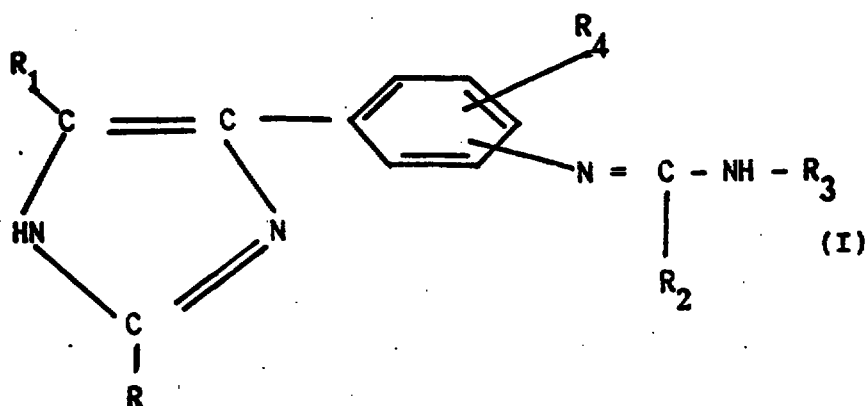


Imidazolyphenyl amidines

This invention relates to novel amidine derivatives of 2-substituted 4-phenylimidazole, to processes for their preparation, and to pharmaceutical compositions containing them. The new compounds are H₂-receptor blocking agents and may be used as gastric acid secretion inhibitors and antiulcer agents.

According to one feature of the present invention there are provided compounds of general formula I



(in which R represents a linear or branched alkyl group, a hydroxy group, a C₁₋₃ alkoxy or alkylthio group, a halogen atom, a C₁₋₃ alkylsulfinyl or alkylsulfonyl group, a sulfamoyl group, an amino group which may be substituted by one or two alkyl groups having 1 to 3 carbon atoms, an acylamino group or a phenyl group; R₁ and R₂, which may be the same or different,

each represents a hydrogen atom or an alkyl group;
R₃ represents a linear or branched alkyl group
optionally containing one heteroatom such as an
oxygen, sulphur or nitrogen atom, an alkenyl group,
5 an alkynyl group, a cyano group, an aryl or aralkyl
group optionally substituted (by, for example,
a lower alkyl or alkoxy group or a halogen atom),
a cycloalkyl or cycloaliphatic alkyl group, a substituted
or unsubstituted heterocyclic group or an alkyl
10 group substituted by a substituted or unsubstituted
heterocyclic group (wherein the substituent on
the heterocyclic group may, for example, be a lower
alkyl or alkoxy group or a halogen atom); and R₄
represents a hydrogen atom, a C₁₋₃ alkyl or alkoxy
15 group, a halogen atom or a cyano or carbamyl group,
tautomeric forms thereof and acid addition salts
of the aforementioned compounds.

For pharmaceutical use, the acid addition
salts referred to above will be physiologically
20 compatible acid addition salts. The term "acid
addition salts" includes salts with inorganic or
organic acids. Suitable physiologically compatible
acid addition salts include, for example, salts
formed with acetic, maleic, fumaric, citric, hydrochloric,
25 tartaric, hydrobromic, nitric or sulfuric acid.
Preferred acid addition salts include salts formed
with hydrochloric, sulfuric, maleic or fumaric
acid.

It is to be understood that, although in
30 general formula I above the double bonds in the
amidine radical and in the imidazolyl ring have
been depicted in a particular configuration, various
tautomeric forms are possible. Furthermore, the
compounds in which R represents a hydroxy or mercapto
35 group may equally exist as the corresponding imidazol-
inone or imidazolinthione forms. The present invention
includes within its scope such tautomeric forms
as regards both the compounds themselves and the

processes for their preparation.

When in the compounds of general formula I above R represents a linear or branched alkyl group it may, for example, be an alkyl group having 1-4 carbon atoms; when R_1 and/or R_2 represent alkyl groups these may, for example, be alkyl groups having 1-4 carbon atoms; when R_3 represents a linear or branched alkyl group it may, for example, be an alkyl group having 1-8 carbon atoms optionally further containing an oxygen atom (e.g. hydroxypropyl, methoxyethyl), a sulfur atom (e.g. methylthioethyl, ethylthioethyl) or a nitrogen atom (e.g. cyanoethyl); when R_3 is an alkenyl group it may, for example, be an alkenyl group having 3-5 carbon atoms; when R_3 is an alkynyl group it may, for example, be an alkynyl group having 3 or 4 carbon atoms; when R_3 is a cycloalkyl or cycloaliphatic alkyl group the ring may, for example, contain from 3 to 6 carbon atoms; when R_3 is an aryl group it may, for example, be a phenyl group optionally substituted (by, for example, a lower alkyl or alkoxy group or a halogen atom); when R_3 is an aralkyl group it may, for example, be a benzyl group whose aromatic portion may be substituted (by, for example, a lower alkyl or alkoxy group or a halogen atom); and when R_3 is a heterocyclic group or an alkyl group substituted by a substituted or unsubstituted heterocyclic group it may, for example, be or contain an unsaturated five or six-membered ring having one or more heteroatoms (optionally substituted by, for example, a lower alkyl or alkoxy group or a halogen atom).

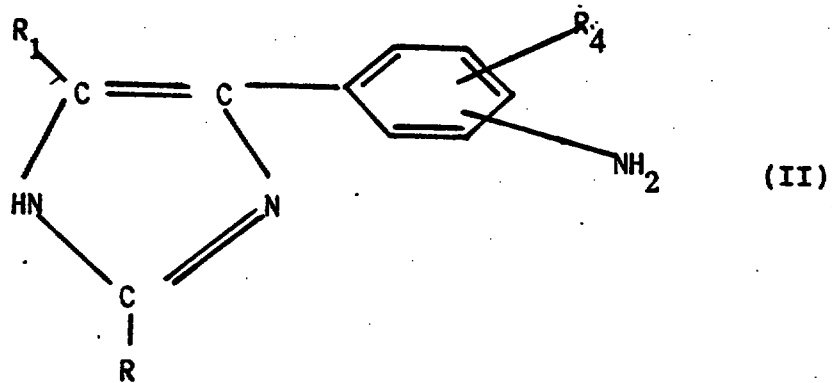
The term "lower" when applied to alkyl or alkoxy groups refers to alkyl or alkoxy groups containing from 1 to 4 carbon atoms.

In the general formula I above the amidine radical may be in the ortho, meta or para position of the benzene ring with respect to the imidazolyl

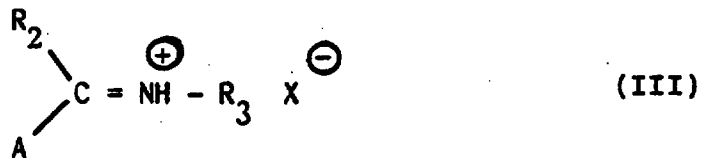
group, and R_4 may be in any position of the benzene ring.

