	C*	M.p. ; °C crystallisation solvent
109	H	Cl	Cl	Cl	R S	120 Hx
110	F	H	Cl	Cl	S	110 Hx
111	F	Cl	Cl	Cl	R S	100 Hx

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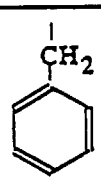
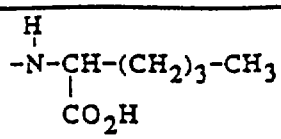
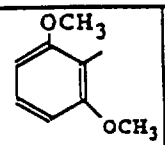
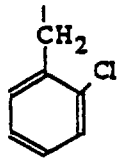
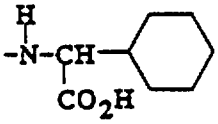
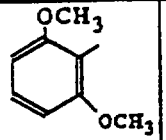
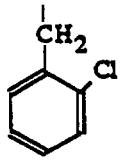
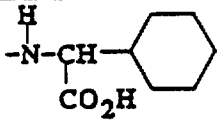
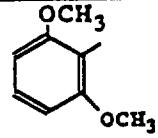
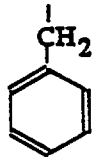
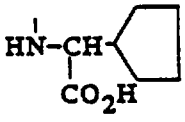
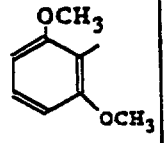
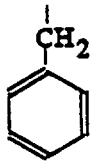
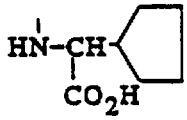
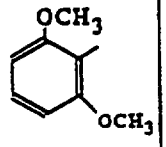
TABLE 8



Example No.	R_I	R_{Ia}		R_V	C*	M.p.; °C crystal. solvent
112		-			S	158 iPr_2O
113	-				S	130 iPr_2O
114	-				S	80 Hx
115	-				R.S	120 CH
116	-				S	60 Hx
117		-			S	69 Hx

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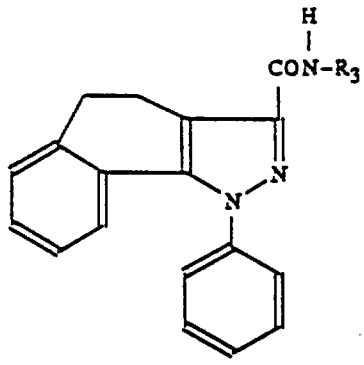


118	-				S	150 Hx
119	-				S	214 CH
120		-			S	94 CH
121		-			R S	109 Hx
122	-				R S	173 Hx

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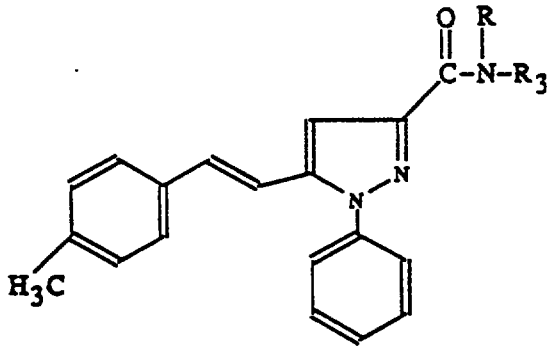


TABLE 9



Example n°	-R_3	C*	M.p. ; °C crystallisation solvent
123	$(CH_3)_2$-CH-CH-CO_2H	S	200 iPr_2O
124	C_6H_5-CH_2-CH-CO_2H	S	110 iPr_2O

TABLE 10



Example n°	R -N-R_3	M.p. ; °C crystallisation solvent
125	C_6H_5-CH-CO_2H NH—	115 Pn
126	$(CH_3)_2$-CH-CH-CO_2H NH—	110 Hx

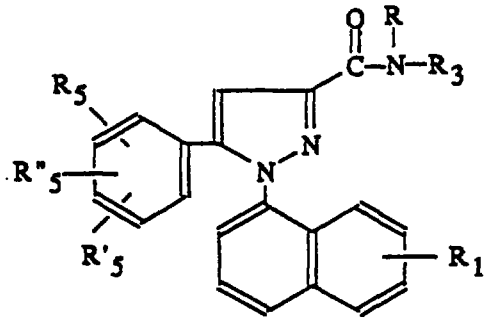
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127	$CH_3-(CH_2)_2-CH(NH-)-CO_2H$	90 Pn
128	$(CH_3)_2-CH-CH_2-CH(NH-)-CO_2H$	100 Hx
129	$CH_3-(CH_2)_3-CH(NH-)-CO_2H$	95 Pn
130	$C_6H_5-CH_2-CH(NH-)-CO_2H$	100 Pn

The compounds 125 to 130 are of S configuration.