The compounds of general formula I as hereinbefore defined may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

a) Reaction of a compound of general formula II



10 (in which R , R_1 and R_4 are as hereinbefore defined) with a compound of formula III



(in which R_2 and R_3 are as hereinbefore defined, $X^\ominus$ represents the anion of an inorganic acid, such as the chloride or fluoroborate anion, and A represents a benzoyloxy group, a chlorine atom or a lower

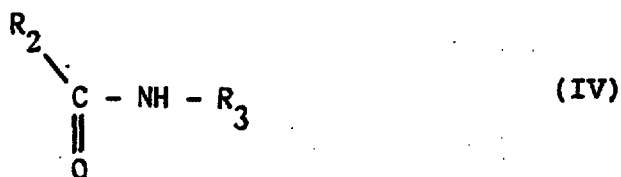
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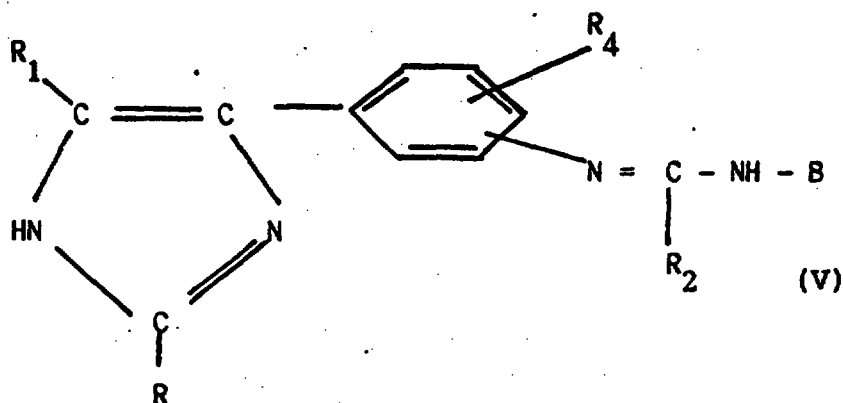
alkoxy group such as a methoxy or ethoxy group).
 The compound of formula III may optionally be made
 to react as a base. The reaction is generally
 effected at temperatures of from 0 to 100°C, preferably
 5 from 20 to 60°C. The reaction is conveniently
 carried out in the presence of an inert organic
 solvent such as, for example, an alcohol having
 1 to 3 carbon atoms, e.g. methanol or ethanol,
 a halogenated hydrocarbon, e.g. dichloromethane,
 10 or dioxan or acetone. Preferred solvents include
 ethanol, dioxan and acetone.

The compounds of formula III used as starting
 materials in the above process may be obtained
 by conventional methods, e.g. by reacting a compound
 15 of formula IV

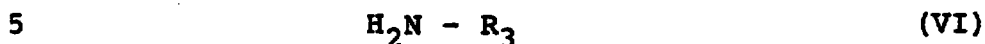


(in which R_2 and R_3 are as hereinbefore defined)
 with benzoyl chloride, triethyloxonium fluoroborate,
 ethyl chloroformate, phosphorus oxychloride or
 20 phosphorus pentachloride.

b) Reaction of a compound of general formula V



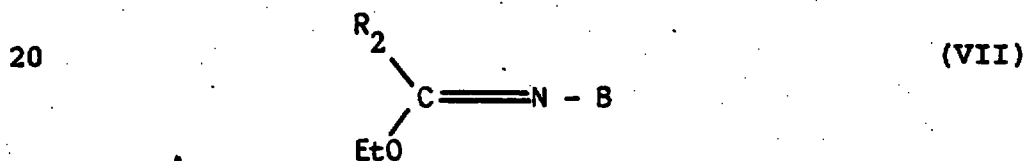
(in which R, R₁, R₂ and R₄ are as hereinbefore defined and B represents a suitable leaving group, such as a cyano, acetyl, carbethoxy or carbamyl group) with an amine of formula VI



(in which R₃ is as hereinbefore defined).

The reaction is conveniently carried out in the presence of water or of an inert organic solvent such as, for example, an alcohol such as
10 methanol or ethanol, dimethylformamide, dioxan or acetonitrile. This reaction may, for example, be effected at temperatures of from 10-50°C, preferably at room temperature.

The compounds of general formula V used as
15 starting materials in the above process may be obtained from processes that are known per se in the literature; for example, by reacting a compound of general formula II above with a compound of formula VII



(in which R₂ and B are as hereinbefore defined). When in the compound of formula V B represents a cyano group, the reaction may optionally be carried out in a single step by reacting a compound of
25 general formula II with cyanamide in the presence of a compound of formula VIII

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(in which R_2 is as hereinbefore defined and Y represents a lower alkyl group, such as a methyl or ethyl group).

The reaction is conveniently carried out in the presence of a suitable inert organic solvent such as, for example, a lower alcohol, an ether, ethyl acetate, acetonitrile or dioxan, or without solvent, at temperatures of from 20 to 80°C. The compound of formula VII may be prepared by conventional methods.

The compounds of general formula I prepared according to the processes a) and b) may optionally be converted with inorganic or organic acids into physiologically compatible acid addition salts, for example by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acid in a suitable solvent. Particularly preferred acids include, for example, hydrochloric, sulfuric, maleic and fumaric acid. The compounds of general formula I and their physiologically compatible acid addition salts are H_2 -receptor blocking agents which inhibit gastric acid secretion.

Particularly preferred compounds according to the present invention are the following:

N-Ethyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 2)

N-Isopropyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 3)

- N-Allyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-
formamidine (Compound 4)
N-t-Butyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-
formamidine (Compound 39)
5 N-Isopropyl-N'-[4-(2-hydroxy-imidazol-4-yl)phenyl]-
formamidine (Compound 28)

Such compounds generally exhibit a better activity as antisecretory/antiulcer agents and are therefore preferred for the treatment of disorders
10 of the gastrointestinal tract.

The antagonistic activity of the compounds according to the invention on histamine H₂-receptors may be demonstrated either in vitro or in vivo by their inhibition of H₂-dependent biological
15 effects, which include the histamine-induced positive chronotropic effect and histamine-induced gastric acid secretion respectively.

The inhibition of the positive chronotropic effect has been investigated in vitro in isolated
20 guinea pig atria suspended in an organ bath (50 ml) containing oxygenated (O₂ : 95% - CO₂ : 5%) Krebs-Henseleit solution (pH 7.4) maintained at 32°C. The myocardial preparation, loaded with 1 g isometric tension, is allowed to stabilize
25 for 60 min., and then the myocardial contractions are recorded through an isomeric lever connected to a strain-gauge coupler, and the instantaneous rate is monitored with a cardiometer coupled to a heatwriting pen recorder. After two control
30 responses (tachycardia) to histamine (10⁻⁶ g.ml⁻¹), the test compounds are added to the bath at the desired final concentration and left for 30 minutes before the atria are again treated with histamine. The chronotropic response obtained in the presence
35 of the antagonist is then compared to the control response to histamine and the percent reduction of the histamine H₂-induced response is calculated. The average effective concentration (EC₅₀) of the

H₂ antagonists is also calculated by the standard procedure according to D.R. Waud, Analysis of Dose-Response Curves, in "Methods in Pharmacology", vol. 3, Smooth muscle, ed. Daniel, E.E., Paton, M., Plenum Press, New York (1975); Ash and Schild, Br. J. Pharmacol. Chemother., 27, 427-439, 1966. The following Table shows the results obtained:

T A B L E I

10 In vitro inhibitory activity in histamine-induced tachycardia (guinea pig atria)

COMPOUND	EC ₅₀ 10 ⁻⁷ M
2	1.5
3	1.8
4	1.2
39	4.0
28	1.94
CIMETIDINE	34.0

The ability of the test compounds to inhibit histamine-induced gastric acid secretion has been investigated in vivo after intravenous or intraduodenal administration in stomach perfused rats, according to the method of Gosh and Schild (Br. J. Pharmacol. Chemother., 13, 54, 1958).