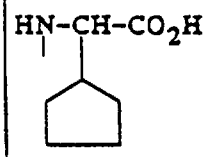
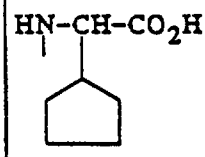
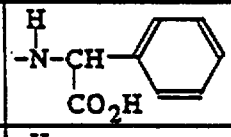
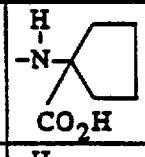
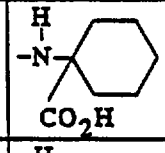
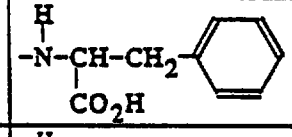
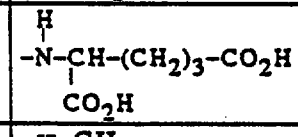
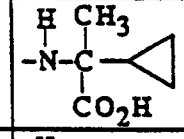
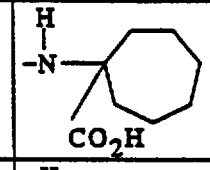
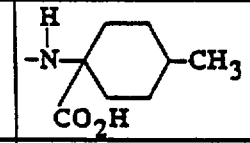
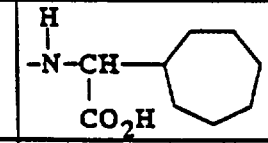
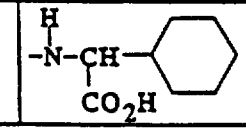
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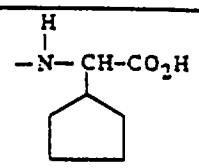
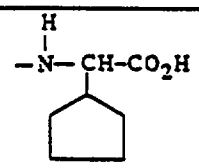
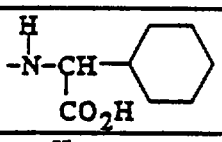
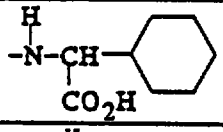
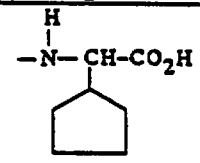
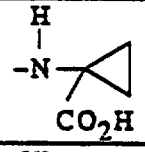
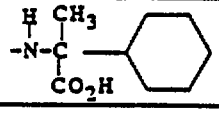
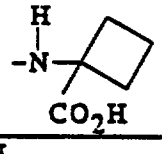
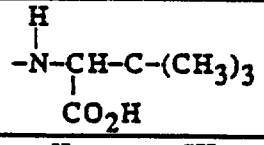
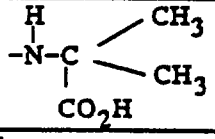
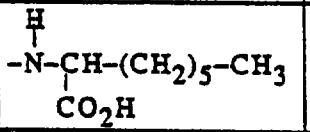
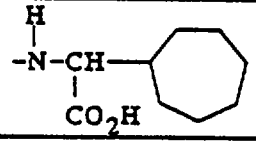
Ex n°	$-N(R)-R_3$	R_1	R_5	R'_5	R''_5	C*	M.p.; °C crystal. solvent
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132	$CH_3-(CH_2)_3-CH(NH-)-CO_2H$	H	H	H	H	S	100 Pn
133	$(CH_3)_2-CH-CH_2-CH(NH-)-CO_2H$	H	H	H	H	S	220 Pn
134	$C_6H_5-CH_2-CH(NH-)-CO_2H$	H	H	H	H	S	110 Pn
135	$CH_3-(CH_2)_3-CH(NH-)-CO_2H$	H	2-OCH_3	6-OCH_3	H	S	113

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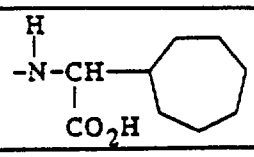
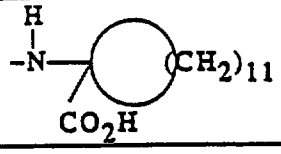
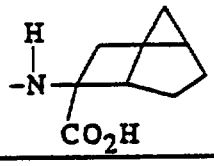
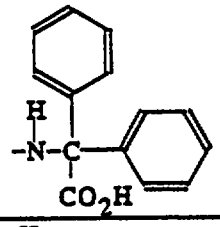
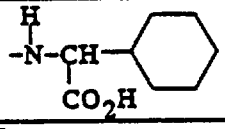
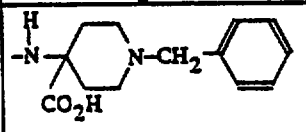
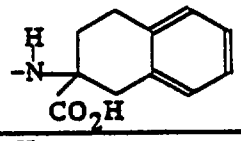
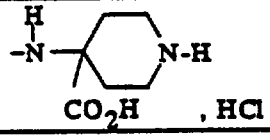
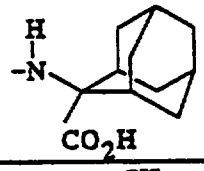
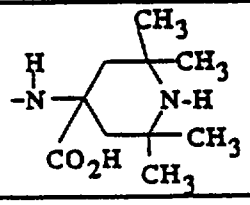


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137		H	2-OCH_3	6-OCH_3	H	R S	136 Pn
138		H	2-OCH_3	6-OCH_3	H	S	125 iPr_2O
139		H	2-OCH_3	6-OCH_3	H	-	122 Hx
140		H	2-OCH_3	6-OCH_3	H	-	>260 Hx
141		H	2-OCH_3	6-OCH_3	H	S	112 iPr_2O
142		H	2-OCH_3	6-OCH_3	H	S	110 iPr_2O
143		H	2-OCH_3	6-OCH_3	H	R S	116 iPr_2O
144		H	2-OCH_3	6-OCH_3	H	-	>260 Hx
145		H	2-OCH_3	6-OCH_3	H	-	>260 Hx
146		H	2-OCH_3	6-OCH_3	H	R S	>260 Hx
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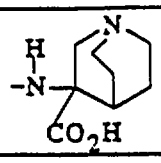
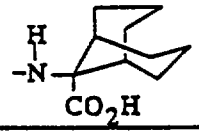
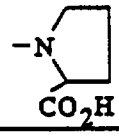
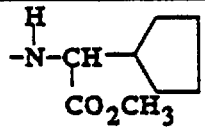
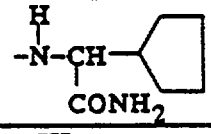
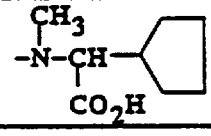
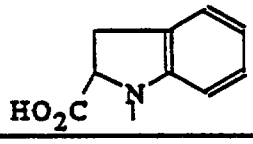
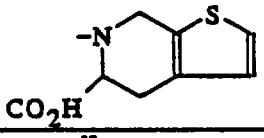
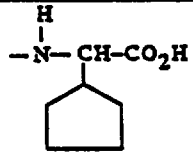
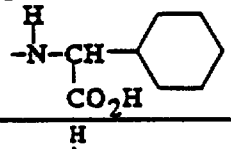
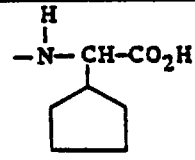
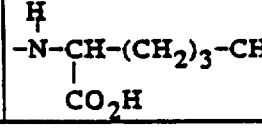
148		H	2-OCH_3	5-OCH_3	H	R S	99 iPr_2O
149		H	2-OCH_3	4-OCH_3	H	R S	110 iPr_2O
150		H	2-OCH_3	5-OCH_3	H	S	223 iPr_2O
151		H	2-OCH_3	4-OCH_3	H	S	109 iPr_2O
152		H	2-OCH_3	6-OCH_3	H	R	247 iPr_2O
153		H	2-OCH_3	6-OCH_3	H	-	128 Hx
154		H	2-OCH_3	6-OCH_3	H	R S	132 iPr_2O
155		H	2-OCH_3	6-OCH_3	H	-	114 Hx
156		H	2-OCH_3	6-OCH_3	H	S	149 iPr_2O
157		H	2-OCH_3	6-OCH_3	H	-	244 iPr_2O
158		H	2-OCH_3	6-OCH_3	H	R S	106 Hx
159		H	2-OCH_3	6-OCH_3	H	S	>260 Hx