The preparation of the animals under general anaesthesia (urethane, 1 g.kg⁻¹ i.p.), and at constant temperature, is achieved by inserting and tying in place polyethylene tubes (PE 50) in the oesophagus and in the pyloric-antral region. After the stomach is washed to remove food residues, continuous perfusion of the stomach with saline at a rate of 0.5 ml.min⁻¹ (37°C) is commenced, primed by a Jobling peristaltic

pump. After 30 min. of perfusion adaptation, the stomach perfusate is collected at 30 min. intervals and titrated for acid content, expressed as μEq of 1N NaOH. As the control acid output becomes constant, intravenous perfusion of histamine ($1 \text{ mg.kg}^{-1}\text{hr}^{-1}$) is commenced and this is maintained throughout the experimental period. After the acid secretion has reached a steady higher value, increasing doses of the test compounds are injected intravenously in order to obtain dose response functions. ED_{50} values are then calculated by standard procedures.

The results are reported in the following Table:

T A B L E II

15 In vivo antisecretory activity in histamine-induced gastric acid secretion
(stomach perfused rat)

COMPOUND	$\text{ED}_{50} \text{ mg.kg}^{-1} (\text{i.v.})^*$
2	0.032
3	0.067
4	0.025
39	0.080
28	0.065
CIMETIDINE	0.560

*The values of activity are expressed taking the compound as a base.

20 According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as hereinbefore defined, or a physiologically

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compatible acid addition salt thereof, in association with one or more pharmaceutical carriers or excipients.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible acid addition salts may be incorporated into conventional pharmaceutical preparations in either solid or liquid form. The compositions may, for example, be presented in a form suitable for oral or parenteral administration. Preferred forms include, for example, capsules, tablets, coated tablets, ampoules and/or vials containing a lyophilized mass of the salt.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, gelatine, magnesium stearate, corn starch, aqueous or non-aqueous vehicles, polyvinylpyrrolidone and/or mannitol.

The compositions may be advantageously formulated as dosage units, each dosage unit being adapted to supply a fixed dose of the active ingredient. Each dosage unit may conveniently contain from 10 mg to 500 mg, preferably from 20 mg to 150 mg, of the active ingredient according to the invention.

The following non-limiting Examples serve to illustrate the present invention.

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Example 1

2-Methyl-4-(4-nitro-phenyl)-1H-imidazole

A mixture of 4-nitro-phenacyl bromide (100 g), acetamide (300 g), and water (15 g) was stirred at 140°C for 8 hours, then poured into water (1500 ml). The solution was filtered and basified with 10% sodium hydroxide solution. The solid which separated was filtered, washed with water and dried to give 48.1 g of the title compound. M.p. 216-219°C.

Following the above procedure, using the appropriate phenacyl bromide and the appropriate amide as starting materials, the following nitrophenyl imidazole derivatives were also prepared:

2-Methyl-4-(3-nitro-phenyl)-1H-imidazole M.p. 146-147°C

2-Ethyl-4-(4-nitro-phenyl)-1H-imidazole M.p. 204-205°C

2-Isopropyl-4-(4-nitro-phenyl)-1H-imidazole M.p. 201-205°C

2,5-Dimethyl-4-(4-nitro-phenyl)-1H-imidazole M.p. 234-235°C

2-Methyl-4-(3-bromo-4-acetamido-phenyl)-1H-imidazole M.p. 152-154°C

2-Phenyl-4-(4-nitro-phenyl)-1H-imidazole M.p. 231-233°C

Example 2

2-Methyl-4-(4-amino-phenyl)-1H-imidazole

2-Methyl-4-(4-nitro-phenyl)-1H-imidazole (28 g) dissolved in methanol (210 ml) was hydrogenated in the presence of Pd/C 10% (1.35 g)

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at atmospheric pressure and at room temperature. When the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the solution was evaporated to dryness to give 23.2 g of the title compound as a spongy solid. Following the above procedure, using the appropriate nitro-phenyl derivative, the following aminophenyl derivatives were also prepared:

<u>2-Methyl-4-(3-amino-phenyl)-1H-imidazole</u>	M.p. 135-136°C
<u>2-Ethyl-4-(4-amino-phenyl)-1H-imidazole</u>	spongy solid
<u>2-Isopropyl-4-(4-amino-phenyl)-1H-imidazole</u>	spongy solid
<u>2,5-Dimethyl-4-(4-amino-phenyl)-1H-imidazole</u>	M.p. 190-192°C
<u>2-Methoxy-4-(4-amino-phenyl)-1H-imidazole</u>	M.p. 242-244°C
<u>2-Acetamido-4-(4-amino-phenyl)-1H-imidazole</u>	M.p. 215-216°C
<u>2-Amino-4-(4-amino-phenyl)-1H-imidazole</u>	M.p. 143-144°C
<u>2-Methyl-4-(3-methyl-4-amino-phenyl)-1H-imidazole</u>	M.p. 135-136°C
<u>2-Methyl-4-(3-methoxy-4-amino-phenyl)-1H-imidazole</u>	M.p. 167-168°C
<u>2-Phenyl-4-(4-amino-phenyl)-1H-imidazole</u>	M.p. 198-199°C

Example 3

2-Methylthio-4-(4-nitro-phenyl)-1H-imidazole

To a solution of sodium (2.3 g) in ethanol (190 ml) was added in portions 2-mercapto-4-(4-nitro-phenyl)-1H-imidazole (21.1g). After 15 minutes' stirring, a solution of iodomethane (14.2 g) in ethanol (50 ml) was added dropwise. After an additional 2 hours' stirring at room temperature, the solution was evaporated to

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dryness. The residual solid was treated with water, Filtered and dried to give 18.1 g of the title compound. M.p. 200-202°C.

2-Methoxy-4-(4-nitro-phenyl)-1H-imidazole (M.p. 295-300°C) was similarly prepared by this procedure, starting from 2-hydroxy-4-(4-nitro-phenyl)-1H-imidazole.

Example 4

2-Methylthio-4-(4-amino-phenyl)-1H-imidazole

Concentrated hydrochloric acid (60 ml) was added dropwise to a stirred suspension of 2-methylthio-4-(4-nitro-phenyl)-1H-imidazole (5.88 g) and granulated tin (8.9 g) in water

(25 ml). After 3 hours' stirring at 100°C, the mixture was cooled to room temperature and filtered. The solid was dissolved in water and the resulting solution was filtered and the filtrate evaporated to dryness. The residual solid was washed with ethanol, filtered and then treated with an ethanolic solution of sodium ethoxide to give the free base (3 g). M.p. 85-86°C.