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160		H	2-OCH_3	6-OCH_3	H	R	>260 Hx
161		H	2-OCH_3	6-OCH_3	H	-	174 Hx
162		H	2-OCH_3	6-OCH_3	H	R S	>260 EtOH
163		H	2-OCH_3	6-OCH_3	H	-	244 iPr_2O
164		H	2-OC_2H_5	6-OC_2H_5	H	S	222 Hx
165		H	2-OCH_3	6-OCH_3	H	-	190 Et_2O
166		H	2-OCH_3	6-OCH_3	H	R S	170 CH_2Cl_2
167		H	2-OCH_3	6-OCH_3	H	-	280 Et_2O
168		H	2-OC_2H_5	6-OC_2H_5	H	-	>260 iPr_2O
169		H	2-OCH_3	6-OCH_3	H	-	>260 H_2O

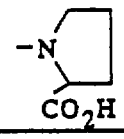
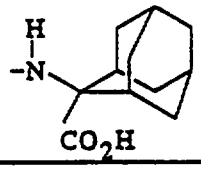
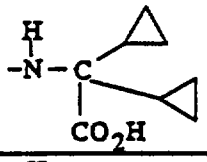
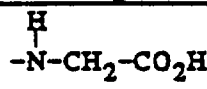
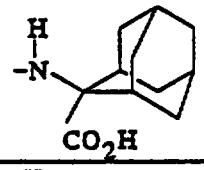
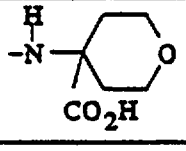
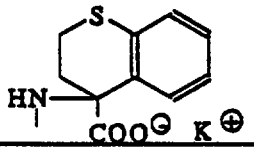
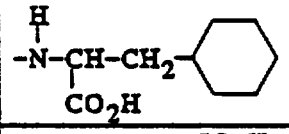
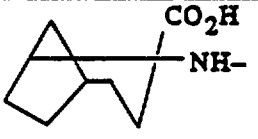
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170		H	2-OCH_3	6-OCH_3	H	R S	>260 CH_2Cl_2 -Et_2O
171		H	2-OCH_3	6-OCH_3	H	-	>260 iPr_2O
172		H	2-OCH_3	6-OCH_3	H	S	120 Pn
173		H	2-OCH_3	6-OCH_3	H	R S	81 Pn
174		H	2-OCH_3	6-OCH_3	H	R S	>260 - iPr_2O
175		H	2-OCH_3	6-OCH_3	H	R S	217 Hx
176		H	2-OCH_3	6-OCH_3	H	R S	>260 iPr_2O
177		H	2-OCH_3	6-OCH_3	H	R S	130 iPr_2O
178		H	2-OCH_3	4-OCH_3	6-OCH_3	R S	229 iPr_2O
179		H	2-OCH_3	4-OCH_3	6-OCH_3	S	>260 iPr_2O
180		4-Cl	2-OCH_3	6-OCH_3	H	R S	125 Hx
181		4-Cl	2-OCH_3	6-OCH_3	H	S	120 Hx

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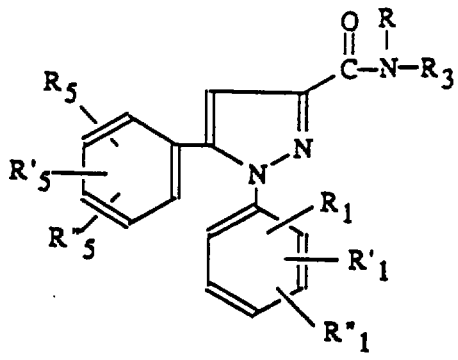


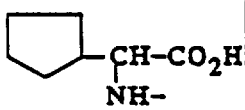
182		4-Cl	2-OCH_3	6-OCH_3	H	S	140 CH
183		H	2-CH_3	6-CH_3	H	-	280 Et_2O
184		H	2-OCH_3	6-OCH_3	H	-	225 Hx
185		H	2-OCH_3	6-OCH_3	H	-	206 iPr_2O
186		4-Cl	2-OCH_3	6-OCH_3	H	-	>260 iPr_2O
187		H	2-OCH_3	6-OCH_3	H	-	180 MeoH $-H_2O$
188		H	2-OCH_3	6-OCH_3	H	R S	>260 Et_2O
189		H	2-OCH_3	6-OCH_3	H	S	109 CH
190		H	2-OCH_3	6-OCH_3	H	R S	130 CH

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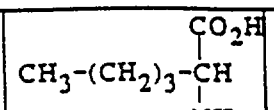
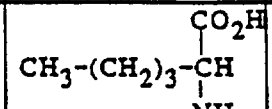
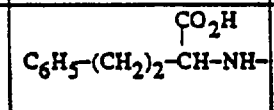
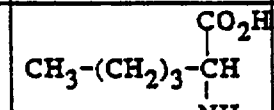
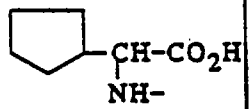
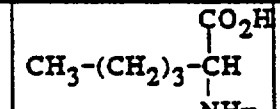
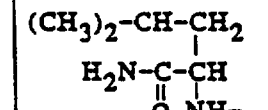
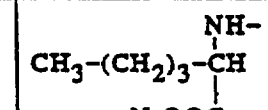
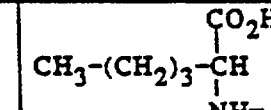
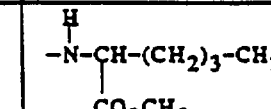
TABLE 12