Following the above procedure, other nitrophenyl derivatives were reduced to give the following amines:

2-Chloro-4-(4-amino-phenyl)-1H-imidazole M.p. 56-58°C

2-Methylsulfinyl-4-(4-amino-phenyl)-1H-imidazole M.p. 83-85°C

2-Sulfamoyl-4-(4-amino-phenyl)-1H-imidazole M.p. 111-113°C

Example 5

2-Chloro-4-(4-nitro-phenyl)-1H-imidazole

A mixture of 2-hydroxy-4-(4-nitro-phenyl)-1H-imidazole (15 g) and phosphorus oxychloride (750 ml) was heated under reflux with

stirring for 24 hours. The solution was evaporated to dryness, and the residue was taken to pH 6.5 with a $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{--}$ buffer and extracted with dichloromethane. After drying, the organic solution was evaporated and the crude product was chromatographed on silica gel to give 6.7 g of the title compound. M.p. 136-138°C.

Example 6

2-Methylsulfinyl-4-(4-nitrophenyl)-1H-imidazole

Hydrogen peroxide (36%, 100 ml) was added over 2 hours with stirring to a hot (60°C) solution of 2-methylthio-4-(4-nitro-phenyl)-1H-imidazole (19.6 g) in methanol (500 ml). After an additional 24 hours' heating at 60°C, the mixture was cooled to room temperature and filtered and the resulting solid was dried to give 16.1 g of the title compound. M.p. 220-222°C.

Example 7

2-Sulfamoyl-4-(4-nitro-phenyl)-1H-imidazole

Chlorine was introduced, through a capillary tube at a moderately rapid rate for 40 minutes, into a stirred ice-cooled mixture of 2-mercapto-4-(4-nitro-phenyl)-1H-imidazole (10 g) in 1N hydrochloric acid (100 ml). The sulfonyl chloride which separated was filtered, washed with cold water and added to an excess of liquid ammonia. After evaporation of the excess ammonia, the residue was taken up in a little dilute ammonium hydroxide solution and filtered through charcoal. The solution was cooled and made slightly acidic and the solid which separated was filtered and recrystallized from water to give 3.4 g of the title compound. M.p. 227-229°C.

Example 8

2-Amino-4-(4-nitro-phenyl)-1H-imidazole

A mixture of α -amino-4-nitro-acetophenone hydrochloride (70 g), cyanamide (40.7 g), water (2100 ml), and conc. acetic acid (70 ml) was taken to pH 4.5 with 30% sodium hydroxide and the whole was heated at 100°C for 45 minutes. The hot solution was filtered and the solid which separated was washed with cold water and dried to give 25 g of the title compound. M.p. 235-240°C (as the hydrochloride).

Example 9

2-Acetamido-4-(4-nitro-phenyl)-1H-imidazole

A mixture of 2-amino-4-(4-nitro-phenyl)-1H-imidazole (17.3 g) in acetic anhydride (100 ml) was heated at 100°C for 1 hour. The solution was evaporated to dryness, and the residue was treated with ether, filtered and dried to give 18.9 g of the title compound. M.p. 242-244°C.

Example 10

2-Ethylamino-4-(4-amino-phenyl)-1H-imidazole

A suspension of 2-acetamido-4-(4-amino-phenyl)-1H-imidazole (16 g) in anhydrous tetrahydrofuran (160 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (12 g) in anhydrous tetrahydrofuran (240 ml). The mixture was heated at 60° for 4 hours.

After cooling and treatment with water, the solvent was evaporated and the residue was dissolved in 10% hydrochloric acid.

The solution was basified with 30% sodium hydroxide solution and the resulting solution was extracted with ethyl acetate. The organic phase was evaporated to dryness to give 8.2 g of the title compound.

M.p. 89-91°C.

Example 11

2-Methyl-4-(3-bromo-4-amino-phenyl)-1H-imidazole

A mixture of 2-methyl-4-(3-bromo-4-acetamido-phenyl)-1H-imidazole (15 g), concentrated hydrochloric acid (10 ml) and water (30 ml) was heated under reflux for 45 minutes. The solution was then cooled to room temperature and basified with 10% sodium hydroxide solution. The residue was filtered, washed with water and dried to give 10 g of the title compound.

M.p. 34-36°C.

Example 12

2-Methyl-4-(3-cyano-4-amino-phenyl)-1H-imidazole

A mixture of 2-methyl-4-(3-bromo-4-amino-phenyl)-1H-imidazole (5.12 g), copper (I) cyanide (2 g), and quinoline (15 ml) was heated under reflux for 4 hours. After cooling and decomposition with an acidic solution of ferric chloride, the mixture was extracted with ethyl acetate. The organic phase was dried and then evaporated to dryness and the residue was treated with water, filtered and dried to give 2.1 g of the title compound. M.p. 89-91°C.

Example 13

2-Methyl-4-(3-carbamoyl-4-amino-phenyl)-1H-imidazole

A mixture of 2-methyl-4-(3-cyano-4-amino-phenyl)-1H-imidazole (6.2 g) and Amberlite ^(RTM)IRA 400 (OH) (12 g) in water (150 ml) was heated under reflux for 5 hours. After cooling and filtration, the solution was evaporated to dryness to give 4.1 g of the title compound. M.p. 137-139°C.

Example 14

2-Methyl-4-(3-methyl-4-nitro-phenyl)-1H-imidazole

2-Methyl-4-(3-methyl-phenyl)-1H-imidazole as the nitrate salt (15 g) was added portionwise to 96% sulfuric acid (40 ml) at room temperature. The solution was heated at 90°C for 1 hour, cooled, diluted with water (200 ml) and neutralized with sodium carbonate solution. The solid which separated was filtered and the solution was made strongly basic with 10% sodium hydroxide solution. The residue which precipitated was filtered and dried to give 5 g of the title compound sufficiently pure to be used in the next step. M.p. 158-160°C.

The following intermediate was also prepared in a similar manner:

2-Methyl-4-(3-methoxy-4-nitro-phenyl)-1H-imidazole

M.p. 191-192°C.



Example 15

N-Cyano-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

A solution of 2-methyl-4-(4-amino-phenyl)-1H-imidazole (15 g) and ethyl N-cyanoformimidate (9.35 g) in ethanol (150 ml) was stirred at room temperature overnight. The crystallized product was collected by filtration, washed with cold ethanol and dried to give 15.2 g of the title compound. M.p. 175-176°C (dec.).

Following the above procedure, using the appropriate starting materials, the following N-cyanoamidines were prepared :

N-cyano-N'-[3-(2-methyl-imidazol-4-yl)phenyl]-

formamidine

M.p. 225-230°C(dec.)

N-cyano-N'-[4-(2-ethyl-imidazol-4-yl)phenyl]-

formamidine

M.p. 227-229°C(dec.)

N-cyano-N'-[4-(2-isopropyl-imidazol-4-yl)phenyl]-

formamidine

M.p. 221-223°C(dec.)

N-cyano-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-

acetamidine

M.p. 152-153°C(dec.)

N-cyano-N'-[4-(2,5-dimethyl-imidazol-4-yl)phenyl]-

formamidine

M.p. 145-148°C(dec.)

N-Cyano-N'-[4-(2-methylmercapto-imidazol-4-yl)phenyl]-formamidine

M.p. 232-235°C (dec)

N-Cyano-N'-[4-(2-hydroxy-imidazol-4-yl)phenyl]-formamidine

M.p. 255-258°C (dec)

N-Cyano-N'-[4-(2-methoxy-imidazol-4-yl)phenyl]-formamidine

M.p. 270°C (dec)

N-Cyano-N'-[4-(2-sulfamoyl-imidazol-4-yl)phenyl]-formamidine

M.p. 241-242°C (dec)

N-Cyano-N' - / 4-(2-acetamido-imidazol-4-yl)phenyl 7-formamidine

M.p. 228-230°C (dec)

N-Cyano-N' - / 4-(2-ethyl-amino-imidazol-4-yl)phenyl 7-formamidine

M.p. 215-216°C (dec)

N-Cyano-N' - / 2-bromo-4-(2-methyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 247-248°C (dec)

N-Cyano-N' - / 2-cyano-4-(2-methyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 239-241°C (dec)

N-Cyano-N' - / 2-carbamoyl-4-(2-methyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 250-252°C (dec)

N-Cyano-N' - / 4-(2-amino-imidazol-4-yl)phenyl 7-formamidine

M.p. 220-222°C (dec)

N-Cyano-N' - / 2-methyl-4-(2-methyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 234-236°C (dec)

N-Cyano-N' - / 2-methoxy-4-(2-methyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 263-266° (dec)

N-Cyano-N' - / 4-(2-phenyl-imidazol-4-yl)phenyl 7-formamidine

M.p. > 280°C

N-Cyano-N' - / 4-(2-methyl-sulfinyl-imidazol-4-yl)phenyl 7-formamidine

M.p. 222-224°C (dec)

Example 16

N-Methyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 1)

N-Cyano-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (2.25 g) was added in one portion to a solution of 33% aqueous methylamine (22.5 ml). After a few minutes a solid separated. The suspension was filtered and the residual solid was washed with water and dried to give 1.2 g of the title compound. Maleate salt (ethanol) M.p. 173-174°C (dec.)

Analysis

$C_{20}H_{22}N_4O_8$	Found %	C 54.07	H 4.79	N 12.31
	Calc. %	C 53.81	H 4.97	N 12.55

The following compounds were prepared in a similar manner starting from the N-cyanoamidine derivatives previously described:

N-Ethyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 2)

Maleate salt (ethanol) M.p. 166-168°C (dec)

Analysis

$C_{21}H_{24}N_4O_8$	Found %	C 54.49	H 5.21	N 12.38
	Calc. %	C 54.78	H 5.25	N 12.17

N-Isopropyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 3)

Maleate salt (ethanol) M.p. 192-193°C (dec)

Analysis

$C_{22}H_{26}N_4O_8$	Found %	C 55.84	H 5.59	N 11.63
	Calc. %	C 55.69	H 5.52	N 11.81

N-Allyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 4)

Maleate salt (ethanol) M.p. 170-171°C (dec)

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Analysis

$C_{22}H_{24}N_4O_8$	Found %	C 56,17	H 5,00	N 12,08
	Calc. %	C 55,93	H 5,12	N 11,86

N-Propargyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 5)

Maleate salt (ethanol) M.p. 160-162°C (dec)

Analysis

$C_{22}H_{22}N_4O_8$	Found %	C 56,23	H 4,70	N 12,05
	Calc. %	C 56,17	H 4,71	N 11,91

N-n-Hexyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 6)

Maleate salt (acetone) M.p. 127-130°C (dec)

Analysis

$C_{25}H_{32}N_4O_8$	Found %	C 57,87	H 6,24	N 10,62
	Calc. %	C 58,13	H 6,24	N 10,85

N-(2-Methoxyethyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine (Compound 7)

Maleate salt (acetone) M.p. 161-163°C (dec)

Analysis

$C_{22}H_{26}N_4O_9$	Found %	C 54,13	H 5,29	N 11,28
	Calc. %	C 53,87	H 5,34	N 11,42



N-(3-Hydroxypropyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-7-formamidine

(Compound 8)

Maleate salt (acetone)

M.p. 166-169°C (dec)

Analysis

$C_{22}H_{26}N_4O$	Found %	C 53.57	H 5.21	N 11.59
	Calc. %	C 53.87	H 5.34	N 11.42

N-(2-Methylthioethyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-7-formamidine

(Compound 9)

Maleate salt (ethanol)

M.p. 170-172°C (dec)

Analysis

$C_{22}H_{26}N_4O_2S$	Found %	C 51.99	H 5.27	N 11.30
	Calc. %	C 52.17	H 5.18	N 11.06

N-(2-Cyanoethyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-7-formamidine

(Compound 10)

Maleate salt (ethanol)

M.p. 162-164°C (dec)

Analysis

$C_{22}H_{23}N_5O$	Found %	C 54.29	H 4.71	N 14.35
	Calc. %	C 54.43	H 4.78	N 14.43

N-Cyclopropylmethyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-7-formamidine

(Compound 11)

Fumarate salt (ethanol)

M.p. 154-157°C (dec)

Analysis

$C_{23}H_{26}N_4O_2$	Found %	C 56.60	H 5.30	N 11.53
	Calc. %	C 56.78	H 5.39	N 11.52

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N-Cyclohexyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 12)

Fumarate salt (ethanol) M.p. 164-166°C (dec)

Analysis

$C_{25}H_{30}N_4O_8$	Found %	C 58,07	H 5,95	N 11,00
	Calc. %	C 58,36	H 5,88	N 10,89

N-Benzyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 13)

Hydrochloride salt (ethanol) M.p. 225-227°C (dec)

Analysis

$C_{18}H_{20}Cl_2N_4$	Found %	C 59,39	H 5,65	N 15,63
	Calc. %	C 59,51	H 5,55	N 15,42

N-Furfuryl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 14)

Hydrochloride salt (ethanol) M.p. 235-237°C (dec)

Analysis

$C_{16}H_{18}Cl_2N_4O$	Found %	C 54,67	H 5,27	N 15,68
	Calc. %	C 54,40	H 5,14	N 15,86

N-Ethyl-N'-[4-(2-ethyl-imidazol-4-yl)-phenyl]-formamidine

(Compound 15)

Maleate salt (ethanol) M.p. 165-167°C (dec)

Analysis

$C_{22}H_{26}N_4O_8$	Found %	C 55.78	H 5.51	N 11.59
	Calc. %	C 55.69	H 5.52	N 11.81

N-Isopropyl-N'-[4-(2-ethyl-imidazol-4-yl)phenyl]-formamidine

(Compound 16)

Maleate salt (ethanol) M.p. 180-181°C (dec)

Analysis

$C_{23}H_{28}N_4O_8$	Found %	C 56.95	H 5.79	N 11.30
	Calc. %	C 56.55	H 5.78	N 11.47

N-Ethyl-N'-[4-(2-isopropyl-imidazol-4-yl)phenyl]-formamidine

(Compound 17)

Maleate salt (ethanol) M.p. 174-175°C (dec)

Analysis

$C_{23}H_{28}N_4O_8$	Found %	C 56.73	H 5.87	N 11.60
	Calc. %	C 56.55	H 5.78	N 11.47

N-Isopropyl-N'-[4-(2-isopropyl-imidazol-4-yl)phenyl]-formamidine

(Compound 18)

Maleate salt (ethanol) M.p. 168-170°C (dec)

Analysis

$C_{24}H_{30}N_4O_8$	Found %	C 57.02	H 6.10	N 11.28
	Calc. %	C 57.36	H 6.02	N 11.15

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N-Isopropyl-N'-[4-(2-phenyl-imidazol-4-yl)phenyl]-Formamidine

(Compound 19)

Maleate salt (ethanol)

M.p. 208-210°C (dec)