Ex. n°	R_1	R'_1	R''_1	$-N(R)-R_3$	R_5	R'_5	R''_5	C*	M.p; °C crystal. solvent
191	H	H	H	$CH_3-(CH_2)_3-CH(CO_2H)-NH-$	3-OCH_3	4-OCH_3	H	S	79 Hx
192	H	H	H	$CH_3-(CH_2)_3-CH(CO_2H)-NH-$	3-OCH_3	4-OCH_3	5-OCH_3	S	69 Hx
193	H	H	H	$CH_3-(CH_2)_3-CH(CO_2H)-NH-$	2-OCH_3	4-OCH_3	6-OCH_3	S	90 Hx
194	H	H	H	$C_6H_5-CH(CO_2H)-CH_2-NH-$	2-OCH_3	6-OCH_3	H	R S	94 Hx
195	3-Cl	4-Cl	H	$CH_3-(CH_2)_3-CH(CO_2H)-NH-$	2-OCH_3	6-OCH_3	H	S	94 Hx
196	3-Cl	4-Cl	H		2-OCH_3	6-OCH_3	H	R S	100 CH

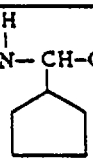
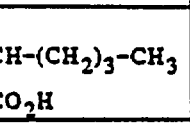
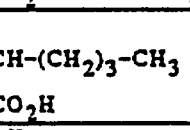
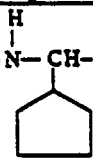
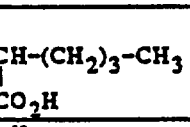
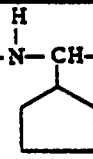
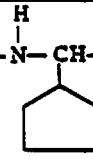
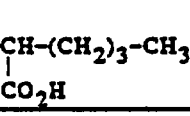
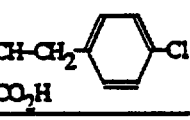
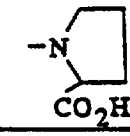
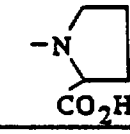
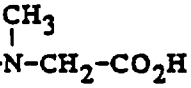
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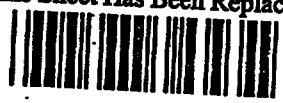
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199	3-Cl	4-Cl	H		H	H	H	S	85 CH
200	3-Cl	4-Cl	H		H	H	H	S	78 Hx
201	3-Cl	4-Cl	H		H	H	H	R S	84 Hx
202	4-t-Bu	H	H		H	H	H	S	85 Hx
203	H	H	H		H	H	H	S	66 Hx
204	3-Cl	4-Cl	H		2-OCH_3	6-OCH_3	H	S	146 H_2O
205	3-Cl	4-Cl	H		2-OCH_3	4-OCH3	6-OCH_3	S	98 CH
206	2-Cl	5-Cl	H		2-OCH_3	6-OCH_3	H	S	64 Pn

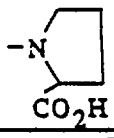
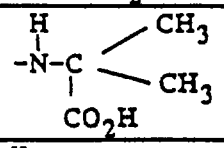
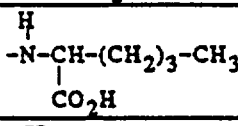
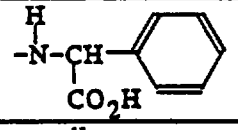
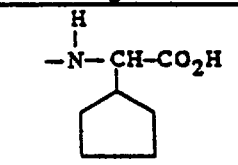
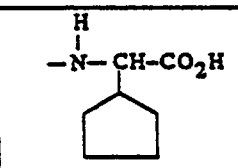
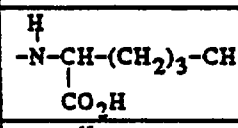
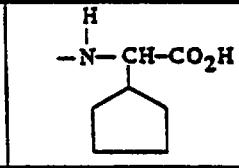
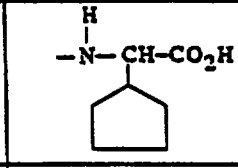
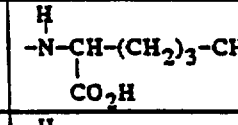
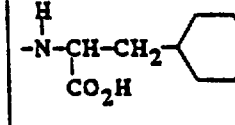
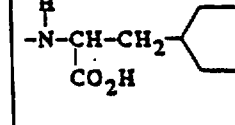
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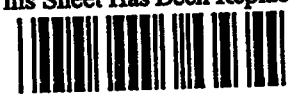
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208	2-Cl	3-Cl	4-Cl		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	219 Pn
209	2-Cl	4-Cl	6-Cl		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	220 Pn
210	2-Cl	4-Cl	6-Cl		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	R S	210 CH
211	$3\text{-}CF_3$	$5\text{-}CF_3$	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	79 Pn
212	$3\text{-}CF_3$	$5\text{-}CF_3$	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	R S	181 Hx
213	2-Cl	3-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	R,S	112 Hx
214	2-Cl	3-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	108 Pn
215	2-Cl	5-Cl	H		$4\text{-}NO_2$	H	H	R S	115 Hx
216	2-Cl	3-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	114 Hx
217	$3\text{-}CF_3$	$5\text{-}CF_3$	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	94 Hx
218	$3\text{-}CF_3$	$5\text{-}CF_3$	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	70 CH