Analysis

$C_{23}H_{24}N_4O_4$	Found %	C 66.01	H 5.95	N 13.20
	Calc. %	C 65.70	H 5.75	N 13.33

N-Isopropyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-acetamidine

(Compound 20)

Maleate salt (ethanol)

M.p. 106-108°C (dec)

Analysis

$C_{23}H_{28}N_4O_8$	Found %	C 56.67	H 5.76	N 11.55
	Calc. %	C 56.55	H 5.78	N 11.47

N-Ethyl-N'-[4-(2,5-dimethyl-imidazol-4-yl)phenyl]-formamidine

(Compound 21)

Maleate salt (acetone)

M.p. 165-167°C (dec)

Analysis

$C_{22}H_{26}N_4O_8$	Found %	C 55.41	H 5.70	N 12.01
	Calc. %	C 55.69	H 5.52	N 11.81

N-Isopropyl-N'-[4-(2,5-dimethyl-imidazol-4-yl)phenyl]-formamidine

(Compound 22)

Maleate salt (acetone)

M.p. 157-159°C (dec)

Analysis

$C_{23}H_{28}N_4O_8$	Found %	C 56.38	H 5.82	N 11.59
	Calc. %	C 56.55	H 5.78	N 11.47

N-Ethyl-N'-[3-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 23)

Maleate salt (acetone)

M.p. 171-173°C (dec)

Analysis

$C_{21}H_{24}N_4O_8$	Found %	C 54.61	H 5.19	N 11.98
	Calc. %	C 54.78	H 5.25	N 12.17

N-Isopropyl-N'-[3-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 24)

Maleate salt (acetone)

M.p. 168-171°C (dec)

Analysis

$C_{22}H_{26}N_4O_8$	Found %	C 55.44	H 5.48	N 11.69
	Calc. %	C 55.69	H 5.52	N 11.81

[Compound 26 follows]

N-Ethyl-N'-[4-(2-methyl mercapto-imidazol-4-yl)phenyl]-formamidine

(Compound 26)

Maleate salt (ethanol)

M.p. 158-160°C (dec)

28

Analysis

$C_{21}H_{24}N_4O_3S$	Found %	C 51,31	H 5,00	N 11,28
	Calc. %	C 51,22	H 4,91	N 11,38

N-Isopropyl-N'-[4-(2-methylmercapto-imidazol-4-yl)phenyl]-formamidine

(Compound 27)

Maleate salt (acetone)

M.p. 150-152°C (dec)

Analysis

$C_{22}H_{26}N_4O_3S$	Found %	C 51,93	H 5,20	N 11,25
	Calc. %	C 52,17	H 5,18	N 11,06

N-Isopropyl-N'-[4-(2-hydroxy-imidazol-4-yl)phenyl]-formamidine

(Compound 28)

Maleate salt (acetone)

M.p. 211-213°C (dec)

Analysis

$C_{17}H_{20}N_4O_5$	Found %	C 56,47	H 5,69	N 15,58
	Calc. %	C 56,66	H 5,59	N 15,55

N-Isopropyl-N'-[4-(2-methylsulfinyl-imidazol-4-yl)phenyl]-formamidine

(Compound 29)

Free amine (water)

M.p. 200-201°C (dec)

Analysis

$C_{14}H_{18}N_4O_2S$	Found %	C 57,82	H 6,23	N 19,15
	Calc. %	C 57,92	H 6,25	N 19,30

N-Isopropyl-N'-[4-(2-sulfamoyl-imidazol-4-yl)phenyl]-formamidine

(Compound 30)

Maleate salt (acetone)

M.p. 243-246°C (dec)

Analysis

$C_{17}H_{21}N_5O_2S$	Found %	C 47.97	H 5.07	N 16.63
	Calc. %	C 48.22	H 5.00	N 16.54

N-Isopropyl-N'-[4-(2-amino-imidazol-4-yl)phenyl]-formamidine

(Compound 31)

Maleate salt (ethanol)

M.p. 212-215°C (dec)

Analysis

$C_{21}H_{25}N_5O_3$	Found %	C 52.80	H 5.23	N 14.81
	Calc. %	C 53.05	H 5.30	N 14.73

N-Isopropyl-N'-[4-(2-acetamido-imidazol-4-yl)phenyl]-formamidine

(Compound 32)

Maleate salt (ethanol)

M.p. 196-198°C (dec)

Analysis

$C_{23}H_{27}N_5O_3$	Found %	C 53.40	H 5.22	N 13.44
	Calc. %	C 53.38	H 5.26	N 13.53

N-Isopropyl-N'-[4-(2-ethylamino-imidazol-4-yl)phenyl]-formamidine

(Compound 33)

Maleate salt (ethanol)

M.p. 225-227°C (dec)

40

Analysis

$C_{23}H_{29}N_5O_8$	Found %	C 54,50	H 5,73	N 14,09
	Calc. %	C 54,86	H 5,81	N 13,91

N-n-Propyl-N'-[2-bromo-4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 34)

Maleate salt (acetone)

M.p. 186-188°C (dec)

Analysis

$C_{22}H_{25}BrN_4O_8$	Found %	C 47,66	H 4,60	N 10,01
	Calc. %	C 47,75	H 4,55	N 10,12

N-Isopropyl-N'-[2-cyano-4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 35)

Maleate salt (ethanol)

M.p. 178-180°C (dec)

Analysis

$C_{23}H_{25}N_5O_8$	Found %	C 55,12	H 4,99	N 13,88
	Calc. %	C 55,30	H 5,05	N 14,02

N-Ethyl-N'-[2-carbamoyl-4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 36)

Maleate salt (acetone)

M.p. 233-235°C (dec)

Analysis

$C_{22}H_{25}N_5O_9$	Found %	C 52,63	H 5,09	N 14,10
	Calc. %	C 52,48	H 5,01	N 13,91

N-Allyl-N'-[2-methyl-4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 37)

Maleate salt (acetone)

M.p. 170-172°C (dec)

Analysis

$C_{23}H_{26}N_4O_8$	Found %	C 57.00	H 5.45	N 11.38
	Calc. %	C 56.78	H 5.39	N 11.52

N-n-Propyl-N'-[2-methoxy-4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 38)

Maleate salt (acetone)

M.p. 201-203°C (dec)

Analysis

$C_{22}H_{28}N_4O_9$	Found %	C 54.44	H 5.59	N 10.97
	Calc. %	C 54.75	H 5.59	N 11.11

Example 17

N-t-Butyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 39)

To a solution of N-t-butyl formamide (5.06 g) in dichloromethane (30 ml) was slowly added at 0°C a solution of triethyloxonium tetrafluoroborate (9.56g) in dichloromethane (50 ml). After 6 hours' stirring at room temperature, a solution of 2-methyl-4-(4-amino-phenyl)-1H-imidazole (4g) in ethanol (20 ml) was added dropwise.

The mixture was stirred overnight, and then evaporated to dryness.

The fluoroborate salt of the desired compound was dissolved in water and the solution was basified with 10% sodium hydroxide solution.

The product which separated was filtered, washed with water and dried to give 2.1 g of the title formamidine.

Sulfate salt (methanol)

M.p. 276-278°C (dec)

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Analysis

$C_{15}H_{22}N_4O_4S$	Found %	C 50,79	H 6,31	N 15,77
	Calc. %	C 50,84	H 6,26	N 15,81

Example 18N-Phenyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine(Compound 40)

2-Methyl-4-(4-amino-phenyl)-1H-imidazole (5 g) was added to a solution of ethyl N-phenylformimidate (5 g) in acetone (25 ml). After 3 hours' stirring at room temperature, a solid separated. The suspension was filtered and the residual solid was dried. The compound was treated with glacial acetic acid in acetone: the acetate salt precipitated, the suspension was filtered and the residual solid was dried to give 4.6 g of the title compound.

Acetate salt (acetone)

M.p. 147-150°C (dec)

Analysis

$C_{21}H_{24}N_4O_4$	Found %	C 63,77	H 6,13	N 14,27
	Calc. %	C 63,62	H 6,10	N 14,13

The following compounds were prepared in a similar manner starting from the appropriate ethyl formimidates :

N-(4-Chlorophenyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine(Compound 41)

Acetate salt (acetone)

M.p. 112-115°C (dec)

Analysis

$C_{21}H_{23}ClN_4O_4$	Found %	C 58,29	H 5,60	N 13,12
	Calc. %	C 58,54	H 5,38	N 13,00

N-(2-Pyridyl)-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine

(Compound 42)

Free amine (acetone) M.p. 59-61°C (dec)

Analysis

$C_{16}H_{15}N_5$	Found %	C 68.99	H 5.30	N 25.36
	Calc. %	C 69.29	H 5.45	N 25.26

N-Isopropyl-N'-[4-(2-chloro-imidazol-4-yl)phenyl]-formamidine

(Compound 43)

Free amine (acetone) M.p. 85-87°C (dec)

Analysis

$C_{12}H_{13}ClN_4$	Found %	C 57.89	H 5.33	N 22.41
	Calc. %	C 57.95	H 5.27	N 22.53

N-Isopropyl-N'-[4-(2-methoxy-imidazol-4-yl)phenyl]-formamidine

(Compound 44)

Maleate salt (methanol) M.p. 236°C (dec)

Analysis

$C_{22}H_{26}N_4O_4$	Found %	C 54.02	H 5.46	N 11.53
	Calc. %	C 53.87	H 5.34	N 11.42

The following non-limiting pharmaceutical Examples illustrate the preparation of compositions according to the invention:

Example 19

Tablets

- active ingredient	50 mg
- lactose	217 mg
- corn starch	30 mg
- magnesium stearate	3 mg

HA

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Method of preparation : the active ingredient, lactose, and corn starch were mixed and homogeneously moistened with water. After screening of the moist mass and drying in a tray dryer, the mixture was again passed through a screen and magnesium stearate was added. Then the mixture was pressed into tablets weighing 300 mg each. Each tablet contains 50 mg of active ingredient.

Example 20

Capsules

- active ingredient 50 mg
- corn starch 170 mg
- magnesium stearate 2 mg

Method of preparation: the active ingredient was mixed with the auxiliary products, and the mixture was passed through a screen and mixed to homogeneity in a suitable device. The resulting mixture was introduced into hard gelatine capsules (222 mg per capsule); each capsule contains 50 mg of active ingredient.

Example 21

Vials

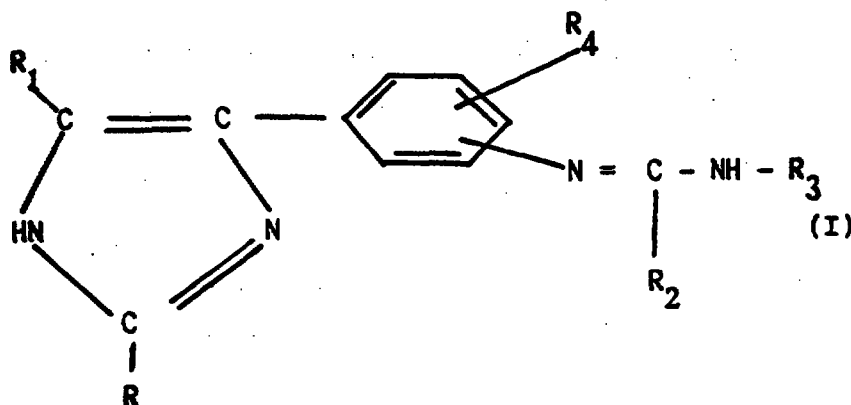
- active ingredient 50 mg
- water for injection q.s. 5 ml

Method of preparation: the active ingredient was dissolved in the water in appropriate amounts, and then the resulting solution was placed in 5 ml vials under sterile conditions. Each vial contains 50 mg of active ingredient.

(45)

**CLAIMS**

1. Compounds of general formula I



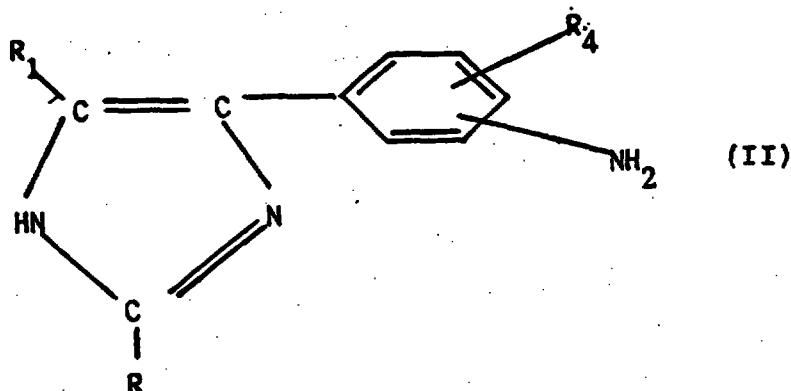
- (in which R represents a linear or branched alkyl group, a hydroxy group, a C₁₋₃ alkoxy or alkylthio group, a halogen atom, a C₁₋₃ alkylsulfinyl or alkylsulfonyl group, a sulfamoyl group, an amino group which may be substituted by one or two alkyl groups having 1 to 3 carbon atoms, an acylamino group or a phenyl group; R₁ and R₂, which may be the same or different, each represents a hydrogen atom or an alkyl group; R₃ represents a linear or branched alkyl group optionally containing one heteroatom such as an oxygen, sulphur or nitrogen atom, an alkenyl group, an alkynyl group, a cyano group, an optionally substituted aryl or aralkyl group, a cycloalkyl or cycloaliphatic alkyl group, a substituted or unsubstituted heterocyclic group or an alkyl group substituted by a substituted or unsubstituted heterocyclic group; and R₄ represents a hydrogen atom, a C₁₋₃ alkyl or alkoxy group, a halogen atom or a cyano or carbamyl group), tautomeric forms thereof and acid addition salts of the aforementioned compounds.