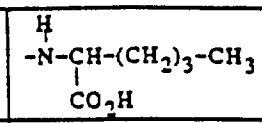
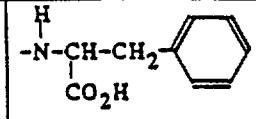
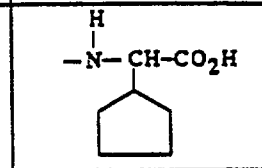
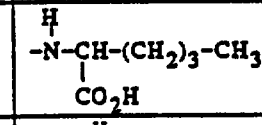
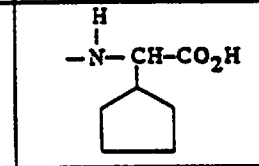
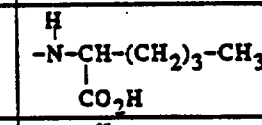
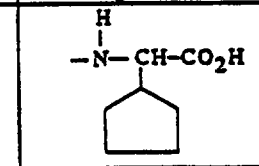
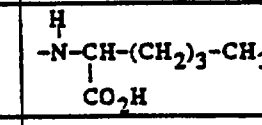
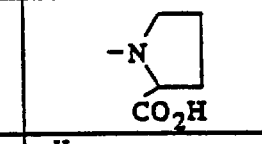
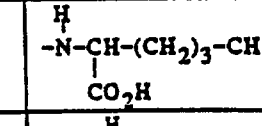
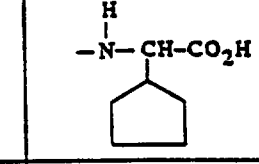
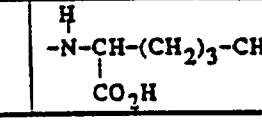
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219	2-Cl	4-Cl	6-Cl		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	110 Hx
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221	3-Cl	4-Cl	H		2-Cl	6-Cl	H	S	98 Pn
222	3-Cl	4-Cl	H		2-Cl	6-Cl	H	S	120 CH
223	3-Cl	4-Cl	H		2-Cl	6-Cl	H	R S	212 Pn
224	2-Cl	4-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	R S	124 Hx
225	2-Cl	4-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	196 Hx
226	3-Cl	4-F	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	R S	110 CH
227	3-Cl	4-Cl	H		2-F	6-F	H	R S	86 iPr_2O
228	3-Cl	4-Cl	H		2-F	6-F	H	S	76 Hx
229	2-Cl	5-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	86 iPr_2O
230	2-Cl	6-Cl	H		$2\text{-}OCH_3$	$6\text{-}OCH_3$	H	S	268 iPr_2O

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231	H	H	H		2-OCH_3	4-OCH_3	H	S	76 Hx
232	H	H	H		4-NO_2	H	H	S	100 Hx
233	4-Cl	H	H		2-OCH_3	6-OCH_3	H	R S	116 CH
234	4-Cl	H	H		2-OCH_3	6-OCH_3	H	S	169 Hx
235	2-Cl	H	H		2-OCH_3	H	H	R S	90 CH
236	2-Cl	H	H		2-OCH_3	H	H	S	87 Hx
237	3-Cl	4-Cl	H		2-OCH_3	H	H	R S	100 Hx
238	3-Cl	4-Cl	H		2-OCH_3	H	H	S	85 Pn
239	2-Cl	5-Cl	H		2-OCH_3	6-OCH_3	H	S	107 Hx
240	3-Cl	4-F	H		2-OCH_3	6-OCH_3	H	S	96 iPr_2O
241	3-Cl	H	H		2-OCH_3	6-OCH_3	H	R S	103 CH
242	3-Cl	H	H		2-OCH_3	6-OCH_3	H	S	83 CH

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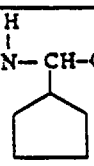
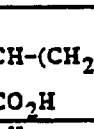
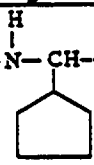
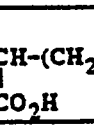
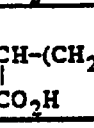
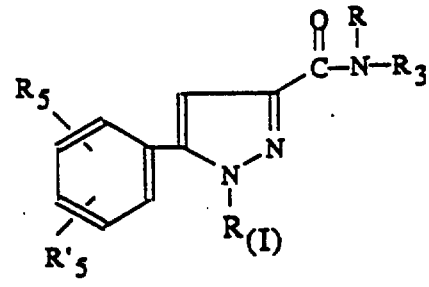
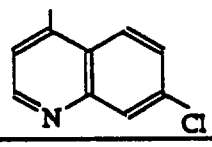
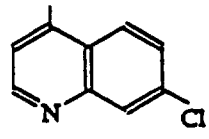
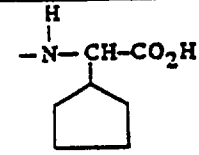
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245	3-Cl	5-Cl	H		2-OCH_3	6-OCH_3	H	R S	109 Hx
246	3-Cl	5-Cl	H		2-OCH_3	6-OCH_3	H	S	97 Pn
247	H	H	H		2-OCH_3	6-OCH_3	H	S	92 Pn

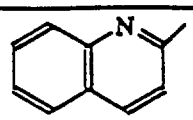
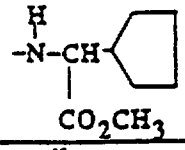
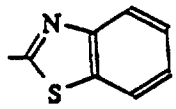
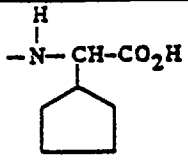
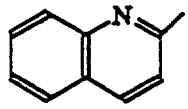
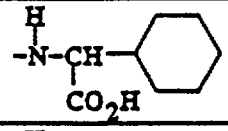
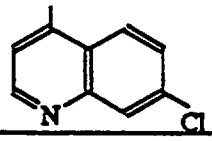
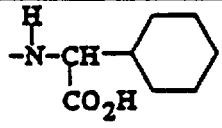
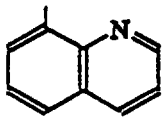
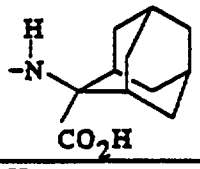
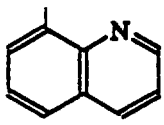
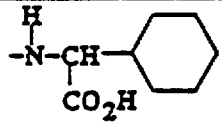
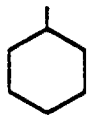
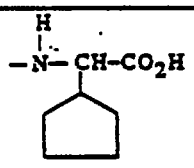
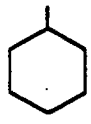
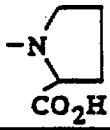
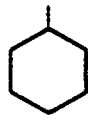
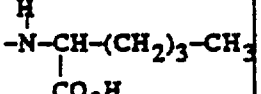
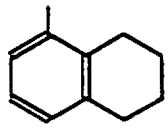
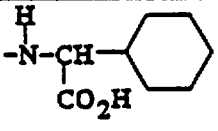
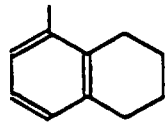
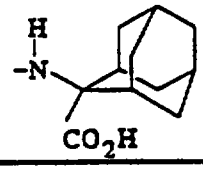
TABLE 13