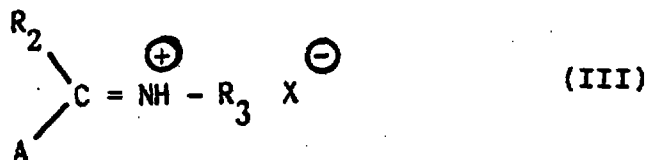
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2. Physiologically compatible acid addition salts of compounds of general formula I as claimed in claim 1.
3. Salts as claimed in claim 2 formed with hydrochloric, sulfuric, maleic or fumaric acid.
4. N-Ethyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine.
5. N-Isopropyl-N'-[4-(2-methyl-imidazol-4-yl)-phenyl]-formamidine.
- 10 6. N-Allyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine.
7. N-t-Butyl-N'-[4-(2-methyl-imidazol-4-yl)phenyl]-formamidine.
8. N-Isopropyl-N'-[4-(2-hydroxy-imidazol-4-yl)phenyl]-formamidine.
- 15 9. Physiologically compatible acid addition salts of compounds as claimed in claims 4 to 8.
10. Maleic, hydrochloric, fumaric or sulfuric acid addition salts of compounds as claimed in claims 4 to 8.
- 20 11. Compounds as claimed in claim 1 as herein specifically described in any one of Examples 15 to 18.
12. A process for the preparation of compounds as claimed in claim 1 which comprises reacting
- 25 a compound of formula II



(in which R, R₁ and R₄ are as defined in claim 1) with a compound of formula III



(in which R_2 and R_3 are as defined in claim 1, X^- represents the anion of an inorganic acid and

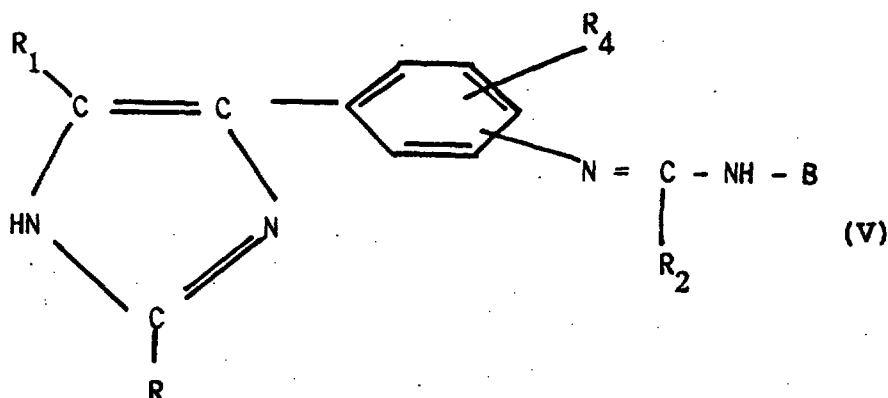
- 5 A represents a benzyloxy group, a chlorine atom or a lower alkoxy group).
13. A process as claimed in claim 12 in which the anion of an inorganic acid is selected from the chloride and fluoroborate anions.
- 10 14. A modification of the process as claimed in claim 12 or claim 13 in which a compound of formula III is made to react as a base.
- 15 15. A process as claimed in any one of claims 12 to 14 in which the reaction is carried out in the presence of an inert organic solvent.
16. A process as claimed in claim 15 in which the inert organic solvent used is selected from ethanol, dioxan or acetone.
17. A process as claimed in any one of claims
- 20 12 to 16 in which the reaction is carried out at temperatures of from 0 to 100°C.
18. A process as claimed in claim 17 in which the reaction is carried out at temperatures of from 20 to 60°C.
- 25 19. A process for the preparation of compounds as claimed in claim 1 which comprises reacting



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a compound of general formula V



(in which R, R₁, R₂ and R₄ are as defined in claim 1 and B represents a suitable leaving group) with
5 an amine of formula VI



(in which R₃ is as defined in claim 1).

20. A process as claimed in claim 19 in which the leaving group B comprises a cyano, acetyl, carbethoxy or carbamyl group.
21. A process as claimed in claim 19 or claim 20 in which the reaction is carried out in the presence of water.
22. A process as claimed in claim 19 or claim 20 in which the reaction is carried out in the presence of an inert organic solvent.
23. A process as claimed in claim 22 in which the inert organic solvent used is selected from an alcohol, dimethylformamide, dioxan or acetonitrile.
24. A process as claimed in any one of claims 19 to 23 in which the reaction is carried out at temperatures of from 10 to 50°C.
25. A process as claimed in claim 24 in which the reaction is carried out at room temperature.
26. A process as claimed in any one of claims 12 to 25 in which a compound of general formula



I as defined in claim 1 initially obtained is subsequently converted into an acid addition salt thereof or

an acid addition salt of a compound of formula

I initially obtained is subsequently converted

5 into a compound of formula I.

27. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

28. A process for the preparation of compounds as claimed in claim 1 substantially as herein described

10 in any one of Examples 15 to 18.

29. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 12 to 28.

30. Pharmaceutical compositions comprising as
15 active ingredient at least one compound of general formula I as defined in claim 1, or a tautomer or physiologically compatible acid addition salt thereof, in association with one or more pharmaceutical carriers or excipients.

20 31. Compositions as claimed in claim 30 in a form suitable for oral or parenteral administration.

32. Compositions as claimed in claim 30 or claim 31 in the form of capsules, tablets, coated tablets, ampoules and/or vials.

25 33. Compositions as claimed in any one of claims 30 to 32 in the form of dosage units.

34. Compositions as claimed in claim 33 in which each dosage unit contains from 10mg to 500mg of active ingredient.

30 35. Compositions as claimed in claim 33 or claim 34 in which each dosage unit contains from 20mg to 150mg of active ingredient.

36. Pharmaceutical compositions as claimed in claim 30 substantially as herein described.

35 37. Pharmaceutical compositions substantially as herein described in any one of Examples 19 to 21.

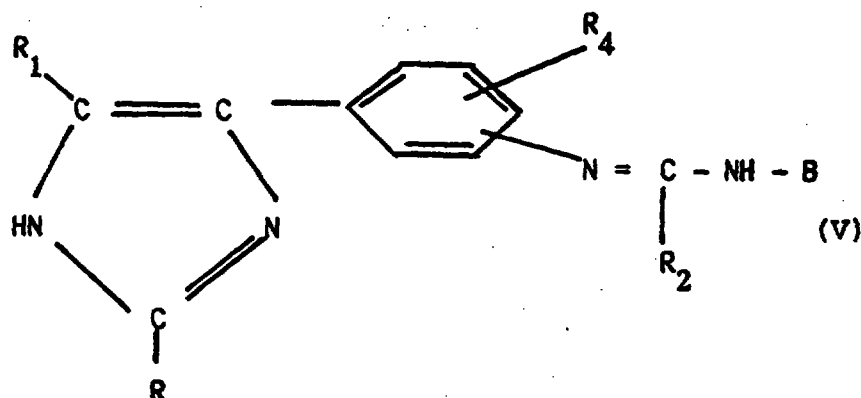


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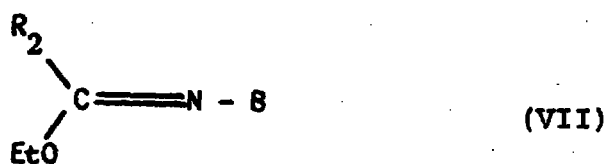
38. Compounds of general formula I as claimed in claim 1, or tautomers or physiologically compatible acid addition salts thereof, for use in the treatment of ulcers and/or disorders of the gastrointestinal tract.

39. Compounds of general formula V



(in which R , R_1 , R_2 and R_4 are as defined in claim 1 and B represents a cyano, acetyl, carbethoxy or carbamyl group).

40. A process for the preparation of compounds as claimed in claim 39 which comprises reacting a compound of general formula II as defined in claim 12 with a compound of formula VII



(in which R_2 is as defined in claim 1 and B is as defined in claim 39).