Ex. n°	R_5	R'_5	$R_{(I)}$		C*	M.p. ; °C crystallisation solvent
248	2-OCH_3	6-OCH_3			R S	107 Pn
249	2-OCH_3	6-OCH_3			R S	131 iPr_2O

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250	2-OCH_3	6-OCH_3			R S	111 Pn
251	2-OCH_3	6-OCH_3			R S	112 iPr_2O
252	2-OCH_3	6-OCH_3			S	117 iPr_2O
253	2-OCH_3	6-OCH_3			S	142 iPr_2O
254	2-OCH_3	6-OCH_3			-	200 iPr_2O
255	2-OCH_3	6-OCH_3			S	260 iPr_2O
256	2-OCH_3	6-OCH_3			R S	118 Pn
257	2-OCH_3	6-OCH_3			S	128 Pn
258	2-OCH_3	6-OCH_3			S	110 Pn
259	2-OCH_3	6-OCH_3			S	> 260 iPr_2O
260	2-OCH_3	6-OCH_3			-	> 260 iPr_2O

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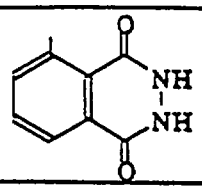
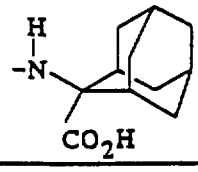
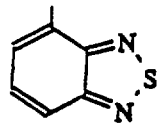
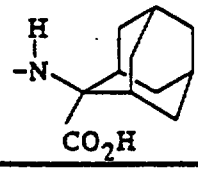
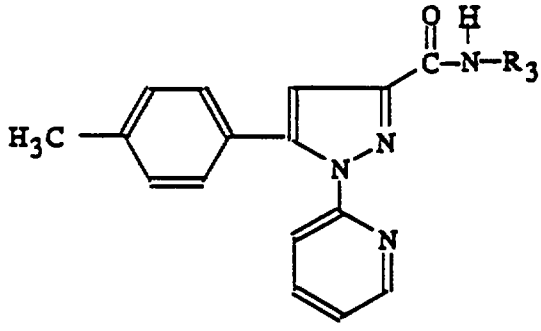
261	2-OCH_3	6-OCH_3			-	> 260 iPr_2O
262	2-OCH_3	6-OCH_3			-	> 260 iPr_2O

TABLE 14

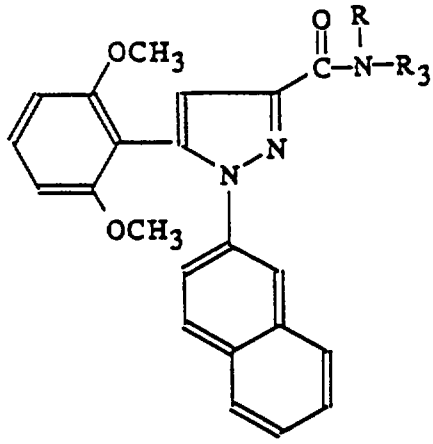


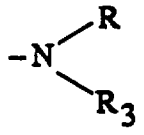
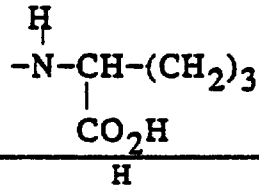
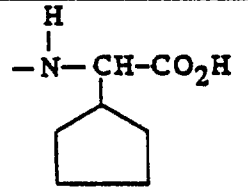
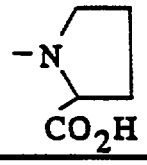
Example n°	R_3	C*	M.p. ; °C crystallisation solvent
263	$C_6H_5-CH_2-\underset{\vert}{CH}-CO_2H$	S	105 Pn
264	$C_6H_5-CH_2-\underset{\vert}{CH}-CO_2CH_3$	S	80 Pn

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TABLE 15



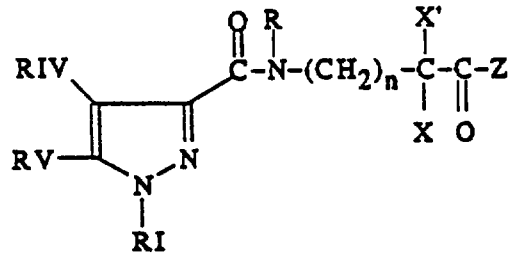
Example n°		C*	M.p. ; °C crystallisation solvent
265		S	110 iPr_2O
266		R S	120 iPr_2O
267		S	125 CH

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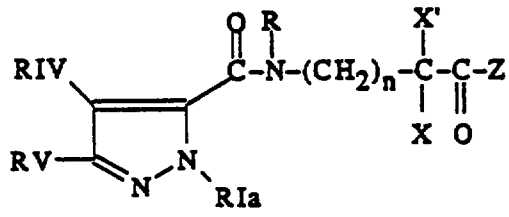


CLAIMS

1. 3-Amidopyrazole of formula (I) or (I'):



(I)



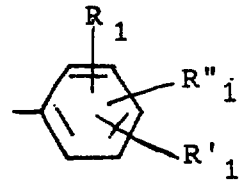
(I')

in which

- R_I represents:

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• a group 

where R_1, R'_1 and $R"_1$ each independently represent a hydrogen atom, a halogen atom, a hydroxyl, a linear or branched C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a trifluoromethyl group, a trifluoromethoxy group, a nitro group, a carboxyl group or an amino group;

- a carboxyalkyl or alkoxycarbonylalkyl group in which the alkyls are C_1-C_4 groups;
- a cycloalkyl group in which the alkyls are C_3-C_6 groups;
- a tetrahydronaphthyl group;
- a pyridyl group;
- a naphthyl group substituted with R_1, R'_1 and $R"_1$ as defined above;
- a benzyl group substituted with R_1, R'_1 and $R"_1$ as defined above;
- a cinnamyl group optionally substituted on the

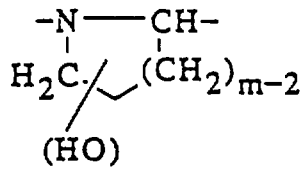
* C L M S *

aromatic ring with a halogen, a hydroxyl or a C_1-C_4 alkoxy;

- a quinolyl or isoquinolyl group optionally substituted with R_1, R'_1 and $R"_1$ as defined above;
- a 2-benzothiazolyl group;
- a quinoxalinyldione group;
- a 1-phthalazinyl group;
- a benzothiadiazolyl group;
- a methylene group substituted with a 5- or 6-membered heterocyclic group such as, in particular, a pyridyl and a thienyl;

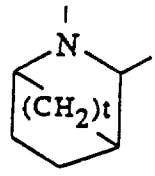
- R_{Ia} represents a benzyl group substituted with R_1, R'_1 and $R"_1$ as defined above;
- R represents hydrogen or a linear or branched C_1-C_4 alkyl;
- n represents 0, 1, 2 or 3;
- either X represents hydrogen and X' represents hydrogen; a linear or branched C_1-C_6 alkyl; an aryl; a C_1-C_4 aminoalkyl; a C_1-C_4 hydroxyalkyl; a carboxyalkyl in which the alkyl group is a C_1-C_4 group; an acetamidoalkylcysteine in which the alkyl group is a C_1-C_4 group; a guanidinoalkyl in which the alkyl group is a C_1-C_4 group; a nitroguanidinoalkyl in which the alkyl group is a C_1-C_4 group; a C_3-C_7 cycloalkyl; an arylalkyl in which the alkyl is a C_1-C_4 group and in which the aryl is optionally substituted with a halogen or a hydroxyl or with a C_1-C_3 alkyl; a heteroarylalkyl in which the heteroaryl represents an imidazolyl or an indolyl unsubstituted or substituted with a C_1-C_4 alkyl, with a hydroxyl or with a C_1-C_4 alkoxy and in which the alkyl is a C_1-C_4 group;
- or, when n is equal to zero, X represents hydrogen and X' and -N-R considered together form a ring, unsubstituted or substituted with a hydroxyl, of formula:

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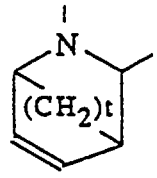
with m = 2,3 or 4

or a ring-system of formula:



with t = 1 or 2

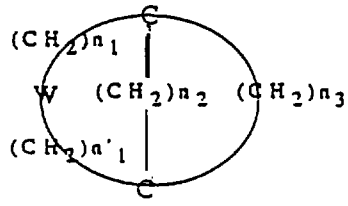
or a ring-system of formula:



with t = 1 or 2

or an indolinyl, perhydroindole or 4,5,6,7-tetrahydro-thieno[2,3-c]pyrid-6-yl ring-system;

- or X and X′ each independently represent a C_1-C_4 alkyl or a C_3-C_6 cycloalkyl; a phenyl;
- or X and X′ are linked and form together a cycloalkyl group having 2 to 12 carbon atoms, optionally substituted with a C_1-C_3 alkyl;
- or X, X′ and the carbon atom to which they are linked form an adamantyl group; an adamantyl group substituted with one or two methyl groups or with a hydroxyl, a C_1-C_3 alkoxy or a halogen atom; a 1-azaadamantyl group; a quinuclidinyl group; a 4-piperidyl group optionally N-substituted with a benzyl group; a 2,2,6,6-tetramethylpiperidyl group; a tetrahydronaphthyl group; a tetrahydropyran-4-yl or tetrahydrothiopyran-4-yl group; a 2,3-dihydro-4H-benzopyran-4-yl group; a 2,3-dihydro-4H-benzothiopyran-4-yl group; a group of formula a



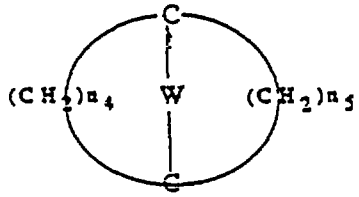
a

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in which n_1 = 0 or 1, n'_1 = 1 or 2, n_2 = 1, n_3 = 2 or 3 and W represents a carbon atom or an oxygen atom, this group of formula a) being attached to -N(R)- and to -C(O)-Z as defined above through one carbon atom of one or other of the rings, or a group of formula b



b

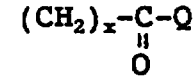
in which n_4 = 2, 3 or 4, n_5 = 2 or 3 and W represents a carbon or oxygen atom, this group of formula b) being attached to -N(R)- and to -C(O)-Z as defined above through one carbon atom of one or other of the two rings,

it being possible for the rings of the above groups a and b to be optionally substituted on one and/or other of the rings with one or two C_1-C_4 alkyl groups and it not being possible for the amino acid to be at the alpha-position with respect to W when W represents oxygen; a bicyclo[2.2.1]hept-5-en-2-yl group; an 8-oxabicyclo[3.2.1]oct-6-en-3-yl group; an 8-thiabicyclo-[3.2.1]oct-3-yl group;

- or X represents hydrogen and X' is an adamantyl group; an adamantyl group substituted with one or two methyls, with a hydroxyl, a C_1-C_3 alkoxy or a halogen atom; a 1-azaadamantyl group; a group of formula a or b as defined above, it not being possible for the bond between these ring-systems and the carbon carrying -COZ and -N-R to be at the alpha-position with respect to W when the latter represents oxygen;
- Z represents a hydroxyl group or a C_1-C_6 alkoxy group; an oxygen atom substituted with a carboxylic acid-protecting group such as a tert-butyl, a

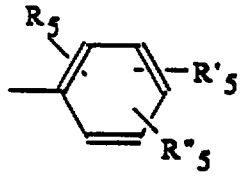
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benzyl, a benzyl substituted with a halogen atom, a C_1-C_6 alkyl, a trifluoromethyl, a trifluoromethoxy or a carboxyl group; an amino group; a nitrogen atom substituted with a carboxyalkyl in which the alkyl is a linear or branched C_1-C_6 group, with the limitation that, if Z represents a nitrogen atom substituted as defined above and if n = 0, then, when X = H, X' cannot be a group:



in which x = 1 or 2 and Q is a hydroxyl, a free amino or amino substituted with a C_1-C_6 dialkyl or a C_1-C_6 alkoxy;

- R_{IV} represents a hydrogen atom, a halogen atom or a C_1-C_6 alkyl;
- R_V represents:

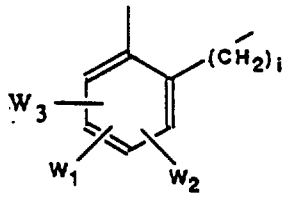
a group 

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where R_5, R'_5 and R''_5 each independently represent a hydrogen atom, a halogen atom, a linear or branched C_1-C_4 alkyl, a hydroxyl, a C_1-C_4 alkoxy, a nitro, a trifluoromethyl, a trifluoromethoxy, a cyano, an amino, a carboxyl, a C_1-C_4 carboxyalkyl or a phenyl;

- a naphthyl group unsubstituted or substituted with a C_1-C_4 alkyl;
- a pyridyl group;
- a styryl group unsubstituted or substituted with a C_1-C_4 alkyl;
- or alternatively R_{IV} and R_V considered together represent:

a group 

in which the phenyl group substitutes the pyrazole at position 5 and the group $-(CH_2)_i-$ in which i = 1

* C L M S *

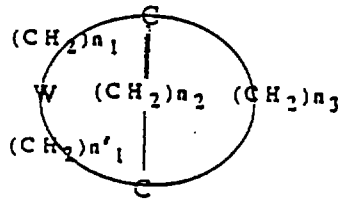
to 3 substitutes the pyrazole at position 4, W_1, W_2 and W_3 substitute the benzene ring and independently represent hydrogen, a halogen or a hydroxyl group;

or one of its possible salts with organic or inorganic acids or with inorganic or organic bases.

2. 3-Amidopyrazoles of formula (I) in which R, X, X', n, Z, R_{IV} and R_V are as defined in claim 1, characterized in that R_1 represents a phenyl or naphthyl group substituted with R_1, R'_1 and R''_1 as defined in claim 1, or one of its possible salts with organic or inorganic acids or with organic or inorganic bases.

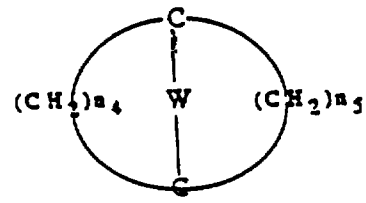
3. 3-Amidopyrazole of formula (I) or (I') in which R, X, X', n, Z, R_I R_{Ia} and R_{IV} are as defined in claim 1, characterized in that R_V represents a phenyl or a naphthyl substituted with R_5, R'_5 and R''_5 as defined in claim 1, R_5, R'_5 and R''_5 preferably being hydrogen or a C_1-C_4 alkoxy; or one of its possible salts with inorganic or organic acids or with organic or inorganic bases.

4. 3-Amidopyrazole of formula (I) in which R, n, R_{IV} and R_V are as defined in claim 1, characterized in that X and X' and the carbon atom to which they are linked form an adamantyl group, a group of formula:



a

in which n_1, n'_1, n_2, n_3 and W are as defined in claim 1, or a group of formula:



b

in which n_4, n_5 and W are as defined in claim 1, the said groups a and b being

attached to $-\overset{R}{\underset{|}{N}}-$ and to -C(O)-Z as defined

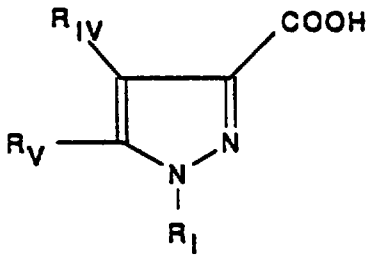
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* C L M S *

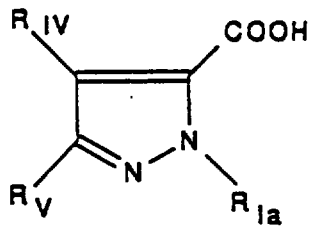
above through the same carbon atom of one or other of the two rings,

it being possible for the rings of the above groups a and b to be optionally substituted on one and/or other of the rings with one or two C_1-C_4 alkyl groups and it not being possible for the amino acid to be at the alpha-position with respect to W when W represents oxygen, or one of its salts with organic or inorganic acids or with organic or inorganic bases.

5. Process for the preparation of the compounds of formula (I) and (I'), characterised in that a functional derivative of a pyrazolecarboxylic acid of formula (II) or (II'):

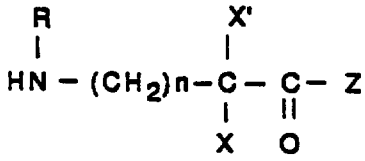


(II)



(II')

in which R_I, R_{IV}, R_V and R_{Ia} are as defined above, is treated with an amino acid, optionally protected by the protective groups customary in peptide synthesis, of formula:



(V)

in which R, n, X, X' and Z are as defined above, and the compound thereby obtained is optionally converted to one of its salts.

6. Pharmaceutical composition containing as active principle a compound according to any one of Claims 1 to 4 or one of its possible pharmaceutically acceptable salts.

7. Pharmaceutical composition according to Claim 6, in the form of a dosage unit.

8. Pharmaceutical composition according to Claim 7,

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characterised in that it contains from 0.25 to 250 mg of active principle mixed with at least one pharmaceutical excipient.

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